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Somatostatin: Linking Cognition and Alzheimer Disease to Therapeutic Targeting

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***Abstract*——Over 4 decades of research support the link between Alzheimer disease (AD) and somatostatin [somatotropin-releasing inhibitory factor (SRIF)]. SRIF and SRIF-expressing neurons play an essential role in brain function, modulating hippocampal activity and memory formation. Loss of SRIF and SRIF-expressing neurons in the brain rests at the center of a series of interdependent pathological events driven by amyloid-*β* peptide (A*β*), culminating in cognitive decline and dementia. The connection between the SRIF and AD further extends to the neuropsychiatric symptoms, seizure activity, and inflammation, whereas preclinical AD investigations show SRIF or SRIF receptor agonist administration capable of enhancing cognition. SRIF receptor subtype-4 activation in particular presents unique attributes, with the potential to mitigate learning and memory decline, reduce comorbid symptoms, and enhance enzymatic degradation of A*β* in the brain. Here, we review the links between SRIF and AD along with the therapeutic implications.**

***Significance Statement*——Somatostatin and somatostatin-expressing neurons in the brain are extensively involved in cognition. Loss of somatostatin and somatostatin-expressing neurons in Alzheimer disease rests at the center of a series of interdependent pathological events contributing to cognitive decline and dementia. Targeting somatostatin-mediated processes has significant therapeutic potential for the treatment of Alzheimer disease.**

I. Introduction

Alzheimer disease (AD) is the most common form of dementia. In the United States alone, there are an estimated 6.9 million people living with AD, which is predicted to grow to 13.8 million by 2060 (https://pubmed.ncbi.nlm.nih.gov/38689398/). AD progresses across a continuum (Jack et al., 2010; Vermunt et al., 2019). AD is

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preceded by a preclinical phase lasting for ~15–20 years, associated with increasing Aβ accumulation within the brain but without cognitive impairment. A prodromal stage marks the initiation of symptoms, characterized by mild cognitive impairment (MCI), and often lasts 3–6 years. The formal dementia stage typically lasts 7–10 years and is categorized into mild, moderate, and severe AD based on the level of patient impairment. Ultimately, the capacity to speak and perform simple tasks is lost, culminating in immobility and death.

Most AD diagnoses are designated as "sporadic," with a number of contributing genetic, environmental, and comorbidity risk factors (Samanta and Ramesh, 2022). This implicates a multifactorial etiology with potential interdependency between risk factors. Increasing age is the greatest risk factor for AD. AD diagnosis at age 65 or older is classified as late-onset AD (LOAD) and accounts for more than 95% of occurrences. AD diagnosis before age 65 is classified as early-onset AD and accounts for less than 5% of occurrences. Fewer than 1% of cases have a recognized inheritable etiology that occurs in an autosomal-dominant AD (ADAD) manner, also known as familial AD. Mutations in any of 3 specific genes [amyloid precursor protein (*APP*) gene, presenilin-1 (*PS1*) gene, and presenilin-2 (*PS2*) gene] results in overproduction of the amyloid-β peptide (Aβ) (Bekris et al., 2010). Inheritance of these mutations nearly guarantees AD development assuming a normal lifespan, with age of onset and rate of progression related to the severity of the mutation (Goldman et al., 2011).

The brains of individuals with AD exhibit two cardinal histopathological features: deposits of Aβ in the form of extracellular plaques and intraneuronal neurofibrillary tangles (NFTs) composed of aggregates of hyperphosphorylated tau protein (Long and Holtzman, 2019). Aβ is a primary research and drug development target due to its early-stage accumulation within the brain and genetic data supporting an Aβ-AD causal relationship (Selkoe and Hardy, 2016). Aβ is generated following the sequential cleavage of APP by β- and γ-secretase in the amyloidogenic pathway. The more hydrophobic species of Aβ (i.e., Aβ_{42} and longer) readily self-aggregate and are associated with greater pathologic contribution compared with less hydrophobic forms (i.e., Aβ_{40} and shorter). The original Aβ-cascade hypothesis posited that the deposition of Aβ in the brain is the initiating step of AD pathogenesis, with subsequent tau deposition and neuronal loss (Hardy and Higgins, 1992). This hypothesis has evolved with the increased recognition as to the role of Aβ peptide oligomers (AβOs). Soluble AβOs are now regarded as the most pathogenic and neurotoxic form of Aβ, with impairment of synaptic structure and function by AβOs preceding the formation of Aβ plaques (Gyure et al., 2001; Lacor et al., 2004; Shankar et al., 2008). There are also a number of reports identifying extensive Aβ plaque deposits in brain tissues taken from individuals who lacked definitive signs of dementia (Katzman et al., 1988; Hulette et al., 1998; Price and Morris, 1999; Aizenstein et al., 2008; Zolochevska and Taglialatela, 2016). It is hypothesized that Aβ plaques may even serve to sequester toxic AβOs (Esparza et al., 2013; Hong et al., 2014), whereas support for AβOs as the AD pathological trigger is extensive and continues to grow. AβOs directly activate N-methyl-D-aspartate (NMDA) receptors increasing neuronal hyperexcitation (Li et al., 2011; Zott et al., 2019), prevent glutamate reuptake (Li et al., 2009b; Zott et al., 2019), enhance oxidative (Sponne et al., 2003; Tabner et al., 2005; De Felice et al., 2007; Yin et al., 2021) and endoplasmic reticulum (ER) stress (Nishitsuji et al., 2009; Umeda et al., 2011; Kam et al., 2022), impair neuronal function (Heinitz et al., 2006; Chung et al., 2020), decrease trophic factors (Kitiyanant et al., 2012; Poon et al., 2013; Sen et al., 2015; Pitt et al., 2017), produce insulin resistance (Zhao et al., 2008, 2009; Ma et al., 2009), activate glial inflammatory mechanisms (Sondag et al., 2009; Maezawa et al., 2011; Ferretti et al., 2012; Yang et al., 2017), stimulate tau hyperphosphorylation (De Felice et al., 2008; Tomiyama et al., 2010; Zempel et al., 2010; Wakeman et al., 2022), produce synaptic deterioration (Lacor et al., 2004, 2007; Shankar et al., 2007, 2008), impair synaptic transport (Pigino et al., 2009; Decker et al., 2010; Poon et al., 2011; Ramser et al., 2013) and plasticity (Townsend et al., 2006; Klyubin et al., 2008; Shankar et al., 2008; Actor-Engel et al., 2021; Yan et al., 2021), and selectively induce neuronal cell death (Lambert et al., 1998; Kim et al., 2003; Salvadores et al.,

ABBREVIATIONS: Aβ, amyloid-β peptide; ACTH, adrenocorticotropic hormone; AD, Alzheimer disease; ADAD, autosomal dominant Alzheimer disease; ADRDA, Alzheimer Disease and Related Disorders Association; AβO, amyloid-β peptide oligomer; ApoE, apolipoproein E; APP, amyloid precursor protein; BBB, blood-brain barrier; BDNF, brain-derived neurotrophic factor; ChEI, cholinesterase inhibitor; CNS, central nervous system; CSF, cerebrospinal fluid; CST, cortistatin; eEF2, eukaryotic translational elongation factor 2; eIF2α, eukaryotic initiation factor 2α; EPM, elevated plus maze; ER, endoplasmic reticulum; FDA, Food and Drug Administration; FST, forced swim test; GPCR, G-protein–coupled receptor; HPA, hypothalamic-pituitary-adrenal; IDE, insulin-degrading enzyme; IGF, insulin-like growth factor; IL, interleukin; LOAD, late-onset Alzheimer disease; LPS, lipopolysaccharide; LTP, long-term potentiation; MCI, mild cognitive impairment; MDD, major depressive disorder; MSR1, macrophage scavenger receptor-1; NBM, nucleus basalis of Maynert; NEP, neprilysin; NFT, neurofibrillary tangle; NINCDS, National Institute of Neurological and Communicative Disorders and Stroke; NMDA, N-methyl-D-aspartate; O-LM, oreins-lacunosum moleculare; PS1, presenilin-1; PS1dE9, presenilin-1 dE9; PSD, postsynaptic density protein; SAMP8, senescence-accelerated mouse prone 8; SRIF, somatostatin; SST, somatostatin receptor; TLE, temporal lobe epilepsy; TNF, tumor necrosis factor; ZO, zonula occludens.

2022). Notably, AβOs isolated from human AD cortical tissue impairs memory behavior when injected into the lateral ventricles of healthy adult rats (Shankar et al., 2008). Thus, although many factors contribute to AD pathogenesis, Aβ and its oligomeric forms represent the most validated therapeutic target for disease mitigation.

To date, eight drugs have been approved by the US Food and Drug Administration (FDA) for AD. Five of these drugs (donepezil, rivastigmine, galantamine, memantine, and memantine combined with donepezil) are designated as palliative therapies for symptom alleviation. Only the recently FDA-approved Aβ-directed antibodies aducanumab, lecanemab, and donanemab are specifically directed toward the underlying pathology. Nevertheless, the effectiveness of Aβ-directed antibodies in mitigating cognitive decline is greatly debated, with added concerns as to their potential to induce life-threatening brain swelling and bleeding (Shi et al., 2022; Couzin-Frankel, 2023). Given the current state of AD drug therapy, there is increasing recognition that therapeutic development needs to take into greater account the complex multifactorial nature of AD and interlinking cellular processes involved (Hampel et al., 2019). Focusing on critical neuronal networks and the targeting of key mediators involved in both neuronal health and disease progression may provide a more successful treatment approach.

Somatostatin [somatotropin-releasing inhibitory factor (SRIF)] and SRIF-expressing neurons are essential in brain function. SRIF-expressing neurons have extensive brain network interconnections, regulating hippocampal activity and memory formation (Honoré et al., 2021). The loss of SRIF and SRIF-expressing neurons in AD is a definitive pathological event (Davies et al., 1980; Rossor et al., 1980; Grouselle et al., 1998), playing a central role in a series of interdependent pathological feedback loops that drive AD progression (Fig. 1). Loss of SRIF and SRIF-expressing neurons further contributes to AD-associated neuropsychiatric symptoms, seizure activity, and inflammation. Moreover, a unique facet of SRIF is its capacity to enhance the activity of Aβ-degrading enzymes in the brain through receptor-mediated action (Saito et al., 2005; Sandoval et al., 2012; Nilsson et al., 2020). Not only does this implicate a decline in brain SRIF as a contributor to Aβ accumulation but it identifies a mechanism by which SRIF receptor (SST)-targeted therapeutics may mitigate the underlying pathology. In light of these considerations, this review aims to provide insight into the connections between SRIF and AD along with the therapeutic implications.

II. Somatostatin and Somatostatin Receptors

SRIF is a neuropeptide heavily involved in the regulation of endocrine, brain, and gastrointestinal processes. Brazeau et al., (1973) first isolated SRIF, identifying its ability to inhibit growth hormone release from the

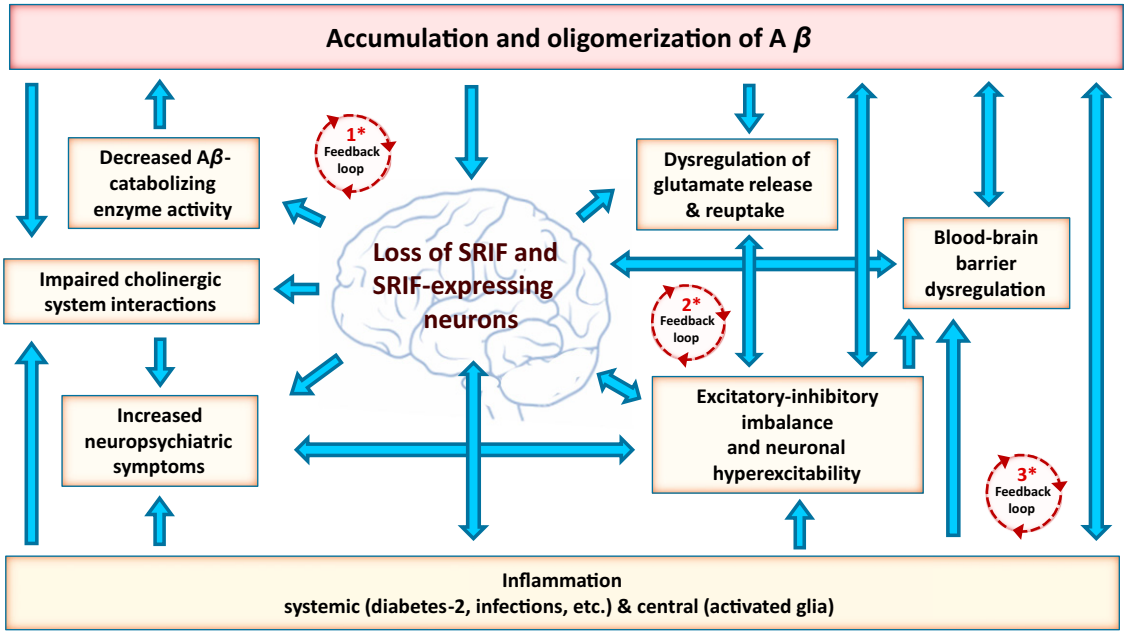

Fig. 1. Flow chart of interactions between SRIF-AD. AD-associated loss of SRIF and SRIF-expressing neurons in the brain rests at the center of a series of interdependent pathological events driven by Aβ and inflammatory processes, culminating in cognitive decline and dementia. * This loss drives positive feedback loops, which feed into each other, promoting an escalating pathology (numbering is not indicative of sequence of events): (1) Loss of SRIF and SRIF-expressing neurons decreases Aβ-degrading enzyme activity, resulting in elevated Aβ brain levels and promotion of neurodegeneration. (2) Loss of SRIF and SRIF-expressing neurons results in a dysregulation of glutamate homeostasis and excitatory-inhibitory balance with corresponding neuronal hyperexcitability, which propagates further Aβ neuronal release and neuronal damage. (3) Loss of SRIF and SRIF-expressing neurons contributes to inflammation. Inflammation results in neuronal dysfunction and degeneration, perpetuating further inflammation. Inflammation-induced BBB dysregulation contributes to increased Aβ brain levels. Inflammation is linked to increased seizure activity and neuropsychiatric symptoms, which are likewise linked to the loss of SRIF and SRIF-expressing neurons as well as BBB dysregulation.

pituitary. Subsequent evaluations show SRIF as a primary regulator of growth hormone, prolactin, corticotrophin-releasing hormone, adrenocorticotropic hormone (ACTH), insulin, glucagon, thyroid-stimulating hormone, and vasoactive intestinal peptide, extensively reviewed elsewhere (Günther et al., 2018). Within the central nervous system (CNS), SRIF primarily acts to inhibit neuronal activity. SRIF exists in two bioactive forms: SRIF-14 and the N-terminally extended SRIF-28. Both SRIF forms have a short plasma half-life of <3 minutes (Patel and Wheatley, 1983). Although both forms are expressed at varying levels throughout the body, SRIF-14 is the predominant form in the brain (Viollet et al., 2008). Both forms are derived from the same precursor protein, prepro-SRIF, with a structure that is highly conserved across vertebrates (Conlon et al., 1997). The expression of the SRIF precursor gene is regulated by a number of growth factors, including insulin, growth hormone, leptin, brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF)-1, and vasoactive intestinal peptide as well as steroids, inflammatory cytokines, and various neurotransmitters (Ampofo et al., 2020). The family of SRIF-related peptides also includes cortistatin (CST) and neuronostatin. CST similarly has two bioactive forms in rats (CST-14 and CST-29) and in humans (CST-17 and CST-29). Although CST is encoded by the CORT gene (Liu et al., 2010), it is highly homologous with SRIF and partially overlaps SRIF brain expression (de Lecea et al., 1997). Neuronostatin is encoded by the SRIF gene and is expressed in the pancreas, spleen, and brain (Samson et al., 2008).

SRIF produces its actions through five receptors ($SST_{1–5}$), with a splice variant of $SST_{2(B)}$ identified in rodents (Vanetti et al., 1992). SRIF binds to all SST subtypes with high affinity, as does CST (Siehler et al., 2008). The SSTs are members of the family-A heteromeric G-protein–coupled receptors (GPCRs) of the rhodopsin-like family. All SSTs possess seven α-helical transmembrane domains, with divergence mostly occurring in the intracellular C-terminus and N-terminus domains. On basis of their phylogeny, structural homologies, and pharmacological properties, the SSTs are categorized into two families: SRIF-1 (SST_2, SST_3, and SST_5) and SRIF-2 (SST_1 and SST_4). The receptors share 39%–57% homology in sequence between the subtypes, and when compared across species there is considerable sequence similarity for a given subtype (81%–99% for mouse, human, and rat homologs) (Günther et al., 2018). Although formal crystal structures are lacking, recent evaluations using cryogenic electron microscopy have characterized the structure of both SST_2 and SST_4 bound to ligands in different activation states (Bo et al., 2022; Robertson et al., 2022; Zhao et al., 2022). These studies show the SST ligand recognition is highly diverse, respective to each receptor, as demonstrated by ligand-induced conformational changes. The SST subtypes are further delineated by regional distribution throughout the human CNS and periphery (Consortium, 2020; Sjöstedt et al., 2020). Nevertheless, SST subtype distributions often overlap within brain regions. Immunocytochemical evaluations conducted in rat brain tissue identified that specific SST subtypes have preferential presynaptic (SST_1) and postsynaptic ($SST_{2,4,5}$) localization, with SST_3 expressed in neuronal cilia (Schulz et al., 2000), albeit a number of exceptions exist as to the adherence of presynaptic and postsynaptic SST subtype localization (Günther et al., 2018).

All SST subtypes are Gi/Go proteins sensitive to pertussis toxin. Upon receptor activation, the Gα subunit inhibits adenylyl cyclase, which inhibits downstream formation of intracellular cAMP (Patel et al., 1994). The β/γ subunits of the GPCR can impact presynaptic and postsynaptic neuronal signaling through regulation of different ion channels. The β/γ subunits can activate G-inwardly rectifying potassium channels, resulting in K^+ efflux out of the neuron and hyperpolarization. The β/γ subunits of the GPCR also bind to the α1 subunit of N-type and P/Q-type voltage-gated calcium channels, resulting in cellular inhibition (Viana and Hille, 1996; Smith et al., 2001). SSTs further modulate other pathways, including cGMP-dependent kinase, protein tyrosine phosphatase, phospholipase C, mitogen-activated protein kinase, phospholipase A_2, nitric oxide synthase, and the Na^+/H^+ exchanger (Günther et al., 2018). The activation or inhibition of a respective pathway is dependent on the primary function of the cell acted upon, mediated through a specific SST subtype.

Receptor interactions add another layer to SST regulation. All SSTs have the capacity to dimerize (Kumar, 2013), with functional interactions between SST subtypes widely reported (Moneta et al., 2002; Cammalleri et al., 2004, 2006, 2009; Aourz et al., 2011; Prévôt et al., 2017). Homo and heterodimerization, or even oligomeric receptor complexes, can result in distinctive signal transduction responses when activated (Mores et al., 2018). Such interactions can change the receptor desensitization, internalization, postendocytic trafficking, and resensitization profiles (Grant et al., 2008; Grant and Kumar, 2010; Mores et al., 2018). The interactive arrestins also serve as scaffolding proteins for alternate intracellular signaling cascades. The recognition of these alternate pathways has led to a search for drug candidates with selective signal bias capable of favoring distinctive biochemical and physiological processes. Nevertheless, exploitation of such biased receptor-ligand complexes toward refined therapeutic targeting remains dependent on the nature of the receptor in the native tissue respective to the disorder.

III. Somatostatin-Expressing Neurons

Networks of SRIF-expressing neurons exist in the neocortex, hippocampal formation (hippocampus, dentate

gyrus, entorhinal cortex, subiculum), amygdala, median eminence, preoptic area, hypothalamus, brainstem, and somatosensory cortex (Martel et al., 2012). Neuronal SRIF is colocalized with the inhibitory amino acid neurotransmitter GABA. Consequently, SRIF-expressing neurons exist as a distinct subset of GABAergic inhibitory neurons. Yet, although GABA is stored in synaptic vesicles that can be released via a single action potential, SRIF is stored in dense-core vesicles, which require high-frequency repetitive action potentials for release (Ludwig and Pittman, 2003). Moreover, unlike GABA, SRIF lacks a selective reuptake mechanism, which enhances the presence in the synaptic cleft. Thus, despite cellular coexpression and complimentary inhibitory actions, SRIF and GABA can have different release rates and receptor interaction timeframes.

A distinguishing property of SRIF-expressing neurons is the high level of spontaneous activity, enabled by intrinsic membrane conductance that can persist in the absence of synaptic input. The activity can be enhanced by other neuromodulators, including norepinephrine and acetylcholine (Paspalas and Papadopoulos, 1999; Fanselow, 2010; Chen et al., 2015). SRIF release is further regulated by GABA (Bonanno et al., 1999; Kanigowski et al., 2023) and the excitatory amino acid glutamate (Tapia-Arancibia and Astier, 1989; Fontana et al., 1996). In the hippocampus, glutamate was shown to stimulate SRIF release through the activation of ionotropic NMDA and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors (Fontana et al., 1996).

Upon release, SRIF acts on the SSTs of adjacent neurons in a paracrine-like manner. Presynaptically, SRIF acts to decrease neurotransmitter release. SRIF notably inhibits glutamate release, decreasing excitatory synaptic transmission in the hypothalamus, hippocampal formation, basal forebrain, and neocortex (Boehm and Betz, 1997; Tallent and Siggins, 1997; Grilli et al., 2004; Momiyama and Zaborszky, 2006; Kozhemyakin et al., 2013). This presynaptic inhibition is primarily mediated through the reduction of voltage-dependent Ca^{2+} currents. Other reports indicate that the modulation of presynaptic K^+ channels is also involved in the inhibition of excitatory transmission via SRIF-mediated action (Tallent and Siggins, 1997). SRIF can likewise inhibit presynaptic GABA release. The application of SRIF has been shown to reduce the amplitude of the evoked GABAergic inhibitory presynaptic currents in basal forebrain cholinergic neurons (Momiyama and Zaborszky, 2006). Postsynaptically, SRIF acts to hyperpolarize neurons in the brain and spinal cord away from their firing threshold through SST-mediated enhancement of K^+ efflux or a reduction of Ca^{2+} influx (Moore et al., 1988; Schweitzer et al., 1998; Kim et al., 2002; Qiu et al., 2008). Thus, postsynaptically, SRIF induces a slow, long-lasting inhibition.

Despite its predominately inhibitory role, SRIF can induce downstream excitatory effects. SRIF is able to increase excitation through inhibitory actions on GABA neurotransmission, contributing to long-term potentiation (LTP) (Scharfman and Schwartzkroin, 1989; Racine et al., 2021). In a study using single-unit recordings in rat hippocampus and parietal cortex, SRIF applied with acetylcholine caused a concentration-dependent increase in acetylcholine-induced excitations (Mancillas et al., 1986). In rat hippocampal slices, SRIF application enhanced acetylcholine release indirectly by a mechanism involving alterations of calcium influx during depolarization (Araujo et al., 1990). Moreover, SRIF actions can be dose dependent, with SRIF applied to cultured neurons inducing excitation at lower doses and inhibition at higher doses (Delfs and Dichter, 1983). This underscores the complex nature governing neuronal activity.

Morphologically, SRIF-expressing neurons are broadly categorized as either interneurons, which act within discrete microcircuits, or long-projecting neurons with distant projections from their cell body. Nevertheless, within these categories, SRIF-expressing neurons show substantial diversity in terms of chemical and genetic markers, intrinsic firing properties, and connectivity (Liguz-Lecznar et al., 2016; Riedemann, 2019). SRIF-expressing interneurons constitute ∼30% of all GABAergic interneurons in the brain (Rudy et al., 2011). The main SRIF-expressing interneurons in the neocortex and hippocampus are Martinotti cells. Neocortical Martinotti cells have their soma located mostly in layers 2/3 and 5 (Urban-Ciecko and Barth, 2016). Their ascending axons extensively arborize in cortical layer 1, spreading horizontally to neighboring columns. The most extensively studied SRIF-expressing interneurons of the hippocampus are those in oreins-lacunosum moleculare (O-LM). These O-LM interneurons serve as a major relay between the entorhinal cortex and the CA1 region of the hippocampus (McBain et al., 1994).

There is a significant degree of neurochemical diversity in SRIF-expressing interneurons. SRIF-expressing interneurons may coexpress a number of other mediators, including neuropeptide Y (Köhler et al., 1987; Ma et al., 2006), calbindin (Muller et al., 2007; Suzuki and Bekkers, 2010), calretinin (Gulyás et al., 2003; Xu et al., 2006), cholecystokinin (Shi et al., 2020), and neuronal nitric oxide synthase (Dun et al., 1994; Perrenoud et al., 2012). A distinct subset of SRIF-expressing neurons express nitric oxide synthase, neuropeptide Y, and the neurokinin-1 receptor for substance P, with the capacity to project to multiple brain regions (Kubota et al., 2011; Endo et al., 2016). Additional types of SRIF-expressing interneurons include those with a bitufted appearance and a subset of basket cells, which are particularly abundant in the frontal and entorhinal cortex (Kvitsiani et al., 2013; Neske et al., 2015).

Long-projecting SRIF-expressing neurons are larger in diameter and have thicker myelin layers than interneurons, which facilitate rapid inhibitory neurotransmission between brain regions (Jinno et al., 2007; Viollet et al., 2008). Although interneurons are the primary focus of learning and memory research, long-projecting SRIF-expressing neurons also play a role. The GABAergic septo-hippocampal circuit highlights this contribution. Although GABAergic neurons from the medial septum to the hippocampus are predominately parvalbumin expressing, they are reciprocally innervated by SRIF-expressing GABAergic neurons projecting from the hippocampus to the medial septum. Memory and spatial navigation are regulated, in part, through this circuit (Müller and Remy, 2018).

IV. Somatostatin in Learning and Memory

SRIF and SRIF-expressing neurons play a pivotal role in learning and memory, with recent reviews addressing the extensive cellular interactions involved (Honoré et al., 2021; Topolnik and Tamboli, 2022). At the most fundamental level, learning and memory are a function of neuronal activity. Synchronized neuronal network interactions give rise to rhythmic patterns of activity, which produce brain wave oscillations that can be measured electrophysiologically. Theta (∼4–12 Hz) and gamma (∼25–100 Hz) network oscillations help link neurons to process new information (Colgin, 2016; Nuñez and Buño, 2021). The theta rhythm is observed in multiple brain regions and is particularly robust in the hippocampal CA1. Theta oscillations, nested within gamma oscillations, are linked to the formation and retrieval of episodic memory (Griffiths and Jensen, 2023). SRIF-expressing neurons regulate both theta and gamma oscillations (Colgin, 2016; Topolnik and Tamboli, 2022). SRIF-expressing neurons terminating in the medial entorhinal cortex synchronize theta activity (Mizuseki et al., 2009; Melzer et al., 2012), mediating spatial and temporal memory coding, which underlies memory formation (Hasselmo and Stern, 2014; Siegle and Wilson, 2014). SRIF-expressing interneurons of the O-LM have shown to control theta type-2 (4–9 Hz) oscillations (Leão et al., 2012; Mikulovic et al., 2018), which are identified learning and memory behaviors associated with fear and anxiety (Castegnetti et al., 2021).

Neuronal silencing/ablation studies substantiate the role of SRIF-expressing interneurons in learning and memory. A study using the contextual fear conditioning model, widely used to study hippocampal-dependent memory behavior (Fanselow, 2010), combined with high-resolution calcium imaging and optogenetic manipulation, demonstrated that silencing SRIF-expressing interneurons in the hippocampal CA1 prevented learning behavior in mice (Lovett-Barron et al., 2014). SRIF-expressing interneuron-induced dendritic inhibition was necessary for the contextual fear learning. In another study using contextual fear conditioning, silencing of hippocampal CA1 SRIF-expressing interneurons in conditional knockin mice during the consolidation phase attenuated the increase in the fear memory (Sharma et al., 2020), confirming that hippocampal CA1 SRIF-expressing interneurons are essential for memory consolidation. The conditional fear learning notably reduced eukaryotic initiation factor 2α (eIF2α) phosphorylation in the SRIF-expressing interneurons. Phosphorylation of the α-subunit of eIF2, the central component of the integrated stress response, is associated with AD neuronal degradation and impaired memory formation (Chang et al., 2002; Oliveira and Klann, 2022), whereas a reduction in eIF2α phosphorylation in hippocampal SRIF-expressing interneurons increased general mRNA translation, bolstered synaptic plasticity, and enhanced long-term memory (Sharma et al., 2020). Lastly, a recent study in which dentate hilar SRIF-expressing interneurons were partially ablated in SRIF–internal ribosome entry site–Cre mice showed memory decline in spatial and object recognition memory behavioral tests compared with control mice (Nagarajan et al., 2023). The ablation led to increased neuronal activity in both the dentate gyrus and hippocampal CA3, consistent with age-associated learning and memory impairment (Yassa et al., 2011; Oh et al., 2016).

Pharmacological evaluations corroborate the integral role of SRIF in learning and memory processing. In an initial series of rodent behavioral studies, intracerebroventricular administration of SRIF in rats improved learned acquisition in the active avoidance foot-shock task evaluations (Bollók et al., 1983; Vécsei et al., 1983a,b) and prevented electroshock-induced amnesia in passive avoidance paradigms compared with vehicle controls (Vécsei et al., 1983c, 1984a). The antiamnesic actions show SRIF to influence both consolidation and retrieval processes as the SRIF antiamnesic effect occurred with treatment performed immediately after the shock or 1 hour prior to the retention test. Nevertheless, SRIF dosing concentration variations exist, with lower SRIF concentrations generally improving passive avoidance memory, whereas the opposite effect occurred with 10-fold higher concentrations (Vécsei et al., 1984b, 1989; Vécsei and Widerlöv, 1988). Correspondingly, use of the SRIF-depleting and antisecreting agent cysteamine (Szabo and Reichlin, 1981) induced significant memory deficits in passive avoidance and spatial discrimination tasks across a number of behavioral models and delivery routes (Haroutunian et al., 1987; Schettini et al., 1988; DeNoble et al., 1989; Fitzgerald and Dokla, 1989; Vécsei et al., 1990; Matsuoka et al., 1994), whereas treatment with SRIF or the $SST_{2,3,5}$ agonist octreotide reversed the cysteamine-induced memory behavior impairments (Schettini et al., 1988; Matsuoka et al., 1994). Additionally, cysteamine administered within 4 hours

following learned acquisition of a behavioral task impaired the memory behavior of the task (Haroutunian et al., 1987; Schettini et al., 1988; Vécsei et al., 1990), again supporting the role of SRIF in memory consolidation. Cysteamine administration also dose-dependently impaired mouse memory behavior in the contextual fear conditioning model (Kluge et al., 2008). The memory impairment was associated with decreased LTP in hippocampal CA1 neurons, further supporting that SRIF memory-mediated effects are hippocampal dependent.

SRIF and SRIF-expressing neuron regulation of learning and memory show an interdependency with cholinergic mechanisms. Interactions between SRIF-expressing neurons and cholinergic pathways are integral in hippocampal and neocortical information processing (Müller and Remy, 2018; Obermayer et al., 2018; Urban-Ciecko et al., 2018). Septal cholinergic input is notably involved in the hippocampal SRIF-expressing interneuron regulation of rodent learning and memory behavior, with a corresponding impact on theta oscillation generation and frequency (Leão et al., 2012; Lovett-Barron et al., 2014; Mikulovic et al., 2018; Espinosa et al., 2022). A recent study using optogenetic stimulation in anesthetized mice showed that lateral septum SRIF-expressing neurons can disinhibit the cholinergic septo-hippocampal pathway, enhancing the amplitude and synchrony of theta oscillations (Espinosa et al., 2022). Moreover, in studies assessing central cholinergic blockade in rats, through either lesioning of the nucleus basalis of Meynert (NBM) or by use of the nonspecific muscarinic antagonist scopolamine, intracerebroventricular administration of SRIF reversed memory behavior impairments in passive avoidance testing (Matsuoka et al., 1994). It is noteworthy that cognitive decline associated with cholinergic neuron loss in the NMB is a consistent finding in humans with AD and MCI (Mesulam, 1976; Whitehouse et al., 1981; Mesulam et al., 2004; Grothe et al., 2010). In evaluations of the SRIF secretagogues FK960 and FK962 in rats, both compounds produced synergistic memory behavior benefits when coadministered with the cholinesterase inhibitor (ChEI) donepezil (Tokita et al., 2002; McCarthy et al., 2011). FK962 further lessened memory deficits in passive avoidance tasks in rats treated with scopolamine or NBM lesioning (Tokita et al., 2005), whereas FK960 reduced deficits in visual discrimination memory behavior in nonhuman primates induced by scopolamine (Matsuoka and Aigner, 1997).

SST subtypes differentially regulate learning and memory. Gastambide et al., (2009, 2010) performed initial learning and memory behavior evaluations using the water-maze task and intrahippocampal injections of subtype-selective SST agonists. Subtype-selective $SST_{1–3}$ agonists showed no effect on acquisition or retention of hippocampal-dependent spatial or striatum-dependent cue-based behavior when compared with vehicle controls, whereas injections of SRIF or the SST_4 agonist L-803,087 impaired acquisition and retention of hippocampal-dependent spatial behavior compared with vehicle controls. Conversely, L-803,087 also showed to dose-dependently enhance cue-based memory compared with vehicle. The researchers concluded that intrahippocampal injections of an SST_4 agonist was associated with switching from the use of a hippocampal-based spatial response to a dorsal striatum cue-based behavioral response (Gastambide et al., 2009, 2010). Subsequent evaluations using wild-type and *Sst*$_2$-knockout mice support a hippocampal-to-dorsal striatum response switch through an interaction between SST_4 and SST_2 (Gastambide et al., 2010). Other reports identify a functional interaction between SST_4 and SST_2 within the hippocampal formation (Moneta et al., 2002; Cammalleri et al., 2006; Prévôt et al., 2017). SST_4 agonist-induced enhancements of learning and memory behaviors likewise occur in mouse models of accelerated aging and AD. Administration of SST_4 agonists NNC 26-9100 (intracerebroventricularly) (Sandoval et al., 2012, 2013) or KS-I-50 (intraperitoneally and orally) (Neumann et al., 2021) enhanced spatial learning and memory using the foot-shock/T-maze task in age-accelerated and AD mouse models when compared with vehicle controls. NNC 26-9100 also enhanced hippocampal-dependent memory behavior in the novel-object recognition test compared with vehicle controls (Sandoval et al., 2012). Although the parceling of SST subtype function as determined by behavioral responses is subject to numerous qualifiers, both SST_2 and SST_4 show to have predominant roles in learning and memory processing, which is consistent with their heightened hippocampal expression (Fehlmann et al., 2000; Sjöstedt et al., 2020).

V. Somatostatin Links to Alzheimer Disease

A. Somatostatin Decline

Declines in brain SRIF and SRIF-expressing neurons in AD coincide with progressive pathology and symptomology (Fig. 2). Although declines in brain SRIF occur as a part of natural aging (Mattson and Arumugam, 2018), the loss is accelerated in AD. Initial studies using AD post-mortem brain tissue identified that SRIF-like immunoreactivity was reduced in the cerebral cortex compared with age-matched controls (Davies et al., 1980; Rossor et al., 1980). Subsequent reports confirmed the AD-associated reductions in SRIF levels and SRIF immunoreactivity in cortical tissues (Beal et al., 1986; Dournaud et al., 1995; Bissette et al., 1998; Grouselle et al., 1998; Kumar, 2005; Saiz-Sanchez et al., 2010; Waller et al., 2020), along with decreased SRIF levels in cerebrospinal fluid (CSF) (Soininen et al., 1984; Atack et al., 1988; Davis et al., 1988; Molchan et al., 1993; Nilsson et al., 2001) compared with age-matched controls. One report found a >70% reduction in AD frontal cortex SRIF-immunoreactive neurons

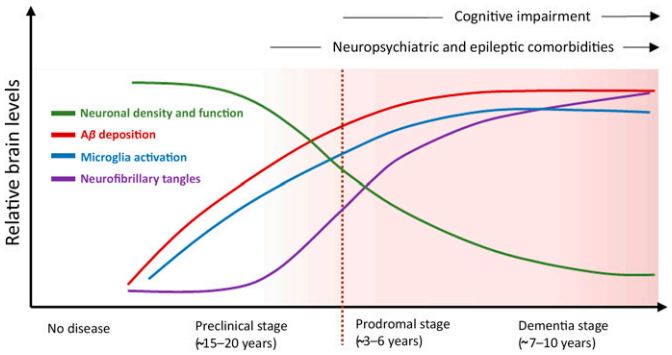

Fig. 2. AD pathological progression. AD occurs across a continuum associated with progressive brain pathology and symptomology [adapted with permission from Long and Holtzman, (2019)].

(Kumar, 2005), with another report showing an ~30% reduction in AD temporal cortex SRIF-immunoreactive interneurons (Waller et al., 2020) compared with respective controls. Decreased SRIF gene expression in the AD frontal and temporal cortices parallel the loss of SRIF-expressing neurons and decline in brain SRIF (Gahete et al., 2010; Guennewig et al., 2021). A recent study generating a single-cell transcriptomic atlas covering 2.3 million cells in post-mortem tissue of the aged human prefrontal cortex from 427 individuals diagnosed with either no cognitive impairment, MCI, or AD identified selectively vulnerable SRIF neuronal subtypes in those with AD (Mathys et al., 2023). The relative abundance of the SRIF inhibitory neuron subtypes showed to be significantly higher in those with cognitive resilience to global AD pathology, neurotic plaque burden, and NFT burden. In those with a confirmed diagnosis of AD, the relative abundance of the vulnerable SRIF neurons was significantly higher in those without cognitive impairment compared to those with observed dementia. SRIF levels in the AD anterior olfactory nucleus also declined by ~50% compared with controls (Saiz-Sanchez et al., 2010). SRIF plays a critical role in olfactory information processing, with mouse models showing that SRIF mediates olfactory detection and discrimination behaviors (Lepousez et al., 2010; Nocera et al., 2019). Notably, olfactory dysfunction is prevalent in individuals with MCI and strongly correlated with AD development (Devanand et al., 2000; Saiz-Sanchez et al., 2010), indicating early SRIF loss in this region as a risk factor for AD.

The relationship between Aβ and SRIF loss is validated in animal models of AD. Evaluations in rats chronically infused (intracerebroventricularly) with Aβ_{40} or A$\beta_{25\text{-}35}$ exhibited significantly reduced SRIF-like immunoreactivity in hippocampal CA1, temporal cortex, and frontoparietal cortex compared with controls (Nag et al., 1999; Nag and Tang, 2001; Aguado-Llera et al., 2005, 2018; Hervás-Aguilar et al., 2005; Burgos-Ramos et al., 2007). In senescence-accelerated mouse prone-8 (SAMP8) mice, a nontransgenic strain that shares many characteristics of human AD pathology (Morley et al., 2012), SRIF-expressing hippocampal CA1 interneurons showed decline at 12 months of age (M. J. Lagartos-Donate et al., preprint, DOI: https://doi.org/10.1101/598599). Correspondingly, at 12 months of age, SAMP8 mice display impairments in learning and memory behavior along with increased Aβ accumulation and oxidative stress in cortical tissues (Morley et al., 2012; Griñán-Ferré et al., 2018). In transgenic mice expressing mutant human APPswe and presenilin-1 dE9 (PS1dE9), an age-dependent increase in Aβ_{40} and Aβ_{42} coincided with deficits in memory behavior, aligning with decreased cortical SRIF levels and cholinergic markers (Savonenko et al., 2005). In mice over-expressing both the Swedish and London mutations of APP (APP751) and PS1 (PS1M146L), Aβ deposition starts as early as 2.5 months (Blanchard et al., 2003), with dystrophic neurites, a loss in SRIF mRNA expression, and a 50%–60% reduction in the numerical density of the SRIF-immunopositive cells in the CA1–CA3 stratum oriens and dentate gyrus at 6 months as compared with wild-type controls (Ramos et al., 2006). The SRIF loss at 6 months was relatively selective, with no significant changes in other neuronal markers respective to GABAergic, glutamatergic, and cholinergic systems. Additionally, there was a linear relationship between declining SRIF mRNA expression and increasing Aβ concentration. A subsequent evaluation by the same group reaffirmed the early SRIF loss with increased Aβ deposits along with heightened inflammatory activity (Moreno-Gonzalez et al., 2009). In an elegant study in which APP/PS1dE9 mice were crossbred with mice expressing enhanced green fluorescent protein under the control of the *Gad1*promoter in conjunction with in vivo two-photon imaging, Schmid et al., (2016) showed an age and Aβ plaque–dependent impairment of structural plasticity of dendritic spines of SRIF-expressing hippocampal O-LM interneurons compared with wild-type controls. A decreased axon survival and dendritic spine density, along with an increased turnover of spines of hippocampal inhibitory neurons, indicated a destabilized synaptic connectivity. These effects corresponded with an impairment of cholinergic input from the medial septum onto O-LM interneurons, consistent with SRIF-cholinergic interdependency.

Aβ-dependent impairments in learning and memory align with disruptions in hippocampal theta and gamma oscillations (Palop and Mucke, 2016; Mably and Colgin, 2018; Andrade-Talavera and Rodríguez-Moreno, 2021). Reports identify that the power of theta oscillations are reduced in several transgenic AD models associated with Aβ accumulation, including 3xTg (Akay et al., 2009; Mondragón-Rodríguez et al., 2018), CRND8 (Goutagny et al., 2013), APP/PS1 (Wang et al., 2002; Scott et al., 2012), and APP23 (Ittner et al., 2014) mice. Direct Aβ injection models also show theta oscillation dysfunction

(Villette et al., 2010; Chung et al., 2020; Park et al., 2020). Reductions in gamma oscillations likewise occur in 3xTg (Mably et al., 2017) and 5xFAD mice (Iaccarino et al., 2016). Significantly, these investigations identify that oscillation dysfunctions occur prior to actual neuronal loss, with ramifications as a potential early AD pathology indicator. Moreover, studies using SRIF-Cre mice showed that the optogenetic activation of SRIF-expressing interneurons could selectively restore the power and synchronicity of the theta and gamma oscillation after injection of soluble AβOs (Chung et al., 2020; Park et al., 2020). Ex vivo voltage-clamp recordings from hippocampal slice CA1 pyramidal cells of the AβO-injected mice indicated that the optogenetic activation of SRIF interneurons enhanced inhibitory postsynaptic currents at these frequencies. This not only identifies a capacity to reverse AβO-related dysregulation through a SRIF interneuron activation but substantiates the impact of AβOs as to early hippocampal dysregulation independent of Aβ plaque formation.

Apolipoprotein E (apoE) evaluations support the relationship between SRIF and AD. ApoE regulates plasma lipid levels by increasing the degradation of particles rich in triglycerides and cholesterol and exists in three major isoforms: ε2, ε3, and ε4. Expression of *APOE*-ε4 is the greatest risk factor for LOAD (Jansen et al., 2019). Relative to *APOE*-ε3 homozygous carriers, individuals expressing one *APOE*-ε4 allele are 2.6–4.2 times more likely to develop AD, which increases to a 12.9–14.5-fold risk for *APOE*-ε4 homozygous carriers (Chai et al., 2021). Possession of the *APOE*-ε4 also lowers the mean age of disease onset and is associated with worse clinical outcomes (Mortensen and Høgh, 2001; Chai et al., 2021). Precisely how *APOE*-ε4 increases AD risk has not been fully determined, yet human and animal evidence shows that the presence of the ε4 genotype positively correlates with enhanced accumulation of interneuronal Aβ and AβOs (Christensen et al., 2010; Zepa et al., 2011). Several studies performed with *APOE*-ε4–knockin mice show enhanced age-dependent loss of SRIF-expressing interneurons, impairments in hippocampal neurogenesis, and deficits in learning and memory compared with controls (Li et al., 2009a; Andrews-Zwilling et al., 2010; Leung et al., 2012; Knoferle et al., 2014). These data correspond with post-mortem evaluations of AD tissue, with *APOE*-ε4 carriers showing substantially lower frontal cortex SRIF levels as compared with *APOE*-ε2/3 carriers (Grouselle et al., 1998). Sex differences further delineate the *APOE*-ε4 and SRIF link. Female *APOE*-ε4–knockin mice exhibit a significantly lower number of SRIF-expressing hilar GABAergic interneurons at 6 months of age when compared with *APOE*-ε3–knockins of the same age (Leung et al., 2012), whereas in male mice the number of SRIF-expressing hilar GABAergic interneurons is similar between *APOE*-ε4–knockin and *APOE*-ε3–knockin at all ages (1–16 months). These findings align with human studies showing that female *APOE*-ε4 carriers are more likely to convert to MCI and AD when compared with male *APOE*-ε4 carriers (Altmann et al., 2014), albeit whether the sex-specific findings in human *APOE*-ε4 carriers can be explained by dysregulations in SRIF still remains to be determined. It is also noteworthy that variations in the SRIF gene are implicated in *APOE*-ε4–related AD risk. In studies of Finnish (Vepsäläinen et al., 2007a) and Chinese (Xue et al., 2009) patients, *APOE*-ε4–positive individuals with the C allele carriers of the SRIF gene single-nucleotide polymorphism rs4988514 had increased AD risk. Conversely, in the Finish cohort study, a major haplotype TTG of SRIF was significantly under-represented among all of the AD patients, including *APOE*-ε4 carriers. Thus, genetic variations in the SRIF gene may serve as modifiers to AD risk.

The impact of AD on SSTs has been the focus of several investigations. Initial radioligand binding studies using radiolabeled SRIF-14 identify a general decrease of SSTs in post-mortem AD brains. Total SST density was reduced by ~50% in both frontal cortex (Brodmann areas 6, 9, and 10) and temporal cortex (Brodmann area 21) compared with age-matched controls (Beal et al., 1985). Total SST density in the hippocampus was likewise reduced by 40%. Scatchard analyses supported that the reductions were due to receptor number rather than altered affinities. The postcentral gyrus, cingulate cortex, temporal pole, or superior temporal gyrus showed no significant changes. In another binding study using SRIF-14, a reduction in SSTs only occurred in the frontal cortex of AD tissue compared with controls (Bergström et al., 1991). In a third radioligand study, a reduced binding in the temporal cortex was identified using both SRIF-14 and the $SST_{2,3,5}$ agonist SMS 204-090, with only SST_2, SST_3, and SST_5 (based on the use of SMS 204-090) being substantially reduced in the frontal cortex compared with controls (Krantic et al., 1992). In immunohistochemical evaluations using SST subtype–specific antibodies, SST_4 and SST_5 expression significantly decreased in the frontal cortex of those with AD compared with controls, with no significant changes observed for either SST_1, SST_2 (moderate decrease), or SST_3 (moderate increase) (Kumar, 2005). Lastly, SST_1, SST_3, and SST_4 each showed decreased mRNA expression in the temporal lobe of those with AD compared with controls (Gahete et al., 2010), whereas SST_2 mRNA expression decreased only in the inferior temporal lobe of those with AD compared with controls (Gahete et al., 2010). Several factors may explain the inconsistencies across these investigations. The most apparent is that the quality of post-mortem brain tissue can vary greatly across samples. Total tissue volumes and regional atrophy can only be compared with age-matched controls

and not the "original" healthy brain affiliated with the AD tissue sample. When considering ligand binding evaluations, the use of either radiolabeled SRIF-14 or $SST_{2,3,5}$ agonist limits the capacity to delineate the specific SST subtype. The immunological semiquantitative measures are relative to antibody adherence determined across a subset of tissue slices, with additional concern as to potential crossreactivities of antibodies. Moreover, mRNA expression is not actual membrane-associated protein nor an indicator of functional binding. Perhaps the most critical takeaway is that the radioligand studies identified a preservation of receptor-ligand binding in AD tissue, suggesting a maintenance of SST viability for pharmacologic targeting after AD develops.

In summary, substantial evidence identifies that the loss of SRIF and SRIF-expressing neurons is a pivotal pathological event in AD progression. Animal models validate Aβ accumulation in the brain, particularly hippocampal tissue, as a primary driver of SRIF-expressing neuron loss. This loss aligns with impairment of cholinergic transmission, theta and gamma oscillations, and learning and memory behavior. Studies in *APOE*-ε4 carriers with elevated rates of AD incidence and associated animal models further support the SRIF-AD link. SSTs generally decrease in AD post-mortem brain tissue compared with aged-matched non-AD controls, with variability in specific SST subtype expression measures depending on brain region and method of evaluation.

*B. Somatostatin and Amyloid-*β *Peptide Catabolism*

Aβ levels in the brain are maintained by a balance of anabolic and catabolic processes in coordination with the blood-brain barrier (BBB) transport mechanisms. Although Aβ overproduction is strongly associated with ADAD, the more gradual decline in Aβ clearance mechanisms is believed to be the driving force in LOAD (Mawuenyega et al., 2010). As LOAD is the most prevalent form of AD (https://pubmed.ncbi.nlm.nih.gov/38689398/), enhancing Aβ-mediated catabolism presents a strategy of significant therapeutic potential (Nalivaeva and Turner, 2019). Neprilysin (NEP) and insulin-degrading enzyme (IDE) are the major Aβ-degrading enzymes in the brain (Nalivaeva and Turner, 2019). Moreover, both NEP and IDE have a unique relationship with SRIF. SRIF is not only a substrate for NEP and IDE but further regulates the activity of both enzymes and the corresponding catabolism of Aβ (Fig. 3).

NEP is a membrane-bound zinc metallopeptidase, with its active site facing the extracellular space. Acting primarily as an endopeptidase, NEP is found peripherally and centrally (Nalivaeva and Turner, 2019). Within the brain, NEP is expressed abundantly in areas associated with memory formation, particularly in the hippocampal formation and layers II/III and V of the neocortex (Fukami et al., 2002). NEP preferentially cleaves small peptides on the N-terminal side of hydrophobic residues, including Aβ. NEP degrades monomeric Aβ (Iwata et al., 2000, 2001; Takaki et al., 2000; Hama et al., 2001; Shirotani et al., 2001; Leissring et al., 2003; Saito et al., 2005) and low-molecular-weight AβOs (Kanemitsu et al., 2003). Loss of NEP is associated with elevated brain Aβ levels and AD pathology. In *Nep*-knockout mice, $A\beta_{40}$ and $A\beta_{42}$ levels are twice as high as wild-type controls (Iwata et al., 2001). In human post-mortem studies of AD brain tissue, NEP activity, mRNA expression, and protein expression decreased compared with age-matched cognitively normal controls (Yasojima et al., 2001a,b; Russo et al., 2005; Miners et al., 2006; Carpenter et al., 2010; Wang et al., 2010; Zhou et al., 2013). A meta-analysis of these AD studies discerned that decreased NEP expression and activity progressed with increasing age, with the effect most pronounced in older individuals (Zhang et al., 2017). Nevertheless, individuals identified with prodromal AD also show reduced NEP levels in CSF relative to controls (Maruyama et al., 2005). Moreover, lower NEP expression levels are observed in *APOE*-ε4 carriers compared with noncarriers (Miners et al., 2006). This implies that reduced NEP activity is not secondary to tissue atrophy. NEP polymorphisms are also identified with increased susceptibility to LOAD (Sakai et al., 2004; Wood et al., 2007). Ultimately, the role of NEP in Aβ clearance and its associated decrease in the AD brain support a NEP-AD link.

SRIF plays a leading role in the NEP regulation of Aβ. Seminal work by Saito et al., (2005) first identified that SRIF increased brain NEP activity. When wild-type mouse-cultured primary neurons were treated with SRIF, NEP activity increased and $A\beta_{42}$ expression decreased compared with controls. Conversely, when the primary neurons were prepared from *Nep*-knockout mice, SRIF treatment did not reduce $A\beta_{42}$ expression relative to controls. *Srif*-knockout mice also exhibited a decrease in hippocampal NEP activity and increase in $A\beta_{42}$ expression compared with wild-type controls, supporting SRIF as a regulator of NEP activity. When primary neurons were treated with either the SST antagonist BIM23056 or Gi-GPCR inhibitor pertussis toxin, NEP activation by SRIF was inhibited, indicating that activation of SSTs by SRIF enhanced downstream Gi-coupled GPCR signal transduction to increase NEP activity. The SRIF treatments had no significant impact on NEP mRNA or protein expression, suggesting that SRIF may regulate NEP through post-translational processes. This work led to the hypothesis that loss of brain SRIF initiates a decline in NEP activity with a corresponding elevation in steady-state Aβ levels (Iwata et al., 2005), driving a pathological feedback loop (Fig. 1). A study using SRIF fused with a linker to enhance BBB uptake (Rofo et al., 2021) substantiated the work by Saito and colleagues. The linker-fused SRIF administered intravenously over multiple doses was shown to

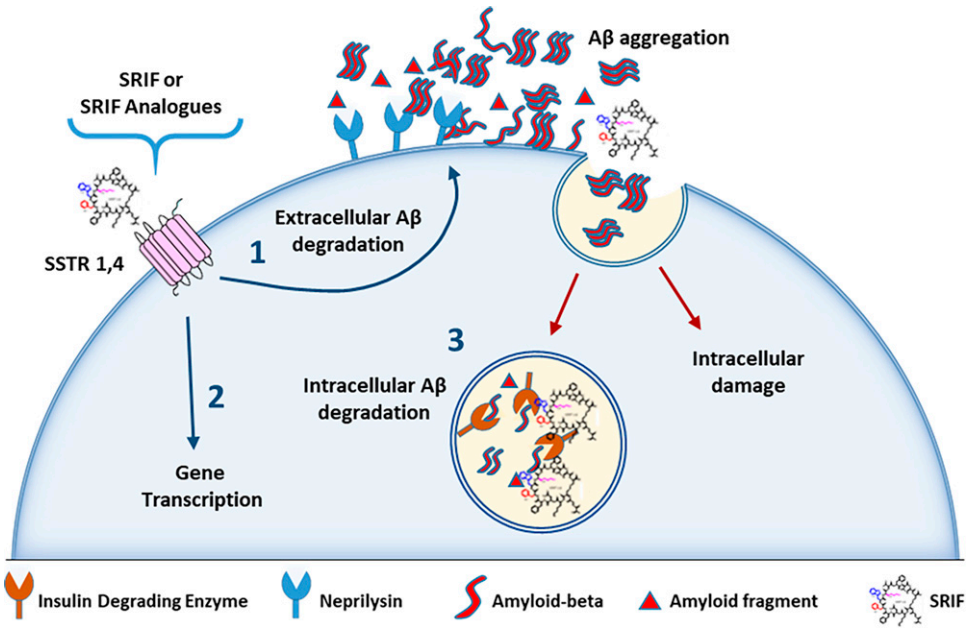

Fig. 3. Schematic of SST-mediated Aβ catabolic mechanisms. The internalization of extracellular Aβ induces cell damage and proapoptotic mechanisms. (1) $SST_{1,4}$ agonist activation induces NEP activity and corresponding extracellular Aβ degradation. (2) SST_4 activation induces transcription of genes associated with generation of proteins involved in Aβ degradation. (3) Insulin-degrading enzyme acts intracellularly, capable of directly interacting with SRIF and Aβ to promote degradation in critical organelles (i.e., peroxisomes, mitochondria, endoplasmic reticulum).

increase hippocampal NEP activity and decrease membrane-bound $A\beta_{42}$ expression levels. Thereby, loss of SRIF is implicated as a triggering event for Aβ accumulation leading to LOAD, whereas pharmacologically targeting brain SSTs presents a means to enhance NEP activity toward a disease-modifying AD treatment.

The recognition of SRIF's effect on NEP activity led to the evaluation of SST subtype agonists and their influence on Aβ degradation. Given the significant alignment of brain SST_4 distribution with areas of heavy NEP expression, a series of studies focused on SST_4 mediation of NEP activity. In SAMP8 mice, single-dose intracerebroventricular administration of the SST_4-selective agonist NNC 26-9100 increased cortical NEP activity, with enhanced learning and memory behavior compared with vehicle controls (Sandoval et al., 2012). NNC 26-9100 treatment correspondingly decreased protein expression of the $A\beta O_{42}$ "trimer" in both extracellular and intracellular fractions of cortical tissue lysates compared with controls. The $A\beta O_{42}$ trimer is notably implicated as an inhibitor of LTP (Townsend et al., 2006; Selkoe, 2008) and is capable of inducing conformational changes in tau protein, leading to disrupted axonal transport (Sherman et al., 2016). Additionally, when NEP-deficient mice were crossbred with APP23 transgenic mice, $A\beta O_{42}$ trimer expression increased along with memory behavior impairments (Huang et al., 2006). NNC 26-9100 coadministered with the NEP inhibitor phosphoramidon (intracerebroventricularly) in SAMP8 mice inhibited the reduction in $A\beta O_{42}$ protein expression, supporting a NEP-dependent mechanism (Sandoval et al., 2013). NNC 26-9100 likewise reduced $A\beta O_{42}$ trimer protein expression in Tg2576 mice (Sandoval et al., 2013). In a third NNC 26-9100 evaluation, single-dose intracerebroventricular administration in 3xTg mice increased cortical NEP mRNA expression by approximately ninefold at 24 hours postinjection compared with vehicle controls (Sandoval et al., 2019). This corresponded with an approximately fivefold increase in SST_4 mRNA expression without changes in any other SST subtype. This finding is consistent with an in vitro study in CHO-K1 cells treated with SRIF, which showed an upregulation of human SST_4 at 24 hours (Hukovic et al., 1996). Nilsson et al., (2020) confirmed that NNC 26-9100 increased NEP activity in primary neurons while showing that the SST_1 agonist CH275 was also capable of increasing NEP activity. Interestingly, primary neurons taken from *Sst*$_1$ or *Sst*$_4$ knockouts showed no difference in NEP activity compared with controls, whereas dual *Sst*$_1$/*Sst*$_4$ knockouts significantly decreased hippocampal NEP activity with increased $A\beta_{40}$ and $A\beta_{42}$ expression. This suggests that SST_1 and SST_4 may be redundant in maintaining NEP activity. Relatedly, SST_1 and SST_4 have shown to interact with the postsynaptic density proteins postsynaptic density protein (PSD)-93 and PSD-95, which target GPCRs to the membrane of dendritic postsynaptic terminals (Christenn et al., 2007). In APPswe/PS1dE9 mice, enhanced expression of PSD-93 upregulated SST_4 on the cellular membrane, increased hippocampal NEP expression, and reduced $A\beta_{40}$ and $A\beta_{42}$ levels (Yu et al., 2017). This implies that enhanced expression of functional SST_4 to the cellular membrane is itself sufficient to increase NEP activity and lower Aβ levels.

Originally named for its ability to metabolize insulin, IDE is a metallopeptidase found throughout the body with broad substrate specificity. IDE predominately exists within the cell cytosol, but is also present in endosomes (Hamel et al., 1991), peroxisomes (Morita et al., 2000), mitochondria (Leissring et al., 2004), and ER (Carpenter et al., 2010). The intracellular

distribution of IDE is consistent with its role as a scavenging enzyme, metabolizing aggregation-prone peptides to maintain cellular homeostasis (Arbo et al., 2020). IDE has high affinity for β-structure–forming substates (Tundo et al., 2017; Kurochkin et al., 2018). In a study using a quenched Aβ_{40} peptide, which fluoresces upon cleavage inside the KLVFF region critical for aggregation, IDE catabolism capacity was evaluated in post-mortem hippocampal tissue from individuals at different stages of AD progression (Stargardt et al., 2013). IDE was shown to be the primary peptidase that degrades cytoplasmic monomeric Aβ_{40} in early-stage AD hippocampal tissue, whereas a decline in IDE corresponds with increased intraneuronal Aβ accumulation, leading to synaptic and neuronal dysfunction that precedes both extracellular plaque deposits and NFTs (Takahashi et al., 2017; Welikovitch et al., 2018). *Ide*-knockout mice likewise show a substantial increase in cerebral Aβ levels (Farris et al., 2003), whereas in transgenic mice overexpressing human IDE the levels of Aβ and plaques in the brain are significantly reduced compared with wild-type controls (Leissring et al., 2003). IDE may also reduce amyloidogenic fibrillization of Aβ_{42} in a nonproteolytic manner as a "dead-end" chaperone, preventing the formation of aggregates by the irreversible trapping of monomers (de Tullio et al., 2008, 2013). Interestingly, the association between type 2 diabetes mellitus and LOAD has been linked to IDE deficits (Farris et al., 2003; Wei et al., 2021), which align with dysregulation of brain glucose metabolism (Connolly et al., 2019; González et al., 2022). Multiple reports identify genetic variations in IDE as a risk factor for LOAD (Ertekin-Taner et al., 2004; Björk et al., 2007; Vepsäläinen et al., 2007b; Wang et al., 2012). Additionally, *APOE*-ε4 carriers exhibited reduced hippocampal IDE mRNA levels compared with noncarriers (Cook et al., 2003), providing another mechanism for how *APOE*-ε4 may increase the risk of LOAD.

SRIF is both a substrate and modulator of IDE. Although IDE can terminate the actions of SRIF, SRIF can also modulate the activity and function of IDE. Allosteric binding of SRIF to the active site of one IDE subunit was shown to increase IDE proteolytic activity, enhancing enzymatic cleavage of fluorogenic Aβ (Ciaccio et al., 2009). Docking evaluations show binding of SRIF to two additional sites on IDE, which can change the substrate specificity of IDE toward different substrates, including Aβ (Tundo et al., 2016). This identifies a complex interaction in which the effect of SRIF binding and modulation is dependent on the substrate as well as on the mode of substrate interaction with different allosteric sites. Although the cellular localization of IDE indicates that such an interaction would be isolated to the intracellular domain, extracellular Aβ binds to the neuronal plasma membrane (Johnson et al., 2011, 2013) and is internalized (Jin et al., 2016). Thus, extracellular Aβ content could be susceptible to such an SRIF-IDE-Aβ interaction. Lastly, IDE may also be regulated through SST activation by SRIF or SST agonists. In 3xTg mice administered the SST_4 agonist NNC 26-9100, IDE mRNA expression increased by ~15-fold compared with vehicle control (Sandoval et al., 2019). This finding aligns with previous data showing decreased intracellular AβO_{40} and AβO_{42} expression in cortical tissue of SAMP8 and 3xTg mice after an identical NNC 26-9100 treatment (Sandoval et al., 2012, 2013). Although the proposition of SST_4 mediation of IDE expression adds to the complexity of the SRIF-IDE-Aβ interaction, it does so in a manner that further supports SRIF capacity to mitigate Aβ levels.

In summary, SRIF acting through SSTs in the brain promotes NEP activity and possibly IDE activity, with the capacity to enhance extracellular and intracellular Aβ catabolism. SST_4 agonist activation in particular was shown to enhance NEP activation while also increasing mRNA expression of NEP and IDE.

C. Somatostatin and Amyloid-β Peptide Aggregation

A growing area in AD research focuses on Aβ cross-seeding. Cross-seeding is a process by which the amyloid structures of one type of protein act to "seed" and facilitate the aggregation of another amyloid protein, resulting in heterologous amyloids (Subedi et al., 2022). Such seeding may provide a mechanistic explanation for the presence of different misfolded proteins present in Aβ plaques (Jucker and Walker, 2018). Recent research suggests that heterotypic Aβ interactions facilitate amyloid assembly and modify amyloid structure between proteins via aggregation-prone regions (Konstantoulea et al., 2022). The aggregation-prone regions of various proteins interacted with AβOs and altered the Aβ aggregation kinetics and fibril morphology. This aligns with the theory that protein misfolding diseases are caused by seed polymerization and abnormal protein assemblies (Glenner, 1980; Prusiner, 1984). A feature of SRIF is its own capacity to self-aggregate and form amyloid-like structures (van Grondelle et al., 2007; Maji et al., 2009). Physiologically, this aggregative ability allows for high-density storage of inert peptides in secretory granules. Yet, it implicates the potential of SRIF to coaggregate with other proteins.

Recent in vitro research advances an intriguing hypothesis as to the potential of SRIF-AβO_{42} aggregation. A report showed SRIF binding to AβO_{42}, forming "mixed assemblies" capable of interfering with Aβ fibrillization (Wang et al., 2017). The SRIF interaction did not occur between Aβ_{42} monomers or AβO_{40} forms. Another group similarly identified the capacity for SRIF to bind AβO_{42} tetramers in vitro (Puig et al., 2020). It was postulated that such SRIF-AβO_{42} assemblies could enhance AD pathogenesis by promoting and/or maintaining a soluble neurotoxic state, with SRIF influencing

Aβ aggregation kinetics (Solarski et al., 2018). This would align with an increase in toxic AβOs and early neuron loss in brain regions of high SRIF concentration. Nevertheless, this SRIF-AβO_{42} aggregate assembly hypothesis is derived from in vitro data and comes with a number of qualifiers. The studies of these mixed assemblies used high concentrations of respective peptides to induce the observed effects [SRIF: 4 μM; Aβ_{42} and AβO_{42}: 2.5, 5 μM (Wang et al., 2017); SRIF: 150 μM; A$\beta O_{42\ (tetramer)}$: 35.5 and 57.5 μM (Puig et al., 2020)], increasing the likelihood of nonphysiologic outcomes. Moreover, proteolytic processes that are part of the normal in vivo environment were not accounted for in the evaluations. These considerations would foreseeably limit the in vivo manifestation of such assemblies, rendering them rare events in the brain. Yet, given the inherent aggregation of Aβ on cellular surfaces wherein a higher rate of interaction with SRIF may occur, such an interaction cannot be ruled out as a seed event. Relatedly, in a recent mouse study of chronic stress, a selective vulnerability of SRIF-expressing neurons of the prefrontal cortex occurred through an exacerbated unfolded protein response of the ER (Tomoda et al., 2022). There was a corresponding increase in SRIF protein aggregation, albeit the nature of the aggregated species was not determined. This would support a stressor-induced in vivo event capable of initiating a SRIF aggregation response. The extrapolation being the greater the intensity and timeframe of exposure to a given stressor or set of stressors the greater potential for such aggregative-prone species to accrue. Nevertheless, Aβ and AβO interactions are not unique to SRIF. The known list of proteins in which monomeric Aβ and AβO forms can bind is substantial and continues to grow (Wang et al., 2017; Konstantoulea et al., 2022). Thus, if SRIF-AβO_{42} assemblies are substantiated in vivo, it may well be one of many potential assemblies. In this context, a heterogeneity in amyloid assemblies could be indicative of differential pathological seeding events, aligning with a multifactorial AD etiology, or simply a result of an almost ubiquitous binding capacity of Aβ in its various forms.

In summary, based on in vitro observations, the formation of SRIF-AβO_{42} aggregate assemblies may serve as a seed event, promoting AD pathology. Further characterization of such mixed assemblies from brain tissue extracts across the stages of AD may provide a more complete picture. Focus on the early prodromal stage of AD in particular is necessary to substantiate any pathological seeding event unique to a specific protein or subset of proteins.

D. Somatostatin and Neuropsychiatric Symptoms

AD is associated with a number of neuropsychiatric symptoms, including depression, apathy, anxiety, fear, agitation, irritability, mood swings, changes in sleeping habits, and psychosis (Zhao et al., 2016; Wiels et al., 2021). These symptoms may also be early indicators to AD (Palmer et al., 2010; Spalletta et al., 2010, 2015; Dietlin et al., 2019; Agüera-Ortiz et al., 2021) (Fig. 2). Although the cause of these symptoms in AD is complex, both neurodegeneration and the body's stress response contribute. In turn, both neurodegeneration and stress response connect SRIF to the neuropsychiatric symptoms. Much of our understanding of these interconnections comes from research in mood disorders, inclusive of major depressive disorder (MDD), schizophrenia, and bipolar disorder.

Mood disorders present with many of the neuropsychiatric symptoms observed in AD. A prominent neurologic feature of mood disorders is the loss of SRIF and SRIF-expressing neurons (Lin and Sibille, 2013; Robinson and Thiele, 2020). The loss of SRIF-expressing interneurons in these disorders is relatively distinct compared with other types of GABAergic interneurons (Duman et al., 2019; Fee et al., 2021; Prévot and Sibille, 2021). MDD, schizophrenia, and bipolar disorder each display marked SRIF declines in brain regions heavily impacted in AD (Table 1). Females show greater declines in SRIF levels across brain regions compared with males (Sibille et al., 2011; Tripp et al., 2011, 2012; Guilloux et al., 2012), which is consistent with females having a higher risk of developing mood disorders in general and in AD specifically (Spalletta et al., 2010; Lee et al., 2017). Changes in theta and gamma activity are likewise exhibited with mood disorders, in alignment with AD (Palop and Mucke, 2016; Mably and Colgin, 2018; Andrade-Talavera and Rodríguez-Moreno, 2021). Theta power during memory retrieval is reduced in MDD compared with healthy controls (Kane et al., 2019). Schizophrenic patients exhibit reduced θ and γ oscillatory activity along with impaired theta phase coupling between the hippocampus and medial prefrontal cortex during memory retrieval compared with control groups (Haenschel et al., 2009; Adams et al., 2020). Animal models of mood disorders likewise show impairment in theta and gamma oscillations, particularly tied to the hippocampus and the hippocampus-prefrontal cortex-amygdala circuit (Okonogi and Sasaki, 2021; Speers and Bilkey, 2021). A cholinergic interplay also exists, with cholinergic dysregulation being well documented in various neuropsychiatric conditions (Dulawa and Janowsky, 2019). The dysregulation of cholinergic projections from the NBM within the basal forebrain to the cerebral cortex notably coincides with a number of neuropsychiatric symptoms (van Dalen et al., 2017), consistent with AD and MCI (Mesulam, 1976; Whitehouse et al., 1981; Mesulam et al., 2004; Grothe et al., 2010). NBM damage correspondingly impacts SRIF-cholinergic interactions. NBM lesioning in rats results in cholinergic denervation associated with the loss of SRIF-immunoreactive neurons (Zhang et al., 1998) and decreased SRIF binding capacity (Epelbaum et al., 1986; Moyse et al., 1993).

TABLE 1
SRIF decline in human mood disorders

Condition	Symptoms Shared with AD	Measure	Regions of SRIF Decline
Major depressive disorder	Depression; anxiety; social withdrawal; apathy; sleep disturbances; fear; agitation; cognitive impairments	SRIF peptide	Cerebrospinal fluid (Agren and Lundqvist, 1984; Kling et al., 1993; Molchan et al., 1993)
		SRIF mRNA	Anterior cingulate cortex (Tripp et al., 2011, 2012; Seney et al., 2015), dorsolateral prefrontal cortex (Sibille et al., 2011)
Schizophrenia	Apathy, social withdrawal, anxiety, agitation, sleep disturbances, cognitive impairments, hallucinations	SRIF peptide	Cerebrospinal fluid (Bissette et al., 1986; Reinikainen et al., 1990), frontal cortex (Nemeroff et al., 1983; Gabriel et al., 1996), occipital cortex (Gabriel et al., 1996), temporal cortex (Gabriel et al., 1996)
		SRIF mRNA	Dorsolateral prefrontal cortex (Palop et al., 2007; Morris et al., 2008; Hashimoto et al., 2008a,b; Fung et al., 2010, 2014; Guillozet-Bongaarts et al., 2014), anterior cingulate cortex (Hashimoto et al., 2008b), motor cortex (Hashimoto et al., 2008b), visual cortex (Hashimoto et al., 2008b), orbitofrontal cortex (Fung et al., 2014), hippocampus (Konradi et al., 2011a)
		SRIF-expressing cells	Entorhinal cortex (Wang et al., 2011), parasubiculum (Wang et al., 2011), amygdala (Pantazopoulos et al., 2017), hippocampus (Konradi et al., 2011a)
Bipolar disorder	Major depression (see above), mood swings	SRIF mRNA	Dorsolateral prefrontal cortex (Sibille et al., 2011; Fung et al., 2014), orbitofrontal cortex (Fung et al., 2014), hippocampus (Fung et al., 2014)
		SRIF-expressing cells	Amygdala (Pantazopoulos et al., 2017), hippocampus (Konradi et al., 2011b)

The body's stress response impacts brain health. Stress underpins anxiety, depression, and the risk of dementia (Justice, 2018; Franks et al., 2021). Stress activates the hypothalamic-pituitary-adrenal (HPA) axis, inducing the release of ACTH from the posterior pituitary and subsequent release of glucocorticoids from the adrenal glands. Increased brain glucocorticoid levels and receptor activity under heightened stress contribute to neuropsychiatric symptom severity (Spijker and van Rossum, 2012; van den Berg et al., 2020). Chronic glucocorticoid treatment in humans (Brown et al., 1999; Barrimi et al., 2013) and animal models of anxiety and depression (Ardayfio and Kim, 2006; David et al., 2009) corroborate the contributions of glucocorticoids to neuropsychiatric symptoms, whereas brain SRIF signaling counters the endocrine-mediated processes that induce glucocorticoid release under stress and blunts the broader stress effect (Stengel and Taché, 2017), opposing the stress-associated elevations in ACTH and epinephrine (Brown et al., 1984). Growing evidence reveals that the dysregulation of the HPA axis and increase in glucocorticoid levels contribute to cognitive decline in AD (Swaab et al., 2005; Milligan Armstrong et al., 2021). Glucocorticoid receptor activity plays an essential role in the regulation of the HPA axis and hippocampal-dependent spatial memory (McEwen et al., 2016), with high concentrations of glucocorticoid receptors present in the hippocampus (Morimoto et al., 1996; Wang et al., 2013). Moreover, increased glucocorticoid levels in animals subjected to chronic stress impair hippocampal GABAergic signaling, which is associated with the loss of SRIF-expressing interneurons in the hippocampus (Cullinan and Wolfe, 2000; Czéh et al., 2015). This aligns with other research showing that chronic stress reduces dendritic cell length within hippocampal CA3 and dentate gyrus and increases the loss of hippocampal CA1 neuronal spines compared with nonstressed animals (Magariños et al., 1997; McEwen, 1999). Chronic stress further results in the remodeling of synaptic connections in the hippocampus, amygdala, medial prefrontal, and orbitofrontal cortex (McEwen et al., 2016), aligning with the regional loss of SRIF and SRIF-expressing neurons observed in mood disorders (Table 1) and AD.

Investigations of anxiety and depression behavior in mice provide insight as to the impact of SRIF loss. In a study of how acute and chronic reduction of SRIF neuronal activity impact anxiety and depression behavior, SRIF-Cre mice were injected in the frontal cortex with either a Cre-dependent adeno-associated viral vector to inhibit SRIF neuronal activity or a control reporter (Soumier and Sibille, 2014). Anxiety [elevated plus maze (EPM)] behavior effects differed between acute and chronic inhibition states. Acute inhibition of SRIF neurons increased anxiety behavior compared with controls. Conversely, chronic SRIF neuron inhibition reduced anxiety behavior compared with controls. Selective ablation of the frontal cortex SRIF neurons likewise reduced anxiety behavior under baseline and chronic stress conditions (Soumier and Sibille, 2014). A subsequent evaluation was conducted in *Srif*-knockout mice to further delineate the chronic effects (Lin and Sibille, 2015). Under chronic stress, *Srif*-knockout mice displayed increased anxiety (EPM) and depression (novelty-suppressed feeding) behavior

compared with wild-type mice. Methodological variables between Cre-dependent SRIF inhibition (Soumier and Sibille, 2014) and *Srif*-knockout mice (Lin and Sibille, 2015) may account for the difference in effect, with the Cre mice evaluations targeted to the frontal cortex and *Srif*-knockout mice having a whole-body and brain impact. Another variable is the impact of glucocorticoids. Under baseline conditions, plasma corticosterone levels were elevated in *Srif*-knockout mice compared with wild-type controls (Lin and Sibille, 2015), consistent with a loss of SRIF feedback inhibition on the HPA axis. Although *Srif*-heterozygous mice also exhibited elevated plasma corticosterone levels at baseline compared with controls, they did not exhibit enhanced anxiety or depressive behavior. Consequently, elevated corticosterone levels in the *Srif*-knockout mice could not be entirely responsible for the increase in anxiety or depression behavior. The *Srif*-knockout mice further showed a reduced gene expression of BDNF along with other genes related to GABAergic neuronal function compared with controls. This corresponds with a recent study in which ablation of dentate hilar SRIF-expressing interneurons in mice decreased BDNF and impaired learning and memory behavior compared with controls (Nagarajan et al., 2023). BDNF plays an important role in the maintenance and survival of SRIF-expressing interneurons (Grosse et al., 2005), increases SRIF gene expression in cortical tissue (Nawa et al., 1994; Villuendas et al., 2001; Sánchez-Muñoz et al., 2011), and enhances hippocampal neurogenesis (Scharfman et al., 2005). A downregulation of BDNF in the hippocampus and prefrontal cortex likewise occurs during chronic stress in rats (Roceri et al., 2004; Murakami et al., 2005). Moreover, several lines of evidence link BDNF deficits to depression (Castrén and Monteggia, 2021). It is notable that the associated stress-induced anxiety and depressive behavior response in mice is mitigated by eIF2 activation via inhibition of the eIF2 kinase (Lin and Sibille, 2015). Stress signals lead to the phosphorylation of eIF2 through kinase activation (Moon et al., 2018), which is in turn associated with AD neuronal degeneration (Chang et al., 2002; Oliveira and Klann, 2022) and AβO exposure in rodent neurons (Lourenco et al., 2013; Ma et al., 2013). These data demonstrate that anxiety and depression behavior associated with the loss of SRIF are contingent on signaling factors that are correspondingly impacted in AD.

Increased activity of SRIF-expressing neurons reduces anxiety and depression behavior. In an investigation of disinhibited SRIF-expressing interneurons using SRIF-Cre:$\gamma 2^{f/f}$ mice versus nondisinhibited $\gamma 2^{f/f}$ controls, increased activity of SRIF-expressing interneurons coincided with a reduction in anxiety (EPM) and depression [forced-swim test (FST), novelty-suppressed feeding] behavior (Fuchs et al., 2017). Stress-naıve SRIF-Cre:$\gamma 2^{f/f}$ mice showed similar SRIF mRNA and protein compared with controls, suggesting that altered SRIF levels could not explain the reduction in anxiety and depression behavior. The reduction in anxiety behavior in SRIF-Cre:$\gamma 2^{f/f}$ mice mimicked the response to benzodiazepines in wild-type controls (Löw et al., 2000). SRIF-Cre:$\gamma 2^{f/f}$ mice also exhibited a reduction in depression (FST) behavior relative to $\gamma 2^{f/f}$ controls. The behavioral changes in the SRIF-Cre:$\gamma 2^{f/f}$ mice coincided with decreased phosphorylation of the mRNA translation factor eukaryotic translational elongation factor 2 (eEF2), consistent with antidepressant doses of ketamine (Li et al., 2010; Autry et al., 2011; Monteggia et al., 2013) and 5-HT_{2C} receptor antagonists (Opal et al., 2014). Phosphorylation of eEF2 is also identified with AD-associated synaptic failure and cognitive impairment (Ma, 2023). Other studies suggest that the antidepressant actions of ketamine are mediated through the inhibition of eEF2 kinase signaling with an associated increase in BDNF (Nosyreva and Kavalali, 2010; Autry et al., 2011). The interplay between SRIF, SRIF-expressing neurons, and BDNF (Nawa et al., 1994; Villuendas et al., 2001; Grosse et al., 2005; Sánchez-Muñoz et al., 2011; Nagarajan et al., 2023) implicates a mechanism wherein SRIF inhibition of eEF2 kinase signaling with a corresponding BDNF elevation produces an antidepressant action. Altogether, the data indicate that chronically increased inhibitory synaptic input from SRIF-expressing interneurons results in behavior alterations and biochemical changes that are similar to established antidepressants (Fuchs et al., 2017).

Preclinical studies support the ability of SRIF administration to reduce anxiety and depression behaviors. SRIF intracerebroventricular dosing in rats reduced anxiety (EPM) and depression (FST) behavior compared with vehicle controls (Engin et al., 2008). The SRIF effect was similar to the benzodiazepine anxiolytic diazepam in reducing theta oscillation frequency while also increasing theta power. Moreover, coinfusion of subeffective doses of SRIF and diazepam significantly reduced anxiety (EPM) behavior, identifying an additive capacity to reduce anxiety. In a follow-up evaluation, intra-amygdalar and intraseptal administration of SRIF-14 or SRIF-28 reduced anxiety behavior (EPM, shock-probe test) in rats (Yeung et al., 2011), whereas intrastriatal administration of SRIF-14 or SRIF-28 did not reduce anxiety behavior, demonstrating that the anxiety-alleviating effects are site specific, consistent with benzodiazepine anxiolytics.

SST subtypes mediate the reduction of anxiety and depression behavior. In rats intracerebroventricularly administered SST_2 agonist L-779,976, anxiety (EPM) and depression (FST) behavior were reduced compared with vehicle controls (Engin and Treit, 2009). The SST_3 agonist L-796,778 likewise reduced depression behavior, but not anxiety behavior, compared with controls. However, the SST_2 and SST_3 agonist

effects were at a high dose (27 μg). Although the SST_1 agonist L-797,591, SST_4 agonist L-803,087, and SST_5 agonist L-817,818 did not produce a significant behavioral effect, neither the SST_4 nor SST_5 agonist were evaluated at a dose above 3 μg. Thus, the dyssynchronous dosing across the agonists rendered the determination of anxiety and depression behavioral actions relative to SST subtype involvement unclear. Nevertheless, a subsequent rat study showed that intra-amygdala or intraseptal administration of SST_2 antagonist PRL2903 blocked the reduction of anxiety (EPM) behavior produced by SRIF, supporting the anxiolytic role of SST_2 (Yeung and Treit, 2012). Mouse studies also support SST_2 involvement in the reduction of anxiety and depression behavior while further showing an SST_4 contribution. Intrahippocampal injection of the SST_2 agonist L-054,264 reduced anxiety (EPM) and depression (FST) behavior in wild-type mice, yet only depression behavior was reduced with the SST_4 agonist L-803,087 (Prévôt et al., 2017). Moreover, anxiety (EPM) behavior was increased in *Sst*$_2$-knockout mice compared with wild-type controls, which is consistent with earlier work in *Sst*$_2$-knockout mice (Viollet et al., 2000). *Sst*$_2$-knockout mice exhibited high basal corticosterone plasma levels respective to wild-type controls (Prévôt et al., 2017), similar to *Srif*-knockout mice (Lin and Sibille, 2015), aligning with an SST_2 mediation of SRIF action in inhibiting ACTH release (Strowski et al., 2002). Although basal plasma corticosterone levels in *Sst*$_4$-knockout mice were similar to wild-type controls, the administration of either an SST_2 or SST_4 agonist reduced plasma corticosterone levels in wild-type mice under stressful conditions. In another study, anxiety (EPM) and depression (FST) behavior increased in *Sst*$_4$-knockout mice compared with wild-type controls (Scheich et al., 2016), whereas intraperitoneal administration of the SST_4 agonist J-2156 in wild-type mice decreased anxiety (EPM) and depression (tail-suspension test) behavior compared with vehicle controls. Overall, these animal model studies support SST_2 and SST_4 as primary mediators of SRIF's depression and anxiety-reducing effects.

In summary, the loss of SRIF and SRIF-expressing neurons contribute to the neuropsychiatric symptoms observed in AD, with contributions from the body's stress response. The brains regions impacted by this loss in AD are consistent with what is observed in mood disorders (Table 1). Preclinical data support SST_2 and SST_4 as the principal subtypes that mediate the actions of SRIF in reducing anxiety and depression behavior, consistent with their heightened densities in brain regions (Consortium, 2020; Sjöstedt et al., 2020) most impacted by mood disorders.

E. Somatostatin and Seizures

Seizures are characterized by abnormal and recurrent bursts of electrical activity in the brain, commonly involving the hippocampus, amygdala, frontal cortex, temporal cortex, and olfactory cortex (Chauhan et al., 2022). Although fundamentally distinct disorders, AD and seizures share key pathological hallmarks and regions of impact (Giorgi et al., 2020; Lehmann et al., 2021). In both seizures and AD, the balance in neuronal network excitatory-inhibitory activity is dysregulated, contributing to hyperexcitation. The excitatory-inhibitory balance dysregulation being the pivotal pathologic connection, traceable to Aβ accumulation (Romoli et al., 2021). Correspondingly, the loss of SRIF and SRIF-expressing interneurons in AD play a prominent role in this neuronal network excitatory-inhibitory imbalance, driving a positive feedback loop to neuronal death (Fig. 1).

Substantial clinical evidence identifies bidirectional influences between AD and seizures. Individuals with seizures have an increased risk of developing dementia (Breteler et al., 1995; Cordonnier et al., 2007; Costa et al., 2019; Gourmaud et al., 2020; Tsai et al., 2021), whereas individuals with AD exhibit greater levels of seizure activity (Imfeld et al., 2013; Vossel et al., 2013, 2016; Cheng et al., 2015; Vöglein et al., 2020; Zelano et al., 2020; Habeych et al., 2021). Moreover, those with AD or amnestic MCI that suffer seizure activity show earlier onset and quicker progression of cognitive decline than those without detectable seizure activity (Vossel et al., 2013, 2016; Vöglein et al., 2020). Individuals with ADAD are particularly prone to seizure activity. Seizure incidence is higher in those with *PSEN1* (Janssen et al., 2003; Snider et al., 2005; Larner, 2010), *PSEN2* (Marcon et al., 2004; Jayadev et al., 2010), or *APP* (Edwards-Lee et al., 2005; Cabrejo et al., 2006; Lindquist et al., 2008) mutations, linking seizures to Aβ over-production. Seizure activity further disrupts oscillatory networks governing theta and gamma rhythms critical in information processing and memory (Lopez-Pigozzi et al., 2016; Malkov et al., 2022). This disruption in oscillatory activity with seizures is analogous to oscillatory disruptions in AD (Palop and Mucke, 2016; Mably and Colgin, 2018; Andrade-Talavera and Rodríguez-Moreno, 2021) and with the loss of SRIF in conjunction with Aβ accumulation (Villette et al., 2010; Chung et al., 2020; Park et al., 2020). Importantly, neuronal hyperexcitation has the capacity to increase Aβ levels. Individuals with late-onset epilepsy of unknown origin show heightened Aβ_{42} levels in their CSF, with 17.5% of patients progressing to AD (Costa et al., 2019). Drug-resistant temporal lobe epilepsy (TLE) increases Aβ_{42} expression in the hippocampus, with the rise of hippocampal phosphorylated-APP correlated with impaired cognitive function (Gourmaud et al., 2020). These findings align with studies in Tg2576 mice showing enhanced neuronal activity resulted in the release of Aβ with corresponding regional vulnerability to Aβ deposition (Cirrito et al.,

2005, 2008; Bero et al., 2011), whereas stress-induced elevations of Aβ in the hippocampal interstitial fluid of Tg2576 mice are blocked in the absence of neuronal activity (Kang et al., 2007).

Preclinical studies verify that Aβ can induce seizure activity. APP/PS1 mice with elevated Aβ levels display increased neuronal hyperexcitability compared with age-matched wild-type controls (Minkeviciene et al., 2009). In recording episodes at the onset of Aβ pathogenesis, at least one unprovoked seizure was detected in 65% of the mice, of which 46% had multiple seizures and 38% had a generalized seizure. In FAD mice (lines hAPP-J20, hAPP-J9, APP23/PS45, and APP/PSEN1dE9), elevated levels of Aβ were associated with increased spontaneous seizure activity in the cortex and hippocampus, with associated remodeling of inhibitory circuits (Palop et al., 2007). A series of studies by Busche and colleagues mechanistically linked Aβ to neuronal hyperexcitation and cognitive dysfuntion. Initial investigations in 6- to 7-month-old APP23/PS45 mice showed that cortical neuron hyperexcitability was affiliated with high Aβ plaque burden (Busche et al., 2008). The hyperactivity was associated with a decrease in GABAergic inhibition. A subsequent evaluation in 6- to 7-month-old APP23/PS45 mice also identified hyperactivity in the plaque-bearing hippocampal CA1 neurons (Busche et al., 2012). Yet, in 1- to 2-month-old APP23/PS45 mice, a selective increase in hyperactive neurons occurred before plaque formation, indicating that soluble Aβ underlies early dysregulation (Busche et al., 2012). In a third investigation, a reduction of soluble AβOs through inhibition of β-secretase activity rescued APP23/PS45 mice from neuronal hyperactivity, long-range circuit dysfunction as related diminished slow-wave activity, and memory defects (Keskin et al., 2017). A recent study by Zott et al., (2019) further demonstrated that when soluble AβOs extracts from AD patient brains were applied to hippocampal CA1 mouse neurons, marked increases in hyperactivity resulted both in vivo and in vitro. These evaluations support both soluble AβOs and Aβ plaques as contributors to neuronal hyperexcitation.

SRIF and SRIF-expressing neuron cellular interactions provide an additional framework of understanding seizure activity in AD (Fig. 4). In the hippocampus, activity-dependent release of SRIF occurs during and after seizures to reduce neuronal hyperexcitation both presynaptically and postsynaptically (Vezzani et al., 1992; Marti et al., 2000a,b). In slice preparations, SRIF administration inhibited excitatory transmission in hippocampal CA1 and CA3 neurons (Tallent and Siggins, 1997, 1999). The SRIF-induced depression of excitatory postsynaptic currents was particularly robust during hyperexcited states, supporting the role of SRIF in mitigating active seizures. Furthermore, SRIF suppressed presynaptic glutamate release from Schaeffer collateral-CA1 synapses (Tallent and Siggins, 1997; Kozhemyakin et al., 2013). As glutamate homeostasis is impaired in AD patients (Masliah et al., 1996; Scott et al., 2011), with soluble AβOs potentiating glutamate-induced neuronal excitation (Li et al., 2011; Zott et al., 2019), the loss of SRIF and SRIF-expressing neurons further impairs the "brake" to glutamate-induced hyperexcitation. Astrocytes also play a role in SRIF-mediated mechanisms, influencing both the input and output SRIF-expressing interneurons of the hippocampus (Honoré et al., 2021). Astrocytes are able to regulate transmission at inhibitory synapses of SRIF-expressing interneurons (Fig. 4), whereas Aβ-induced astrogliosis and dysregulation of astrocyte functions contribute to glutamate dysregulation and hyperexcitability, with astrocyte-mediated inflammation further promoting seizure activity (Dejakaisaya et al., 2021; Vezzani et al., 2022).

Seizure activity itself results in the loss of SRIF-expressing neurons (Tallent and Qiu, 2008). The loss of SRIF-expressing interneurons was first identified in the hilus of the dentate gyrus after repeated seizures in rats (Sloviter, 1987). SRIF-expressing interneuron loss in hippocampal CA1 and CA3 has since been confirmed across numerous seizure models (Houser, 2014). Moreover, the seizure vulnerability that comes about with the loss of SRIF-expressing neurons may be exacerbated by concurrent dysregulation of cholinergic circuitry in AD. In a study of TLE, the cholinergic medial-septum hippocampal circuit that plays a primary antiseizure role was dependent on downstream SRIF effector action (Wang et al., 2020). In rats, deafferentation of hippocampal cholinergic neurons resulted in the loss of hilar SRIF-expressing neurons, worsening the seizure-induced loss of SRIF-expressing neurons (Jolkkonen et al., 1997). Interestingly, an interrelated effect is observed with language processing. Language difficulties are well recognized in patients with epileptic seizures (Unterberger et al., 2021) and AD (Szatloczki et al., 2015). It has been proposed that excitatory-inhibitory imbalances foster language impairment and evolve largely from conjoined impairment of cholinergic and SRIF processes aligning with Aβ load in AD (Almeida and Radanovic, 2022).

Several studies have attempted to delineate the roles SST subtypes in seizure activity. In an early investigation, the $SST_{2,3,5}$ agonist octreotide injected into the hippocampus of rats significantly reduced the number and duration of kainite-induced seizures (Vezzani et al., 1991). Similarly, intracerebroventricular administration of octreotide or its analog lanreotide prevented or attenuated pilocarpine-induced status epilepticus in more than 65% of rats (Kozhemyakin et al., 2013). In associated slice evaluations, the SRIF inhibition of glutamate release at Schaffer collateral-CA1 pyramidal neuron synapses was mediated through presynaptic SST_2

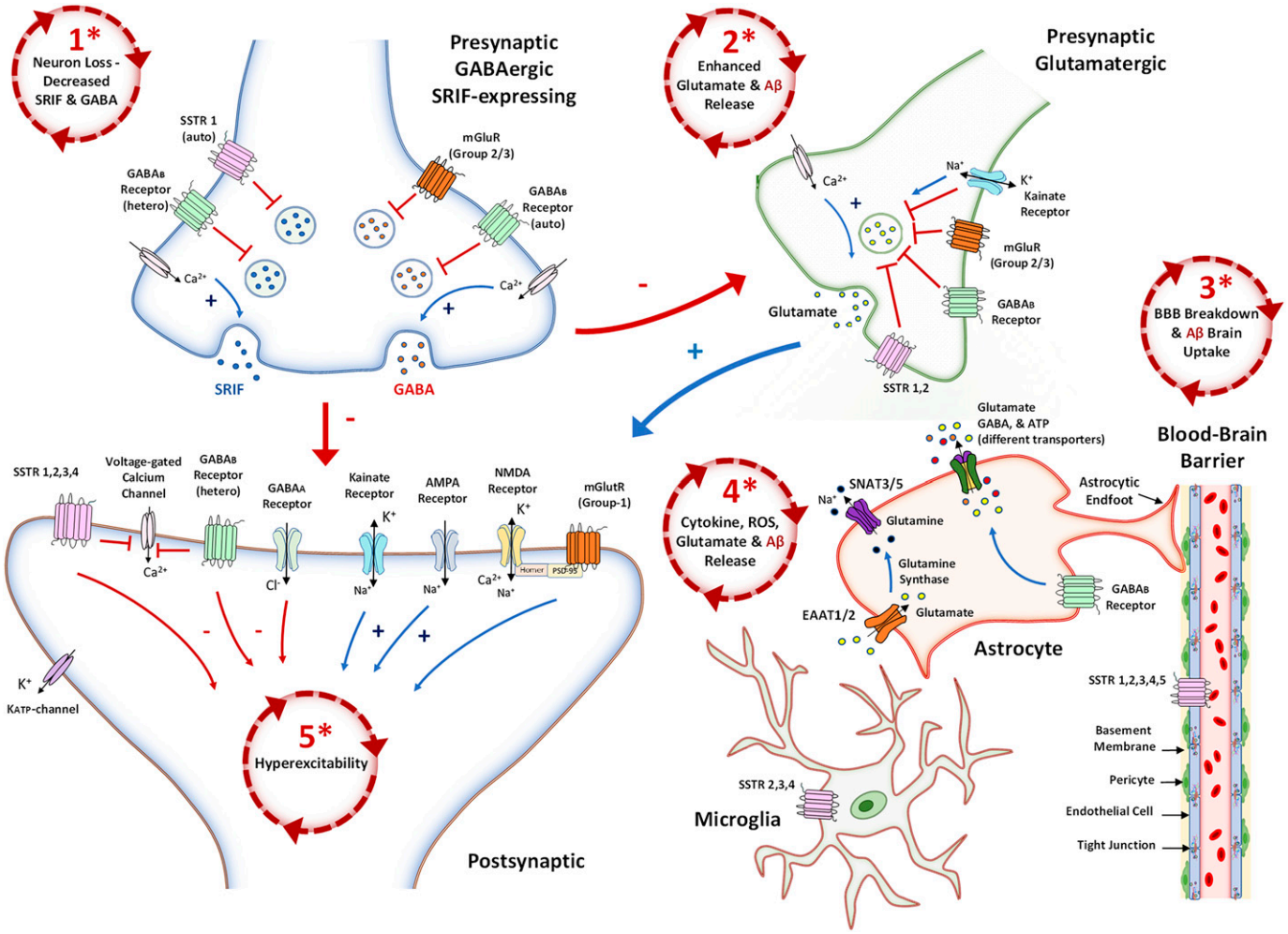

Fig. 4. Schematic of SRIF-associated cellular interactions governing neuronal excitatory-inhibitory actions in the neocortex and hippocampus with AD impact. SRIF-expressing GABAergic neurons release SRIF and GABA in a calcium-dependent manner, producing primarily inhibitory actions on neurons both presynaptically and postsynaptically through SSTs. Presynaptic glutamatergic neurons release glutamate in a calcium-dependent manner, producing primarily excitatory actions through receptor activation [reviews: Reiner and Levitz, (2018), Negrete-Díaz et al., (2022), and Chen et al., (2023)]. Released glutamate can be taken up by astrocytes via the excitatory amino acid transporter (EAAT1/2), which can be converted to glutamine. Glutamine is released via astrocyte sodium-coupled amino acid transporter (SNAT 3/5). Astrocytes actively modulate hippocampal circuits; as part of the "tripartite synapse," they regulate glutamate, GABA, and ATP. SRIF-expressing interneuron inhibition of excitatory transmission is, in part, mediated by astrocytic $GABA_B$, which regulates gliotransmitter release (Matos et al., 2018; Shen et al., 2022) [astrocyte release of gliotransmitters and corresponding autoregulatory mechanisms in AD and epilepsy reviewed elsewhere: (Dejakaisaya et al., 2021; Price et al., 2021)]. Astrocytic endfeet wrap around the BBB endothelium and pericytes, maintaining BBB integrity. Microglia surveil the brain, removing debris. * The cellular dynamic is dysregulated in AD (numbering is not necessarily indicative of sequence of events): (1) Elevated Aβ induces the loss of presynaptic GABAergic SRIF-expressing neurons, reducing inhibitory control. (2) Hyperexcitation increases glutamate and Aβ release. Elevated Aβ and loss of SRIF-expressing neuron feedback control contributes to dysregulated glutamate release. (3) BBB breakdown associated with inflammation and altered astrocyte endfeet interaction increases uptake of toxic blood components into the brain, including Aβ. (4) Aβ and inflammatory cytokines activate astrocytes and microglia. Astrocytes undergo astrogliosis, decreasing glutamate uptake transport and conversion to glutamine while increasing release of proinflammatory cytokines and glutamate. Microglial activation increases proinflammatory cytokine release and generation of reactive oxygen species (ROS). (5) Loss of inhibitory signaling and enhanced glutamate levels drive postsynaptic hyperexcitation.

(Kozhemyakin et al., 2013). In a study using a series of selective SST subtype agonists, intrahippocampal administration of the SST_2 agonist L-779,976, SST_3 agonist L-796,778, or SST_4 agonist L-803,087 were each found to protect rats against pilocarpine-induced seizures (Aourz et al., 2011). Moreover, a cooperative interaction between subtypes was identified. The antagonism of SST_3 with SST3-ODN-8 blocked the anticonvulsant effect of an SST_4 agonist, whereas the antagonism of SST_2 with cyanamid-154806 inhibited the anticonvulsants effect of SST_3 and SST_4 agonists. Functional interactions between SST_1/SST_2 (Cammalleri et al., 2004), SST_1/SST_4 (Cammalleri et al., 2009), and SST_2/SST_4 (Moneta et al., 2002) have likewise been observed in mouse hippocampal slice evaluations of epileptiform activity. Furthermore, SST_2, SST_3, and SST_4 each have shown to moderate cortical excitability and seizure severity in mice (Qiu et al., 2008). In *Sst*$_2$-, *Sst*$_3$-, and *Sst*$_4$-knockout mice treated with the $GABA_A$ receptor antagonist pentylenetetrazole to induce seizures, all mice exhibited shorter latencies to different seizure stages with increased seizure severity when

compared with wild-type mice. However, when systemically injected with kainite to induce seizures, only *Sst*$_4$ knockouts showed increased seizure sensitivity. Additionally, SST_4 coupled to M-channels was shown to be essential to its inhibition of epileptiform activity the hippocampal CA1. These data support the differential impact of SST subtype activity relative to the form of seizure induction in association with distinctive regions of effect and cellular processes. Although data support SST_4 playing a major role in mitigating seizure activity in mice, an earlier study showed that treatment with the SST_4 agonist L-803,087 induced excitatory effects in hippocampal CA1 slices of wild-type mice (Moneta et al., 2002). The excitatory effect was diminished by coadministration of octreotide. Yet, the same study showed that intrahippocampal injection of the SST_2 agonists octreotide, BIM23120, or L-779976 did not affect kainite-induced seizures. Differences in SST subtype agonists used, dosing ranges, routes of administration, timeframes, manners of seizure induction, and in vivo versus in vitro evaluations each play a role in the discrepancies between studies. Slice evaluations notably impact neuron connectivity. Dyssynchronous regional and temporal changes in SST subtypes following seizures in rats (Csaba et al., 2004; Kwak et al., 2008) and mice (Iwasawa et al., 2019) further implicate differences in receptor regulation. For example, SST_2 has shown to be sensitive to SRIF-mediated downregulation, resulting in a sustained loss of surface expression in the dentate gyrus after seizures (Dournaud et al., 1998; Csaba et al., 2004). Resected human hippocampal tissue from patients with intractable seizures correspondingly shows evidence of SST_2 downregulation (Csaba et al., 2005). It is also notable that the decline in hippocampal SST_2 with acute seizure activity is consistent with investigations of Aβ infusion (A$\beta_{25–35}$ and A$\beta_{1–42}$) (Aguado-Llera et al., 2018).

In summary, the interconnection between seizure occurrence and AD is traceable to increased brain Aβ levels and loss of SRIF-expressing neuronal function. The excitatory-inhibitory imbalance underlying seizure activity involves the dysregulation of multiple cellular processes, key of which is the interplay between glutamatergic and GABAergic SRIF-expressing neurons. Despite a lack of definitive delineation of SST subtype effect in seizure activity, most studies support SST_2 and SST_4 activation in the mitigation of hippocampal hyperexcitability, with likely interactions between SST subtypes.

F. Somatostatin and Inflammation

Neuroinflammation plays a prominent role in AD pathogenesis, marked by production of proinflammatory cytokines and reactive oxygen species (Leng and Edison, 2021). Neuroinflammation accelerates neurodegeneration and is associated with many AD risk factors, including seizures (Rana and Musto, 2018; Komoltsev et al., 2021; Vezzani et al., 2022) and neuropsychiatric symptoms (Benedetti et al., 2020; Milligan Armstrong et al., 2021; Troubat et al., 2021). Preclinical studies show that the loss of SRIF-expressing entorhinal and hippocampal neurons is heightened under inflammatory conditions (Gavilán et al., 2007; Moreno-Gonzalez et al., 2009), whereas SRIF can mitigate CNS inflammation, modulate microglial cell activation states, and help maintain BBB integrity under inflammatory conditions.

Neuroinflammation is accompanied by the activation and proliferation of microglia, the resident macrophage of the brain. Microglia continuously survey the CNS microenvironment, responding to inflammatory mediators, such as Aβ and damage signals (Leng and Edison, 2021). The activation states of microglia are typically classified as proinflammatory "M1" and anti-inflammatory "M2" based on cytokine release profiles and functional outcomes. This classification generally conveys a protective M2 phenotype with the removal of pathogens, cellular debris, and Aβ and a cytotoxic M1 phenotype affiliated with enhanced neuroinflammation and worsening AD pathology (Leng and Edison, 2021). Thus, the microglial response can be beneficial or detrimental depending on the level and timeframe of activation. Microglia also have extensive reciprocal communication with neurons, capable of actively modulating neuronal signaling (Li et al., 2012; Szepesi et al., 2018). Recent work in APP/PS1 mice identified that 98% of SRIF-expressing interneurons in the hippocampal CA1 receive putative microglia contacts (Gervais et al., 2022). The microglia displayed enhanced contact onto interneuronal somata in APP/PS1 mice compared with wild-type controls, capable of controlling neuronal activity.

Reactive microglia closely colocalize with Aβ in AD brain tissue (McGeer et al., 1987; Tooyama et al., 1990). In an evaluation of post-mortem AD human brain tissue, smaller AβOs more robustly activate microglia and increased neurotoxicity compared with larger AβO species (Yang et al., 2017). An age-dependent accumulation of soluble AβOs in APP/PS1 mice showed to be a primary factor in the microglia switch to the cytotoxic M1 form (Jimenez et al., 2008), consistent with other preclinical studies (Sondag et al., 2009; Maezawa et al., 2011; Ferretti et al., 2012). Aβ-induced microglia activation increases the release of proinflammatory cytokines, inclusive of tumor necrosis factor (TNF)-α, interleukin (IL)-1β, IL-6, interferon-γ, and monocyte chemoattractant protein-1 (Combs et al., 2001; Floden et al., 2005; Martin et al., 2017). In turn, these cytokines lead to AD-associated synaptic loss (Leng and Edison, 2021) and BBB dysregulation (Gullotta et al., 2023). These cytokines also act on their receptors to enhance signaling through the nuclear factor κB pathway, which upregulates β-secretase activity with a

corresponding increase in Aβ generation (Chen et al., 2012). Notably, Aβ-activated microglia directly contribute to the significant early loss of SRIF-expressing neurons in the entorhinal cortex of PS1/APP mice associated with elevated proinflammatory cytokines (Moreno-Gonzalez et al., 2009), which is consistent with early neurodegeneration in the entorhinal cortex in human AD tissue studies (Gómez-Isla et al., 1996).

SRIF modulation of microglia response was first evaluated in BV2, N9, and primary rodent microglia cell lines, each expressing SST_2, SST_3, and SST_4 (Fleisher-Berkovich et al., 2010). SRIF treatment enhanced microglia migration and increased Aβ_{42} phagocytosis across cell lines in a concentration-dependent manner. However, immunostimulation of microglia by bacterial lipopolysaccharide (LPS) prior to treatment almost completely abolished the Aβ phagocytosis effect, indicating an inflammatory-sensitive SRIF effect. A study of the SST_4 agonist NNC 26-9100 treatment in BV2 cells likewise showed an increase in the uptake of fluorescent-tagged Aβ_{42} under noninflammatory conditions compared with vehicle controls (Schober et al., 2021). Nonetheless, another study found that SRIF treatment inhibited LPS-induced microglial activity and reactive oxygen species production as well as decreased TNF-α, IL-1β, and prostaglandin-E_2 levels (Bai et al., 2015). Investigations further identify the ability of SRIF to inhibit LPS-induction of inducible nitric oxide synthase expression and neuronal degeneration associated with the suppression of microglia inflammatory activation (Bai et al., 2015; Hernández et al., 2020). NNC 26-9100 similarly inhibits LPS-induced nitric oxide in BV2 cells (Schober et al., 2021). Moreover, in response to LPS-induced inflammation, treatment of BV2 cells with the SST_4 agonist SM-I-26 decreased mRNA expression of proinflammatory cytokines *Tnf-α* and *Il-6* while increasing mRNA expression of the anti-inflammatory cytokine *Il-10* and the antioxidant *catalase* (Silwal et al., 2021). It was hypothesized that SST_4 agonist treatment may switch activated microglia from a proinflammatory M1 to an anti-inflammatory M2 phenotype (Silwal et al., 2021), which has been proposed as a mechanism to treat neurodegenerative diseases (Guo et al., 2022).

Transgenic AD mouse modeling studies support an SST_4 mediation of Aβ clearance by microglia. The intracerebroventricular administration of NNC 26-9100 in 3xTg mice decreased cortical *Cd33* and increased of macrophage scavenger receptor-1 (*Msr1*) mRNA expression (Sandoval et al., 2019). Cd33 is predominately expressed in microglia (Jiang et al., 2014), positively correlating to amyloid burden and LOAD (Griciuc et al., 2013). Cd33 protein expression is elevated in post-mortem AD brain tissue as compared with controls, indicating that a reduction in Cd33 may be beneficial (Griciuc et al., 2013). Msr1 is a microglia cell surface receptor involved in Aβ phagocytosis, with increased expression identified with enhanced Aβ phagocytosis (Chung et al., 2001; Frenkel et al., 2013). Knockout of *Msr1* in APPswe/PS1dE9 mice increased Aβ levels as well as mortality rate (Frenkel et al., 2013). Interestingly, *Nep* and *Ide* mRNA expression were also significantly lower in the brains of APPswe/PS1dE9 *Msr1*-knockouts compared with APPswe/PS1dE9 controls, indicating Msr1 involvement in Aβ peptidase regulation. Correspondingly, SRIF treatment of BV2 cells is reported to increase IDE protein and mRNA expression, IDE secretion, and Aβ degradation (Tundo et al., 2012). Although the roles of other SST subtypes have not been ascertained, the results of these studies indicate that SST_4 plays a key role in microglia function, albeit human microglia studies remain to confirm these observations.

The BBB is a semipermeable barrier that tightly regulates the movement of substances between the systemic circulation and CNS (Liebner et al., 2018). The endothelial cells of the BBB lack fenestrations and form tight junctions that greatly reduce paracellular permeability. The tight junctions are maintained by several specialized proteins, principle of which are claudin-5, occludin, and zonula occludens (ZO)-1. BBB integrity is further maintained by surrounding pericytes, astrocytes, and neurons, which, with the endothelium, are formally defined as the neurovascular unit (Fig. 4). BBB breakdown attributed to Aβ and inflammation occurs in both human AD and preclinical AD models (Montagne et al., 2017). BBB in vitro modeling shows that AβOs upregulate matrix metalloproteinases and downregulate tight junction proteins ZO-1, claudin-5, and occludin, with corresponding increases in paracellular permeability (Kook et al., 2012; Wan et al., 2015). These models likewise show an AβO-induced increase in protein expression of the receptor for advanced glycation end-products, which transports Aβ into the brain. A number of proinflammatory cytokines, including IL-1β, IL-6, IL-17, INF-γ, and TNF-α, reduce claudin-5, ZO-1, and occludin expression, with corresponding disruption of BBB tight junctions, and enhance paracellular permeability (Takata et al., 2021). Additionally, in an in vitro model using human-derived BBB endothelial cells, IL-1β and TNF-α decreased Aβ efflux associated with a decrease in efflux transporter protein expression (Versele et al., 2022). The encompassing data support a positive feedback loop in which elevated Aβ and inflammation drive BBB dysregulation, reducing the capacity to clear brain Aβ and furthering inflammation and BBB dysfunction (Fig. 1). Inflammation likewise impacts other cells of the neurovascular unit, contributing to neurovascular uncoupling and diminished cerebral blood flow (Nelson et al., 2016). Reduced cerebral blood flow and corresponding hypoperfusion contribute to the chain of events that ultimately contribute to neuronal death. In

another interlinking of AD-related conditions, it is significant that inflammation-induced BBB dysfunction also plays a role in epileptic activity (Fattorusso et al., 2021; van Vliet and Marchi, 2022) and neuropsychiatric disorders (Welcome, 2020; Medina-Rodriguez and Beurel, 2022).

SRIF reduces the inflammation-induced dysregulation of the BBB. In human brain CMEC/D3 endothelial cells, treatment with LPS, TNF-α, or interferon-γ resulted in a loss of tight junction cellular integrity (Basivireddy et al., 2013). The LPS and cytokine treatment decreased SRIF expression and secretion from the endothelium, associated with the loss of ZO-1 protein expression at the tight junctions. Treatment with SRIF, the SST_2 agonist L-779,976, or the SST_4 agonist L-803,087 each reversed the ZO-1 expression loss. Interestingly, the inflammatory treatment increased the endothelial protein expression of SST_2 and SST_4, suggesting that the increased expression of SST_2 and SST_4 may serve to counter BBB tight junctional disruption. SRIF treatment further inhibited inflammation-mediated changes in expression of extracellular signal-regulated kinases and inducible nitric oxide synthase. Caco-2 endothelial cells show similar effects, with SRIF treatment increasing occludin and ZO-1 protein expression while inhibiting LPS-induced redistribution of tight junction proteins (Lei et al., 2014). Moreover, in CMEC/D3 cells treated with Aβ, SRIF treatment decreased tight junction protein disruption, paracellular permeability, and matrix metalloproteinase-2 (MMP2) protein expression compared with vehicle controls (Paik et al., 2019). MMP2 notably contributes to BBB breakdown in AD and is regulated through proinflammatory cytokines (Weekman and Wilcock, 2016).

Inflammatory effects that extend to other cells of the neurovascular unit are impacted by SRIF. Pericytes are a type of mural cell of the microcirculation that wrap around endothelial cells, maintaining the structural and functional integrity of the BBB and blood-retinal barrier. Pericyte degeneration leads to neurovascular uncoupling, reduces oxygen to the brain, and induces metabolic stress (Kisler et al., 2017). In an AD post-mortem tissue examination compared with cognitively normal controls, pericyte number and coverage in the cortex and hippocampus were reduced by 59% and 60%, respectively (Sengillo et al., 2013). This reduction correlated with the magnitude of BBB breakdown to plasma-derived proteins. There is also accelerated pericyte loss in the post-mortem brain tissue of *APOE-ε4* compared with *APOE-ε3* carriers, aligning with a heightened degree of BBB breakdown in *APOE-ε4* carriers (Halliday et al., 2016). In an evaluation of isolated human pericytes, proinflammatory and proapoptotic actions result when exposed to conditioned media from LPS-stimulated BV-2 microglia (Mazzeo et al., 2017), whereas the addition of SRIF to the LPS treatment of microglia resulted in media that stopped the inflammation-induced damage of the pericytes by reducing the proinflammatory mediators and counteracting the imbalance between apoptotic and survival intermediates.

In summary, inflammation contributes to AD pathology in alignment with the loss of SRIF and SRIF-expressing neurons, whereas SRIF acting through SSTs has an anti-inflammatory effect. SST_4 agonist activation has been shown to lessen inflammatory activation of microglia in in vitro rodent cell studies. SRIF mitigation of inflammation-induced BBB dysregulation in human cell line studies implicates SST_4 and SST_2 as the primary mediators of this effect. Although more extensive in vivo characterization of anti-inflammatory activities is required, evidence supports a SRIF and specific SSTs capable of mitigating AD-associated inflammatory processes.

VI. Therapeutic Implications of Somatostatin Receptor Agonists in Alzheimer Disease

The decline of SRIF and loss of SRIF-expressing neurons in the brains of AD patients is linked to pathological progression and cognitive decline. This supports the targeting of SRIF-associated mechanisms for AD treatment. From a practical perspective, the use of SRIF as a means of treatment is problematic as it is a large peptide that does not readily cross the BBB and has an extremely short half-life. Moreover, concern as to the potential of toxic SRIF-Aβ aggregate assemblies arises with an approach that substantially elevates SRIF levels in the brain (Solarski et al., 2018). Correspondingly, the SRIF secretogues FK960 and FK962, which showed early promise in preclinical studies (Matsuoka and Aigner, 1997; Matsuoka and Satoh, 1998; Tokita et al., 2002, 2005; McCarthy et al., 2011), never advanced through a completed clinical trial. The most viable route is the advancement of an enzymatically stable small-molecule SST subtype–selective agonist with effective brain uptake. With the additional consideration as to the targeted SST subtype, a selective agonist would help to limit the side-effect profile. Yet, despite the known potential of SST agonists for AD treatment, the few clinical evaluations conducted provide little tangible insight (Table 2).

A. Clinical Evaluations

The first human investigation of an SRIF-focused treatment relative to cognitive decline in AD evaluated the $SST_{2,3,5}$ agonist seglitide using a double-blinded, placebo-controlled crossover study design (Cutler et al., 1985). Seglitide was infused at a variable dose for 5.5 hours in 10 patients "presumed" to have mild AD based solely on the outcomes of a Mini-Mental State Examination. There was no benefit in arithmetic or pair-associated or serial learning compared with receiving

placebo. However, testing was conducted only 3–5 hours after infusion. There was also no detectable seglitide in the CSF, indicating a lack of CNS uptake. Another double-blinded, placebo-controlled study evaluated the $SST_{2,3,5}$ agonist octreotide in 14 patients meeting the National Institute of Neurologic and Communicative Disorders and Stroke (NINCDS) Alzheimer's Disease and Related Disorders Association (ADRDA) criteria for AD (Mouradian et al., 1991). This study used a variable dosing regimen with infusions lasting 20 minutes, 3 hours, or 8 hours, with one 8-hour patient also receiving an infusion of the cholinesterase inhibitor physostigmine (0.3 mg/h). An extensive battery of learning and memory performance tests was conducted, with no significant improvement in any treatment paradigm compared with receiving placebo. Similar to the first study, this evaluation was limited by the testing timeframe, with evaluations performed either directly following infusion (20-minute group) or carried out during the last hour of infusion (3- and 8-hour groups). In another placebo-controlled trial performed in 23 AD patients meeting NINCDS-ADRDA criteria, octreotide was infused (150 μg/h) for 90 minutes followed by a 30-minute stabilization period and then a 30-minute cognitive testing period (Craft et al., 1999). AD patients showed improved declarative story-recall memory but not in selective attention using the Stroop interference test compared with receiving placebo. AD patients receiving octreotide under conditions of hyperglycemia did not show improvement in declarative story-recall memory when compared with receiving placebo, suggesting that hyperglycemia negatively impacted the effect of octreotide. In similarly aged healthy controls, cognitive tests were similar across all treatments. Furthermore, octreotide reduced plasma cortisol, corticotropin, and epinephrine levels in those with AD when compared with receiving placebo, implicating peripherally mediated actions in the memory effect. A follow-up double-blind crossover study with octreotide infusion (150 μg/h) using a similar assessment paradigm was performed in 16 memory-impaired patients (7 AD patients meeting NINCDS-ADRDA criteria for probable AD and 9 amnestic-MCI patients), along with 19 similarly aged cognitively intact patients (Watson et al., 2009). The effect of octreotide on delayed memory was dependent both on the presence or absence of *APOE-ε4* and presence or absence of memory impairment. In the cognitively intact older adults, octreotide significantly improved delayed story recall when compared with receiving placebo. Within those that were memory impaired, *APOE-ε4*–negative patients with the least amount of cognitive impairment showed greater octreotide-induced memory facilitation. Nevertheless, the improvements in the *APOE-ε4*–negative patients were marginal.

The limited cognitive benefit in the clinical studies of SRIF analogs comes with several qualifiers. First, the SST agonists used are problematic. The physiochemical characteristics of seglitide and octreotide are unsuitable for traversing the BBB (Banks et al., 1990; Jaehde et al., 1994; Fricker et al., 2002), and actual receptor engagement in cortical or hippocampal tissue was not confirmed. Additionally, although both seglitide and octreotide are most often noted for their high binding affinity to SST_2, they also have high binding affinity for SST_3 and SST_5. This negates the ability to delineate specific SST subtype effects. Critically, no selective SST_1 or SST_4 analog has ever been tested in AD or amnestic MCI patients. Secondly, testing parameters limit the ability to draw meaningful conclusions. The low patient numbers, variable dosing levels, mixing of AD and MCI patient populations, and different diagnostic determinations reduce the capacity to delineate outcomes or crosscompare between studies. Most significant are the short timeframes, with cognitive assessments either being conducted over the actual injection period or within hours after injection. This restricts interpretation to an acute window of effect when numerous peripheral variables are more likely to impact results. Most critically, no long-term treatment studies have been conducted as to the capacity of a BBB-permeable selective SST subtype agonist to mitigate AD symptomology or pathology.

B. Moving Forward

The advancement of an SST agonist for AD treatment must first determine which subtype to focus energies. As addressed in this review, both SST_2 and SST_4 are heavily involved in higher cognitive processes with the potential to enhance cognition. However, SST_2 targeting presents greater liability. Although SST_2 is expressed throughout the brain, it has significant peripheral distribution with pronounced pituitary expression (Consortium, 2020; Sjöstedt et al., 2020) and extensive endocrine actions (Günther et al., 2018). This suggests a higher likelihood of SST_2-related side effects, whereas SST_4 targeting presents several advantages. SST_4 is not heavily expressed in the periphery and has no pituitary expression (Consortium, 2020; Sjöstedt et al., 2020). SST_4 agonist evaluations show no effect on glucagon, growth hormone, or insulin release (Rohrer and Schaeffer, 2000), indicating limited endocrine-associated actions. Moreover, the SST_4 agonist peripheral actions that have been identified are inflammatory-state dependent, with the capacity to mitigate inflammatory associated pain (Helyes et al., 2001, 2006, 2009, Lei et al., 2014; Elekes et al., 2008; Van Op den Bosch et al., 2009). Such peripheral effects are not innately problematic and may provide an added value to the AD population. The low level of receptor internalization following agonist treatment (Kreienkamp et al., 1998; Schreff et al., 2000) and a relatively rapid rate of receptor recycling (Smalley et al., 2001) further support SST_4 as a reliable and sustainable target. Lastly, SST_4 agonists have

TABLE 2
Clinical trials of SST agonist analogs in cognition performance testing

Medication Studied	Study Parameters	Outcomes
Seglitide (Cutler et al., 1985)	• Double-blind, placebo-controlled crossover trial • Ten patients "presumed to have mild AD" based on MMSE score • Dosing (i.v.): 30 minutes at 120 μg followed by 5.5 hours at 40 μg/h • Testing window: 3–5 hours postinfusion	• No significant effect in arithmetic, serial, or paired-associate learning was found compared with receiving placebo.
Octreotide (Mouradian et al., 1991)	• Double-blind, placebo-controlled crossover trial • Fourteen patients meeting NINCDS-ADRDA criteria for AD • Dosing (i.v.), three groups: 1) 20-minute infusion at 0.5 or 1.5 mg/min, 2) 3-hour infusion at 15 mg/h, 3) 8-hour infusion at 15 mg/h • Testing window: directly after infusion for 20-minute group or during last hour of infusion for 3-or 8-hour infusion groups	• No significant effect for 20-minute group across logical memory, sentence memory, Reye verbal learning, digital span, verbal/figure fluency, or perseverations compared with receiving placebo. • Cognitive measures similar in 3-hour group when compared with receiving placebo (ADAS total cognitive and noncognitive assessment scores, verbal and visual selective reminding tasks).
Octreotide (Craft et al., 1999)	• Double-blind, placebo-controlled crossover trial • Twenty-three patients meeting NINCDS-ADRDA criteria for probable AD and 14 similarly aged older adult healthy controls • Dosing (i.v.), four groups: 1) hyperinsulinemia, 2) hyperglycemia-dextrose + 150 μg/h octreotide, 3) placebo, and 4) 150 μg/h octreotide, ~90-minute infusion • Performed following fasting • Testing window: 30 minutes postinfusion for 30 minutes	• Octreotide improved story-recall memory in those with AD compared with receiving placebo but no impact on selective attention. • Octreotide under conditions of hyperglycemia had no significant impact on any cognitive measures compared with receiving placebo. • Cognitive measures were similar across all treatments for similarly aged older adult healthy controls.
Octreotide (Watson et al., 2009)	• Double-blind, placebo-controlled crossover trial • Memory-impaired patients (seven patients meeting NINCDS-ADRDA criteria for probable AD, nine patients for amnestic-MCI) and 19 cognitively intact older adults • Dosing (i.v.): 90 minutes at 150 μg/h • Testing window: postinfusion for 45 minutes	• Octreotide improved delayed story-recall memory testing in cognitively intact older adults when compared with receiving placebo. • A positive correlation between delayed recall score and percentage change from baseline with octreotide in memory-impaired *APOE*-ε4-negative patients.

ADAS, AD assessment scale; MMSE, Mini-Mental State Exam.

shown to increase brain NEP activity with associated reduction of Aβ/AβOs levels (Sandoval et al., 2012, 2013, 2019; Yu et al., 2017; Nilsson et al., 2020), suggesting an SST_4 agonist as disease modifying. Given the high expression of SST_4 in the neocortex and hippocampus (Consortium, 2020; Sjöstedt et al., 2020), regions heavily impacted by Aβ accumulation in AD, enhancement of NEP activity would be focused to the regions of greatest need. Such a brain-targeted activation likewise reduces concerns related to peripheral NEP activity. Furthermore, as decline in Aβ clearance is the primary cause of elevated Aβ/AβO levels in LOAD (Mawuenyega et al., 2010), enhancement of Aβ/AβO clearance through the SST_4-NEP pathway could be of particular benefit for the majority of the AD population.

The compatibility of new therapies with established AD drug treatments is another important consideration. Given the multifactorial pathogenesis of AD, combination treatments geared to different targets may provide the greatest benefit (Cummings et al., 2019). Established symptomatic treatments, ChEIs and memantine, may work well when combined with an SST_4 agonist. ChEIs have been a mainstay of AD treatment of over 20 years, maximizing the availability of endogenous acetylcholine through inhibition of its catabolism. A number of studies identify long-term use of ChEIs produce cognitive benefits in AD patients (Rogers et al., 2000; Doody et al., 2001; Doraiswamy et al., 2002; Courtney et al., 2004; Farlow et al., 2005; Xu et al., 2021). Moreover, discontinuation of ChEIs in those with moderate-to-severe AD significantly increases the probability of nursing home placement within the first year (Howard et al., 2015), suggesting that the use of ChEIs plays an important role in reducing caregiver burden. Yet, the effectiveness of ChEIs in AD continues to be debated, with the benefits often being quite modest and accompanied by numerous side effects (Ruangritchankul et al., 2021). Adverse events with ChEIs notably increase in older populations with dementia (Kröger et al., 2015). The high degree of the operational interdependency of the cholinergic system with SRIF and SRIF-expressing neurons in the regulation of cognition, along with the ability of SRIF to mitigate cholinergic deficits and facilitate cholinergic activity (Mancillas et al., 1986; Araujo et al., 1990; Matsuoka et al., 1994; Nakata et al., 1996; Matsuoka and Aigner, 1997; Tokita et al., 2002, 2005), espouses a combined treatment approach. Foreseeably, such a combination could facilitate lower dosing of ChEIs, reducing the ChEI side effect profile and potentially extending the viable window of ChEI use. There is also the possibility of an additive disease-modifying effect, with evidence that ChEIs may inhibit brain tissue atrophy (Hashimoto et al., 2005; Dubois et al., 2015; Cavedo et al.,

2016) along with the SST_4 agonist's capacity to enhance Aβ catabolism within the brain (Sandoval et al., 2012, 2013, 2019; Nilsson et al., 2020).

Memantine, a low-affinity noncompetitive voltage-dependent NMDA receptor antagonist blocks the excitotoxic effects of glutamate that can lead to neuronal dysfunction. It was the first drug approved by the FDA to treat moderate-to-severe AD. Early memantine studies identified cognitive improvements in moderate-to-severe AD patients, with and without coadministration of a ChEI (Reisberg et al., 2003; Tariot et al., 2004). Yet, recent evaluations of memantine in those with moderate-to-severe AD across more comprehensive data sets show only a small clinical benefit while being ineffective in mild AD (McShane et al., 2019). Although the use of a more potent NMDA antagonists has been suggested (Selkoe, 2019), the side effects of memantine are already extensive (Rossom et al., 2004), rendering such an approach problematic, whereas SRIF mitigates glutamate release and associated neuronal hyperexcitability through receptor activation (Boehm and Betz, 1997; Tallent and Siggins, 1997; Kozhemyakin et al., 2013), with evidence supporting SST_4 mediation of this effect (Qiu et al., 2008; Aourz et al., 2011; Hou and Yu, 2013). Thus, a combination of memantine and an SST_4 agonist may allow for lower effective dosing of memantine in AD treatment, reducing side effects and prolonging beneficial effects.

Alleviation of AD comorbid neuropsychiatric symptoms and seizures present another promising aspect of an SST_4 agonist approach. Unsurprisingly, these conditions share neurologic and neurochemical characteristics, with the loss of SRIF and SRIF-expressing neurons being a prominent feature in alignment with AD. Individuals with epilepsy are more likely to develop certain neuropsychiatric disorders, whereas those with neuropsychiatric disorders are more likely to develop epilepsy (Tolchin et al., 2020). Upwards of 50% of individuals with epilepsy present a neuropsychiatric comorbidities (Salpekar and Mula, 2019). A poorer AD prognosis is also associated with the presentation of neuropsychiatric symptoms (Palmer et al., 2010; Spalletta et al., 2012, 2015; Agüera-Ortiz et al., 2021) and seizures (Breteler et al., 1995; Cordonnier et al., 2007; Costa et al., 2019; Gourmaud et al., 2020; Tsai et al., 2021). These conditions, which are already difficult to treat independent of AD, can be particularly difficult to treat in those with AD. A recent study observed that the use of atypical antipsychotics for treating neuropsychiatric symptoms in those with AD had no effect on improving neuropsychiatric symptoms and was associated with a decline in cognitive and global function (Oh et al., 2021). A systematic literature review further demonstrated that atypical antipsychotics for the treatment of dementia-related psychosis in older adults are associated with a small numerical symptom improvement but with a high risk of adverse events, including cognitive decline and potentially higher mortality (Yunusa et al., 2021). Antiseizure medication outcomes fair little better. Antiseizure medication side effects range from reduced cognition and enhanced agitation to hyponatremia and decreased bone density (Vossel et al., 2017). Preclinical studies support SST_4 agonist use for the mitigation of both neuropsychiatric symptoms (Scheich et al., 2016; Prévôt et al., 2017) and seizure severity (Qiu et al., 2008; Cammalleri et al., 2009; Aourz et al., 2011; Hou and Yu, 2013). Although the effectiveness of an SST_4 agonist approach for these conditions in humans requires additional research, current data provide a sound footing for human investigation that could run in tandem with larger AD clinical trials. There is also a strong argument for the evaluation of an SST_4 agonist for the treatment of neuropsychiatric symptoms and seizures independent of AD given the high rate of drug resistance to many currently used medications (Bystritsky, 2006; Voineskos et al., 2020; Fattorusso et al., 2021).

Beyond direct SST agonist targeting, pathways involved in SRIF and SRIF-expressing neuron regulation provide additional avenues for therapeutic development. BDNF induces SRIF gene expression (Villuendas et al., 2001; Sánchez-Muñoz et al., 2011), supports SRIF-expressing interneuron survival (Grosse et al., 2005), and is associated with a reduction in Aβ aggregation, Aβ-induced neurotoxicity, and synaptic dysfunction (Caffino et al., 2020). IGF1 produces a protective effect against Aβ respective to enhanced SRIF tone and SST expression (Aguado-Llera et al., 2005, 2018), with hippocampal IGF1 protein expression linked to the maintenance of neuronal integrity and cognitive function (Sun et al., 2005). Estrogens protect from Aβ-induced cell death and prevent the depletion of hippocampal SRIF through an IGF1-mediated mechanism (Perianes-Cachero et al., 2015) as well as improve synaptic plasticity, diminish brain inflammation, and reduce Aβ-associated injury (Uddin et al., 2020). Although eIF2α phosphorylation is involved in inflammation (Lourenco et al., 2013), epilepsy (Carnevalli et al., 2004, 2006), and neuronal degeneration in AD tissue (Chang et al., 2002; Oliveira and Klann, 2022), dephosphorylation of eIF2α in SRIF-expressing interneurons promotes memory formation (Sharma et al., 2020). Phosphorylation of eEF2 is also identified with AD synaptic failure and cognitive impairments (Ma, 2023), impacting BDNF and depression (Nosyreva and Kavalali, 2010; Autry et al., 2011) as well as the excitatory-inhibitory balance of GABAergic neurons (Heise et al., 2017). Each of these molecules present pharmacological targets with advantages and disadvantages that reach beyond the SRIF and SRIF-expressing neurons yet highlight the underlying theory as to SRIF-mediated mechanisms

capable of enhancing cognition and/or reducing the pathological influence of Aβ.

VII. Conclusions

Over 4 decades of research across cellular, animal, and human studies establish the substantial interconnections between SRIF and AD. The loss of SRIF and SRIF-expressing neurons in the brains of AD patients drives a series of pathologic changes linked to nearly every AD symptom (Fig. 1). Although research into the mechanisms that underlie the vulnerability of SRIF-expressing neurons is ongoing, the considerable evidence presented in this review supports SSTs as valid targets for AD treatment. Among the SSTs, SST_4 presents ideal attributes. Moving forward, careful consideration needs to be given to small-molecule design. A small-molecule program must not only focus on receptor affinity and selectivity but optimization of pharmacokinetics and BBB permeability. A successful drug candidate will not only depend on the effective exploitation of the encompassing knowledge of SRIF analog design but a holistic understanding of AD pathological progression toward appropriate clinical trial design and outcomes assessment. Although there remains more to be learned of the SRIF-AD interconnection, drug discovery and development must advance to the testing of our most promising targets.

Data Availability

This review article contains no datasets generated or analyzed during the present study.

Authorship Contributions

Wrote or contributed to the writing of the manuscript: Sandoval, Witt.

References

Actor-Engel HS, Schwartz SL, Crosby KC, Sinnen BL, Prikhodko O, Ramsay HJ, Bourne JN, Winborn CS, Lucas A, Smith KR, et al. (2021) Precision Mapping of Amyloid-beta Binding Reveals Perisynaptic Localization and Spatially Restricted Plasticity Deficits. *eNeuro* **8**:ENEURO.0416-21.2021.

Adams RA, Bush D, Zheng F, Meyer SS, Kaplan R, Orfanos S, Marques TR, Howes OD, and Burgess N (2020) Impaired theta phase coupling underlies frontotemporal dysconnectivity in schizophrenia. *Brain* **143**:1261–1277.

Agren H and Lundqvist G (1984) Low levels of somatostatin in human CSF mark depressive episodes. *Psychoneuroendocrinology* **9**:233–248.

Aguado-Llera D, Arilla-Ferreiro E, Campos-Barros A, Puebla-Jiménez L, and Barrios V (2005) Protective effects of insulin-like growth factor-I on the somatostatinergic system in the temporal cortex of beta-amyloid-treated rats. *J Neurochem* **92**:607–615.

Aguado-Llera D, Canelles S, Frago LM, Chowen JA, Argente J, Arilla E, and Barrios V (2018) The Protective Effects of IGF-I against beta-Amyloid-related Downregulation of Hippocampal Somatostatinergic System Involve Activation of Akt and Protein Kinase A. *Neuroscience* **374**:104–118.

Agüera-Ortiz L, García-Ramos R, Grandas Pérez FJ, López-Álvarez J, Montes Rodríguez JM, Olazarán Rodríguez FJ, Olivera Pueyo J, Pelegrin Valero C, and Porta-Etessam J (2021) Depression in Alzheimer's Disease: A Delphi Consensus on Etiology, Risk Factors, and Clinical Management. *Front Psychiatry* **12**:638651.

Aizenstein HJ, Nebes RD, Saxton JA, Price JC, Mathis CA, Tsopelas ND, Ziolko SK, James JA, Snitz BE, Houck PR, et al. (2008) Frequent amyloid deposition without significant cognitive impairment among the elderly. *Arch Neurol* **65**:1509–1517.

Akay M, Wang K, Akay YM, Dragomir A, and Wu J (2009) Nonlinear dynamical analysis of carbachol induced hippocampal oscillations in mice. *Acta Pharmacol Sin* **30**:859–867.

Almeida VN and Radanovic M (2022) Semantic processing and neurobiology in Alzheimer's disease and Mild Cognitive Impairment. *Neuropsychologia* **174**:108337.

Altmann A, Tian L, Henderson VW, and Greicius MD; Alzheimer's Disease Neuroimaging Initiative Investigators (2014) Sex modifies the APOE-related risk of developing Alzheimer disease. *Ann Neurol* **75**:563–573.

Alzheimer's Association (2023) Alzheimer's disease facts and figures. *Alzheimers Dement* **19**:1598–1695.

Ampofo E, Nalbach L, Menger MD, and Laschke MW (2020) Regulatory Mechanisms of Somatostatin Expression. *Int J Mol Sci* **21**:4170.

Andrade-Talavera Y and Rodríguez-Moreno A (2021) Synaptic Plasticity and Oscillations in Alzheimer's Disease: A Complex Picture of a Multifaceted Disease. *Front Mol Neurosci* **14**:696476.

Andrews-Zwilling Y, Bien-Ly N, Xu Q, Li G, Bernardo A, Yoon SY, Zwilling D, Yan TX, Chen L, and Huang Y (2010) Apolipoprotein E4 causes age- and Tau-dependent impairment of GABAergic interneurons, leading to learning and memory deficits in mice. *J Neurosci* **30**:13707–13717.

Aourz N, De Bundel D, Stragier B, Clinckers R, Portelli J, Michotte Y, and Smolders I (2011) Rat hippocampal somatostatin sst3 and sst4 receptors mediate anticonvulsive effects in vivo: indications of functional interactions with sst2 receptors. *Neuropharmacology* **61**:1327–1333.

Araujo DM, Lapchak PA, Collier B, and Quirion R (1990) Evidence that somatostatin enhances endogenous acetylcholine release in the rat hippocampus. *J Neurochem* **55**:1546–1555.

Arbo BD, Cechinel LR, Palazzo RP, and Siqueira IR (2020) Endosomal dysfunction impacts extracellular vesicle release: Central role in Abeta pathology. *Ageing Res Rev* **58**:101006.

Ardayfio P and Kim K-S (2006) Anxiogenic-like effect of chronic corticosterone in the light-dark emergence task in mice. *Behav Neurosci* **120**:249–256.

Atack JR, Beal MF, May C, Kaye JA, Mazurek MF, Kay AD, and Rapoport SI (1988) Cerebrospinal fluid somatostatin and neuropeptide Y. Concentrations in aging and in dementia of the Alzheimer type with and without extrapyramidal signs. *Arch Neurol* **45**:269–274.

Autry AE, Adachi M, Nosyreva E, Na ES, Los MF, Cheng P-F, Kavalali ET, and Monteggia LM (2011) NMDA receptor blockade at rest triggers rapid behavioural antidepressant responses. *Nature* **475**:91–95.

Bai L, Zhang X, Li X, Liu N, Lou F, Ma H, Luo X, and Ren Y (2015) Somatostatin prevents lipopolysaccharide-induced neurodegeneration in the rat substantia nigra by inhibiting the activation of microglia. *Mol Med Rep* **12**:1002–1008.

Banks WA, Schally AV, Barrera CM, Fasold MB, Durham DA, Csernus VJ, Groot K, and Kastin AJ (1990) Permeability of the murine blood-brain barrier to some octapeptide analogs of somatostatin. *Proc Natl Acad Sci USA* **87**:6762–6766.

Barrimi M, Aalouane R, Aarab C, Hafidi H, Baybay H, Soughi M, Tachfouti N, Nejjari C, Mernissi FZ, and Rammouz I (2013) [Prolonged corticosteroid-therapy and anxiety-depressive disorders, longitudinal study over 12 months]. *Encephale* **39**:59–65.

Basivireddy J, Somvanshi RK, Romero IA, Weksler BB, Couraud P-O, Oger J, and Kumar U (2013) Somatostatin preserved blood brain barrier against cytokine induced alterations: possible role in multiple sclerosis. *Biochem Pharmacol* **86**:497–507.

Beal MF, Mazurek MF, Svendsen CN, Bird ED, and Martin JB (1986) Widespread reduction of somatostatin-like immunoreactivity in the cerebral cortex in Alzheimer's disease. *Ann Neurol* **20**:489–495.

Beal MF, Mazurek MF, Tran VT, Chattha G, Bird ED, and Martin JB (1985) Reduced numbers of somatostatin receptors in the cerebral cortex in Alzheimer's disease. *Science* **229**:289–291.

Bekris LM, Yu C-E, Bird TD, and Tsuang DW (2010) Genetics of Alzheimer disease. *J Geriatr Psychiatry Neurol* **23**:213–227.

Benedetti F, Aggio V, Pratesi ML, Greco G, and Furlan R (2020) Neuroinflammation in Bipolar Depression. *Front Psychiatry* **11**:71.

Bergström L, Garlind A, Nilsson L, Alafuzoff I, Fowler CJ, Winblad B, and Cowburn RF (1991) Regional distribution of somatostatin receptor binding and modulation of adenylyl cyclase activity in Alzheimer's disease brain. *J Neurol Sci* **105**:225–233.

Bero AW, Yan P, Roh JH, Cirrito JR, Stewart FR, Raichle ME, Lee J-M, and Holtzman DM (2011) Neuronal activity regulates the regional vulnerability to amyloid-beta deposition. *Nat Neurosci* **14**:750–756.

Bissette G, Cook L, Smith W, Dole KC, Crain B, and Nemeroff CB (1998) Regional Neuropeptide Pathology in Alzheimer's Disease: Corticotropin-Releasing Factor and Somatostatin. *J Alzheimers Dis* **1**:91–105.

Bissette G, Widerlöv E, Walléus H, Karlsson I, Eklund K, Forsman A, and Nemeroff CB (1986) Alterations in cerebrospinal fluid concentrations of somatostatinlike immunoreactivity in neuropsychiatric disorders. *Arch Gen Psychiatry* **43**:1148–1151.

Björk BF, Katzov H, Kehoe P, Fratiglioni L, Winblad B, Prince JA, and Graff C (2007) Positive association between risk for late-onset Alzheimer disease and genetic variation in IDE. *Neurobiol Aging* **28**:1374–1380.

Blanchard V, Moussaoui S, Czech C, Touchet N, Bonici B, Planche M, Canton T, Jedidi I, Gohin M, Wirths O, et al. (2003) Time sequence of maturation of dystrophic neurites associated with Abeta deposits in APP/PS1 transgenic mice. *Exp Neurol* **184**:247–263.

Bo Q, Yang F, Li Y, Meng X, Zhang H, Zhou Y, Ling S, Sun D, Lv P, Liu L, et al. (2022) Structural insights into the activation of somatostatin receptor 2 by cyclic SST analogues. *Cell Discov* **8**:47.

Boehm S and Betz H (1997) Somatostatin inhibits excitatory transmission at rat hippocampal synapses via presynaptic receptors. *J Neurosci* **17**:4066–4075.

Bollók I, Vécsei L, and Telegdy G (1983) The effects of interaction between propranolol and somatostatin on the active avoidance behavior, open-field activity and electroconvulsive shock-induced amnesia of rats. *Neuropeptides* **3**:263–270.

Bonanno G, Carità F, Cavazzani P, Munari C, and Raiteri M (1999) Selective block of rat and human neocortex GABA(B) receptors regulating somatostatin release by a

GABA(B) antagonist endowed with cognition enhancing activity. *Neuropharmacology* **38**:1789–1795.
Brazeau P, Vale W, Burgus R, Ling N, Butcher M, Rivier J, and Guillemin R (1973) Hypothalamic polypeptide that inhibits the secretion of immunoreactive pituitary growth hormone. *Science* **179**:77–79.
Breteler MM, de Groot RR, van Romunde LK, and Hofman A (1995) Risk of dementia in patients with Parkinson's disease, epilepsy, and severe head trauma: a register-based follow-up study. *Am J Epidemiol* **142**:1300–1305.
Brown MR, Rivier C, and Vale W (1984) Central nervous system regulation of adrenocorticotropin secretion: role of somatostatins. *Endocrinology* **114**:1546–1549.
Brown ES, Rush AJ, and McEwen BS (1999) Hippocampal remodeling and damage by corticosteroids: implications for mood disorders. *Neuropsychopharmacology* **21**:474–484.
Burgos-Ramos E, Hervás-Aguilar A, Puebla-Jiménez L, Boyano-Adánez MC, and Arilla-Ferreiro E (2007) Chronic but not acute intracerebroventricular administration of amyloid beta-peptide(25-35) decreases somatostatin content, adenylate cyclase activity, somatostatin-induced inhibition of adenylate cyclase activity, and adenylate cyclase I levels in the rat hippocampus. *J Neurosci Res* **85**:433–442.
Busche MA, Chen X, Henning HA, Reichwald J, Staufenbiel M, Sakmann B, and Konnerth A (2012) Critical role of soluble amyloid-beta for early hippocampal hyperactivity in a mouse model of Alzheimer's disease. *Proc Natl Acad Sci USA* **109**:8740–8745.
Busche MA, Eichhoff G, Adelsberger H, Abramowski D, Wiederhold K-H, Haass C, Staufenbiel M, Konnerth A, and Garaschuk O (2008) Clusters of hyperactive neurons near amyloid plaques in a mouse model of Alzheimer's disease. *Science* **321**:1686–1689.
Bystritsky A (2006) Treatment-resistant anxiety disorders. *Mol Psychiatry* **11**:805–814.
Cabrejo L, Guyant-Maréchal L, Laquerrière A, Vercelletto M, De la Fournière F, Thomas-Antérion C, Verny C, Letournel F, Pasquier F, Vital A, et al. (2006) Phenotype associated with APP duplication in five families. *Brain* **129**:2966–2976.
Caffino L, Mottarlini F, and Fumagalli F (2020) Born to Protect: Leveraging BDNF Against Cognitive Deficit in Alzheimer's Disease. *CNS Drugs* **34**:281–297.
Cammalleri M, Cervia D, Dal Monte M, Martini D, Langenegger D, Fehlmann D, Feuerbach D, Pavan B, Hoyer D, and Bagnoli P (2006) Compensatory changes in the hippocampus of somatostatin knockout mice: upregulation of somatostatin receptor 2 and its function in the control of bursting activity and synaptic transmission. *Eur J Neurosci* **23**:2404–2422.
Cammalleri M, Cervia D, Langenegger D, Liu Y, Dal Monte M, Hoyer D, and Bagnoli P (2004) Somatostatin receptors differentially affect spontaneous epileptiform activity in mouse hippocampal slices. *Eur J Neurosci* **20**:2711–2721.
Cammalleri M, Martini D, Timperio AM, and Bagnoli P (2009) Functional effects of somatostatin receptor 1 activation on synaptic transmission in the mouse hippocampus. *J Neurochem* **111**:1466–1477.
Carnevalli LS, Pereira CM, Jaqueta CB, Alves VS, Paiva VN, Vattem KM, Wek RC, Mello LEAM, and Castilho BA (2006) Phosphorylation of the alpha subunit of translation initiation factor-2 by PKR mediates protein synthesis inhibition in the mouse brain during status epilepticus. *Biochem J* **397**:187–194.
Carnevalli LS, Pereira CM, Longo BM, Jaqueta CB, Avedissian M, Mello LEAM, and Castilho BA (2004) Phosphorylation of translation initiation factor eIF2alpha in the brain during pilocarpine-induced status epilepticus in mice. *Neurosci Lett* **357**:191–194.
Carpenter JE, Jackson W, de Souza GA, Haarr L, and Grose C (2010) Insulin-degrading enzyme binds to the nonglycosylated precursor of varicella-zoster virus gE protein found in the endoplasmic reticulum. *J Virol* **84**:847–855.
Castegnetti G, Bush D, and Bach DR (2021) Model of theta frequency perturbations and contextual fear memory. *Hippocampus* **31**:448–457.
Castrén E and Monteggia LM (2021) Brain-Derived Neurotrophic Factor Signaling in Depression and Antidepressant Action. *Biol Psychiatry* **90**:128–136.
Cavedo E, Dubois B, Colliot O, Lista S, Croisile B, Tisserand GL, Touchon J, Bonafe A, Ousset PJ, Rouaud O, et al.; Hippocampus Study Group (2016) Reduced Regional Cortical Thickness Rate of Change in Donepezil-Treated Subjects With Suspected Prodromal Alzheimer's Disease. *J Clin Psychiatry* **77**:e1631–e1638.
Chai AB, Lam HHJ, Kockx M, and Gelissen IC (2021) Apolipoprotein E isoform-dependent effects on the processing of Alzheimer's amyloid-beta. *Biochim Biophys Acta Mol Cell Biol Lipids* **1866**:158980.
Chang RCC, Wong AKY, Ng H-K, and Hugon J (2002) Phosphorylation of eukaryotic initiation factor-2alpha (eIF2alpha) is associated with neuronal degeneration in Alzheimer's disease. *Neuroreport* **13**:2429–2432.
Chauhan P, Philip SE, Chauhan G, and Mehra S (2022) The anatomical basis of seizures, in *Epilepsy* (Czuczwar SJ, ed) pp 15–23, Brisbane, Australia.
Chen T-S, Huang T-H, Lai M-C, and Huang C-W (2023) The Role of Glutamate Receptors in Epilepsy. *Biomedicines* **11**:783.
Chen N, Sugihara H, and Sur M (2015) An acetylcholine-activated microcircuit drives temporal dynamics of cortical activity. *Nat Neurosci* **18**:892–902.
Chen C-H, Zhou W, Liu S, Deng Y, Cai F, Tone M, Tone Y, Tong Y, and Song W (2012) Increased NF-kappaB signalling up-regulates BACE1 expression and its therapeutic potential in Alzheimer's disease. *Int J Neuropsychopharmacol* **15**:77–90.
Cheng C-H, Liu C-J, Ou S-M, Yeh C-M, Chen T-J, Lin Y-Y, and Wang S-J (2015) Incidence and risk of seizures in Alzheimer's disease: A nationwide population-based cohort study. *Epilepsy Res* **115**:63–66.
Christenn M, Kindler S, Schulz S, Buck F, Richter D, and Kreienkamp H-J (2007) Interaction of brain somatostatin receptors with the PDZ domains of PSD-95. *FEBS Lett* **581**:5173–5177.
Christensen DZ, Schneider-Axmann T, Lucassen PJ, Bayer TA, and Wirths O (2010) Accumulation of intraneuronal Abeta correlates with ApoE4 genotype. *Acta Neuropathol* **119**:555–566.
Chung H, Brazil MI, Irizarry MC, Hyman BT, and Maxfield FR (2001) Uptake of fibrillar beta-amyloid by microglia isolated from MSR-A (type I and type II) knockout mice. *Neuroreport* **12**:1151–1154.
Chung H, Park K, Jang HJ, Kohl MM, and Kwag J (2020) Dissociation of somatostatin and parvalbumin interneurons circuit dysfunctions underlying hippocampal theta and gamma oscillations impaired by amyloid beta oligomers in vivo. *Brain Struct Funct* **225**:935–954.
Ciaccio C, Tundo GR, Grasso G, Spoto G, Marasco D, Ruvo M, Gioia M, Rizzarelli E, and Coletta M (2009) Somatostatin: a novel substrate and a modulator of insulin-degrading enzyme activity. *J Mol Biol* **385**:1556–1567.
Cirrito JR, Kang J-E, Lee J, Stewart FR, Verges DK, Silverio LM, Bu G, Mennerick S, and Holtzman DM (2008) Endocytosis is required for synaptic activity-dependent release of amyloid-beta in vivo. *Neuron* **58**:42–51.
Cirrito JR, Yamada KA, Finn MB, Sloviter RS, Bales KR, May PC, Schoepp DD, Paul SM, Mennerick S, and Holtzman DM (2005) Synaptic activity regulates interstitial fluid amyloid-beta levels in vivo. *Neuron* **48**:913–922.
Colgin LL (2016) Rhythms of the hippocampal network. *Nat Rev Neurosci* **17**:239–249.
Combs CK, Karlo JC, Kao SC, and Landreth GE (2001) beta-Amyloid stimulation of microglia and monocytes results in TNFalpha-dependent expression of inducible nitric oxide synthase and neuronal apoptosis. *J Neurosci* **21**:1179–1188.
Conlon JM, Tostivint H, and Vaudry H (1997) Somatostatin- and urotensin II-related peptides: molecular diversity and evolutionary perspectives. *Regul Pept* **69**:95–103.
Connolly NMC, Theurey P, and Pizzo P (2019) Glucose dysregulation in pre-clinical Alzheimer's disease. *Aging (Albany NY)* **11**:5296–5297.
Consortium GT (2020) The GTEx Consortium atlas of genetic regulatory effects across human tissues. *Science* **369**:1318–1330.
Cook DG, Leverenz JB, McMillan PJ, Kulstad JJ, Ericksen S, Roth RA, Schellenberg GD, Jin L-W, Kovacina KS, and Craft S (2003) Reduced hippocampal insulin-degrading enzyme in late-onset Alzheimer's disease is associated with the apolipoprotein E-epsilon4 allele. *Am J Pathol* **162**:313–319.
Cordonnier C, Hénon H, Derambure P, Pasquier F, and Leys D (2007) Early epileptic seizures after stroke are associated with increased risk of new-onset dementia. *J Neurol Neurosurg Psychiatry* **78**:514–516.
Costa C, Romoli M, Liguori C, Farotti L, Eusebi P, Bedetti C, Siliquini S, Cesarini EN, Romigi A, Mercuri NB, et al. (2019) Alzheimer's disease and late-onset epilepsy of unknown origin: two faces of beta amyloid pathology. *Neurobiol Aging* **73**:61–67.
Courtney C, Farrell D, Gray R, Hills R, Lynch L, Sellwood E, Edwards S, Hardyman W, Raftery J, Crome P, et al.; AD2000 Collaborative Group (2004) Long-term donepezil treatment in 565 patients with Alzheimer's disease (AD2000): randomised double-blind trial. *Lancet* **363**:2105–2115.
Couzin-Frankel J (2023) Alzheimer's drug approval gets a mixed reception. *Science* **379**:126–127.
Craft S, Asthana S, Newcomer JW, Wilkinson CW, Matos IT, Baker LD, Cherrier M, Lofgreen C, Latendresse S, Petrova A, et al. (1999) Enhancement of memory in Alzheimer disease with insulin and somatostatin, but not glucose. *Arch Gen Psychiatry* **56**:1135–1140.
Csaba Z, Pirker S, Lelouvier B, Simon A, Videau C, Epelbaum J, Czech T, Baumgartner C, Sperk G, and Dournaud P (2005) Somatostatin receptor type 2 undergoes plastic changes in the human epileptic dentate gyrus. *J Neuropathol Exp Neurol* **64**:956–969.
Csaba Z, Richichi C, Bernard V, Epelbaum J, Vezzani A, and Dournaud P (2004) Plasticity of somatostatin and somatostatin sst2A receptors in the rat dentate gyrus during kindling epileptogenesis. *Eur J Neurosci* **19**:2531–2538.
Cullinan WE and Wolfe TJ (2000) Chronic stress regulates levels of mRNA transcripts encoding beta subunits of the GABA(A) receptor in the rat stress axis. *Brain Res* **887**:118–124.
Cummings JL, Tong G, and Ballard C (2019) Treatment Combinations for Alzheimer's Disease: Current and Future Pharmacotherapy Options. *J Alzheimers Dis* **67**:779–794.
Cutler NR, Haxby JV, Narang PK, May C, Burg C, and Reines SA (1985) Evaluation of an analogue of somatostatin (L363,586) in Alzheimer's disease. *N Engl J Med* **312**:725.
Czéh B, Varga ZKK, Henningsen K, Kovács GL, Miseta A, and Wiborg O (2015) Chronic stress reduces the number of GABAergic interneurons in the adult rat hippocampus, dorsal-ventral and region-specific differences. *Hippocampus* **25**:393–405.
David DJ, Samuels BA, Rainer Q, Wang J-W, Marsteller D, Mendez I, Drew M, Craig DA, Guiard BP, Guilloux J-P, et al. (2009) Neurogenesis-dependent and -independent effects of fluoxetine in an animal model of anxiety/depression. *Neuron* **62**:479–493.
Davies P, Katzman R, and Terry RD (1980) Reduced somatostatin-like immunoreactivity in cerebral cortex from cases of Alzheimer disease and Alzheimer senile dementa. *Nature* **288**:279–280.
Davis KL, Davidson M, Yang RK, Davis BM, Siever LJ, Mohs RC, Ryan T, Coccaro E, Bierer L, and Targum SD (1988) CSF somatostatin in Alzheimer's disease, depressed patients, and control subjects. *Biol Psychiatry* **24**:710–712.
De Felice FG, Velasco PT, Lambert MP, Viola K, Fernandez SJ, Ferreira ST, and Klein WL (2007) Abeta oligomers induce neuronal oxidative stress through an N-methyl-D-aspartate receptor-dependent mechanism that is blocked by the Alzheimer drug memantine. *J Biol Chem* **282**:11590–11601.
De Felice FG, Wu D, Lambert MP, Fernandez SJ, Velasco PT, Lacor PN, Bigio EH, Jerecic J, Acton PJ, Shughrue PJ, et al. (2008) Alzheimer's disease-type neuronal tau hyperphosphorylation induced by A beta oligomers. *Neurobiol Aging* **29**:1334–1347.
de Lecea L, Ruiz-Lozano P, Danielson PE, Peelle-Kirley J, Foye PE, Frankel WN, and Sutcliffe JG (1997) Cloning, mRNA expression, and chromosomal mapping of mouse and human preprocortistatin. *Genomics* **42**:499–506.

de Tullio MB, Castelletto V, Hamley IW, Martino Adami PV, Morelli L, and Castaño EM (2013) Proteolytically inactive insulin-degrading enzyme inhibits amyloid formation yielding non-neurotoxic abeta peptide aggregates. *PLoS One* **8**:e59113.
de Tullio MB, Morelli L, and Castaño EM (2008) The irreversible binding of amyloid peptide substrates to insulin-degrading enzyme: a biological perspective. *Prion* **2**:51–56.
Decker H, Lo KY, Unger SM, Ferreira ST, and Silverman MA (2010) Amyloid-beta peptide oligomers disrupt axonal transport through an NMDA receptor-dependent mechanism that is mediated by glycogen synthase kinase 3beta in primary cultured hippocampal neurons. *J Neurosci* **30**:9166–9171.
Dejakaisaya H, Kwan P, and Jones NC (2021) Astrocyte and glutamate involvement in the pathogenesis of epilepsy in Alzheimer's disease. *Epilepsia* **62**:1485–1493.
Delfs JR and Dichter MA (1983) Effects of somatostatin on mammalian cortical neurons in culture: physiological actions and unusual dose response characteristics. *J Neurosci* **3**:1176–1188.
DeNoble VJ, Hepler DJ, and Barto RA (1989) Cysteamine-induced depletion of somatostatin produces differential cognitive deficits in rats. *Brain Res* **482**:42–48.
Devanand DP, Michaels-Marston KS, Liu X, Pelton GH, Padilla M, Marder K, Bell K, Stern Y, and Mayeux R (2000) Olfactory deficits in patients with mild cognitive impairment predict Alzheimer's disease at follow-up. *Am J Psychiatry* **157**:1399–1405.
Dietlin S, Soto M, Kiyasova V, Pueyo M, de Mauleon A, Delrieu J, Ousset PJ, and Vellas B (2019) Neuropsychiatric Symptoms and Risk of Progression to Alzheimer's Disease Among Mild Cognitive Impairment Subjects. *J Alzheimers Dis* **70**:25–34.
Doody RS, Dunn JK, Clark CM, Farlow M, Foster NL, Liao T, Gonzales N, Lai E, and Massman P (2001) Chronic donepezil treatment is associated with slowed cognitive decline in Alzheimer's disease. *Dement Geriatr Cogn Disord* **12**:295–300.
Doraiswamy PM, Krishnan KRR, Anand R, Sohn H, Danyluk J, Hartman RD, and Veach J (2002) Long-term effects of rivastigmine in moderately severe Alzheimer's disease: does early initiation of therapy offer sustained benefits? *Prog Neuropsychopharmacol Biol Psychiatry* **26**:705–712.
Dournaud P, Boudin H, Schonbrunn A, Tannenbaum GS, and Beaudet A (1998) Interrelationships between somatostatin sst2A receptors and somatostatin-containing axons in rat brain: evidence for regulation of cell surface receptors by endogenous somatostatin. *J Neurosci* **18**:1056–1071.
Dournaud P, Delaere P, Hauw JJ, and Epelbaum J (1995) Differential correlation between neurochemical deficits, neuropathology, and cognitive status in Alzheimer's disease. *Neurobiol Aging* **16**:817–823.
Dubois B, Chupin M, Hampel H, Lista S, Cavedo E, Croisile B, Louis Tisserand G, Touchon J, Bonafe A, Ousset PJ, et al.; Hippocampus Study Group (2015) Donepezil decreases annual rate of hippocampal atrophy in suspected prodromal Alzheimer's disease. *Alzheimers Dement* **11**:1041–1049.
Dulawa SC and Janowsky DS (2019) Cholinergic regulation of mood: from basic and clinical studies to emerging therapeutics. *Mol Psychiatry* **24**:694–709.
Duman RS, Sanacora G, and Krystal JH (2019) Altered Connectivity in Depression: GABA and Glutamate Neurotransmitter Deficits and Reversal by Novel Treatments. *Neuron* **102**:75–90.
Dun NJ, Dun SL, Wong RK, and Förstermann U (1994) Colocalization of nitric oxide synthase and somatostatin immunoreactivity in rat dentate hilar neurons. *Proc Natl Acad Sci USA* **91**:2955–2959.
Edwards-Lee T, Ringman JM, Chung J, Werner J, Morgan A, St George Hyslop P, Thompson P, Dutton R, Mlikotic A, Rogaeva E, et al. (2005) An African American family with early-onset Alzheimer disease and an APP (T714I) mutation. *Neurology* **64**:377–379.
Elekes K, Helyes Z, Kereskai L, Sándor K, Pintér E, Pozsgai G, Tékus V, Bánvölgyi A, Németh J, Szuts T, et al. (2008) Inhibitory effects of synthetic somatostatin receptor subtype 4 agonists on acute and chronic airway inflammation and hyperreactivity in the mouse. *Eur J Pharmacol* **578**:313–322.
Endo T, Yanagawa Y, and Komatsu Y (2016) Substance P Activates Ca2+-Permeable Nonselective Cation Channels through a Phosphatidylcholine-Specific Phospholipase C Signaling Pathway in nNOS-Expressing GABAergic Neurons in Visual Cortex. *Cereb Cortex* **26**:669–682.
Engin E, Stellbrink J, Treit D, and Dickson CT (2008) Anxiolytic and antidepressant effects of intracerebroventricularly administered somatostatin: behavioral and neurophysiological evidence. *Neuroscience* **157**:666–676.
Engin E and Treit D (2009) Anxiolytic and antidepressant actions of somatostatin: the role of sst2 and sst3 receptors. *Psychopharmacology (Berl)* **206**:281–289.
Epelbaum J, Lamour Y, Enjalbert A, Hamon M, Dutar P, and Kordon C (1986) Modifications in the cortical regional distribution of choline acetyltransferase, somatostatin and somatostatin binding sites in the normal rat and following lesion of the nucleus basalis. *Brain Res* **371**:376–379.
Ertekin-Taner N, Allen M, Fadale D, Scanlin L, Younkin L, Petersen RC, Graff-Radford N, and Younkin SG (2004) Genetic variants in a haplotype block spanning IDE are significantly associated with plasma Abeta42 levels and risk for Alzheimer disease. *Hum Mutat* **23**:334–342.
Esparza TJ, Zhao H, Cirrito JR, Cairns NJ, Bateman RJ, Holtzman DM, and Brody DL (2013) Amyloid-beta oligomerization in Alzheimer dementia versus high-pathology controls. *Ann Neurol* **73**:104–119.
Espinosa N, Alonso A, Caneo M, Moran C, and Fuentealba P (2022) Optogenetic Suppression of Lateral Septum Somatostatin Neurons Enhances Hippocampus Cholinergic Theta Oscillations and Local Synchrony. *Brain Sci* **13**:1.
Fanselow MS (2010) From contextual fear to a dynamic view of memory systems. *Trends Cogn Sci* **14**:7–15.
Farlow MR and Lilly ML; ENA713 B352 Study Group (2005) Rivastigmine: an open-label, observational study of safety and effectiveness in treating patients with Alzheimer's disease for up to 5 years. *BMC Geriatr* **5**:3.
Farris W, Mansourian S, Chang Y, Lindsley L, Eckman EA, Frosch MP, Eckman CB, Tanzi RE, Selkoe DJ, and Guenette S (2003) Insulin-degrading enzyme regulates the levels of insulin, amyloid beta-protein, and the beta-amyloid precursor protein intracellular domain in vivo. *Proc Natl Acad Sci USA* **100**:4162–4167.
Fattorusso A, Matricardi S, Mencaroni E, Dell'Isola GB, Di Cara G, Striano P, and Verrotti A (2021) The Pharmacoresistant Epilepsy: An Overview on Existant and New Emerging Therapies. *Front Neurol* **12**:674483.
Fee C, Prevot TD, Misquitta K, Knutson DE, Li G, Mondal P, Cook JM, Banasr M, and Sibille E (2021) Behavioral Deficits Induced by Somatostatin-Positive GABA Neuron Silencing Are Rescued by Alpha 5 GABA-A Receptor Potentiation. *Int J Neuropsychopharmacol* **24**:505–518.
Fehlmann D, Langenegger D, Schuepbach E, Siehler S, Feuerbach D, and Hoyer D (2000) Distribution and characterisation of somatostatin receptor mRNA and binding sites in the brain and periphery. *J Physiol Paris* **94**:265–281.
Ferretti MT, Bruno MA, Ducatenzeiler A, Klein WL, and Cuello AC (2012) Intracellular Abeta-oligomers and early inflammation in a model of Alzheimer's disease. *Neurobiol Aging* **33**:1329–1342.
Fitzgerald LW and Dokla CP (1989) Morris water task impairment and hypoactivity following cysteamine-induced reductions of somatostatin-like immunoreactivity. *Brain Res* **505**:246–250.
Fleisher-Berkovich S, Filipovich-Rimon T, Ben-Shmuel S, Hülsmann C, Kummer MP, and Heneka MT (2010) Distinct modulation of microglial amyloid beta phagocytosis and migration by neuropeptides. *J Neuroinflammation* **7**:61.
Floden AM, Li S, and Combs CK (2005) Beta-amyloid-stimulated microglia induce neuron death via synergistic stimulation of tumor necrosis factor alpha and NMDA receptors. *J Neurosci* **25**:2566–2575.
Fontana G, De Bernardi R, Ferro F, Gemignani A, and Raiteri M (1996) Characterization of the glutamate receptors mediating release of somatostatin from cultured hippocampal neurons. *J Neurochem* **66**:161–168.
Franks KH, Bransby L, Saling MM, and Pase MP (2021) Association of Stress with Risk of Dementia and Mild Cognitive Impairment: A Systematic Review and Meta-Analysis. *J Alzheimers Dis* **82**:1573–1590.
Frenkel D, Wilkinson K, Zhao L, Hickman SE, Means TK, Puckett L, Farfara D, Kingery ND, Weiner HL, and El Khoury J (2013) Scara1 deficiency impairs clearance of soluble amyloid-beta by mononuclear phagocytes and accelerates Alzheimer's-like disease progression. *Nat Commun* **4**:2030.
Fricker G, Nobmann S, and Miller DS (2002) Permeability of porcine blood brain barrier to somatostatin analogues. *Br J Pharmacol* **135**:1308–1314.
Fuchs T, Jefferson SJ, Hooper A, Yee P-H, Maguire J, and Luscher B (2017) Disinhibition of somatostatin-positive GABAergic interneurons results in an anxiolytic and antidepressant-like brain state. *Mol Psychiatry* **22**:920–930.
Fukami S, Watanabe K, Iwata N, Haraoka J, Lu B, Gerard NP, Gerard C, Fraser P, Westaway D, St George-Hyslop P, et al. (2002) Abeta-degrading endopeptidase, neprilysin, in mouse brain: synaptic and axonal localization inversely correlating with Abeta pathology. *Neurosci Res* **43**:39–56.
Fung SJ, Fillman SG, Webster MJ, and Shannon Weickert C (2014) Schizophrenia and bipolar disorder show both common and distinct changes in cortical interneuron markers. *Schizophr Res* **155**:26–30.
Fung SJ, Webster MJ, Sivagnanasundaram S, Duncan C, Elashoff M, and Weickert CS (2010) Expression of interneuron markers in the dorsolateral prefrontal cortex of the developing human and in schizophrenia. *Am J Psychiatry* **167**:1479–1488.
Gabriel SM, Davidson M, Haroutunian V, Powchik P, Bierer LM, Purohit DP, Perl DP, and Davis KL (1996) Neuropeptide deficits in schizophrenia vs. Alzheimer's disease cerebral cortex. *Biol Psychiatry* **39**:82–91.
Gahete MD, Rubio A, Durán-Prado M, Avila J, Luque RM, and Castaño JP (2010) Expression of Somatostatin, cortistatin, and their receptors, as well as dopamine receptors, but not of neprilysin, are reduced in the temporal lobe of Alzheimer's disease patients. *J Alzheimers Dis* **20**:465–475.
Gastambide F, Lepousez G, Viollet C, Loudes C, Epelbaum J, and Guillou J-L (2010) Cooperation between hippocampal somatostatin receptor subtypes 4 and 2: functional relevance in interactive memory systems. *Hippocampus* **20**:745–757.
Gastambide F, Viollet C, Lepousez G, Epelbaum J, and Guillou J-L (2009) Hippocampal SSTR4 somatostatin receptors control the selection of memory strategies. *Psychopharmacology (Berl)* **202**:153–163.
Gavilán MP, Revilla E, Pintado C, Castaño A, Vizuete ML, Moreno-González I, Baglietto-Vargas D, Sánchez-Varo R, Vitorica J, Gutiérrez A, et al. (2007) Molecular and cellular characterization of the age-related neuroinflammatory processes occurring in normal rat hippocampus: potential relation with the loss of somatostatin GABAergic neurons. *J Neurochem* **103**:984–996.
Gervais É, Iloun P, Martianova E, Gonçalves Bessa AC, Rivest S, and Topolnik L (2022) Structural analysis of the microglia-interneuron interactions in the CA1 hippocampal area of the APP/PS1 mouse model of Alzheimer's disease. *J Comp Neurol* **530**:1423–1437.
Giorgi FS, Saccaro LF, Busceti CL, Biagioni F, and Fornai F (2020) Epilepsy and Alzheimer's Disease: Potential mechanisms for an association. *Brain Res Bull* **160**:107–120.
Glenner GG (1980) Amyloid deposits and amyloidosis. The beta-fibrilloses (first of two parts). *N Engl J Med* **302**:1283–1292.
Goldman JS, Hahn SE, Catania JW, LaRusse-Eckert S, Butson MB, Rumbaugh M, Strecker MN, Roberts JS, Burke W, Mayeux R, et al.; American College of Medical Genetics and the National Society of Genetic Counselors (2011) Genetic counseling and testing for Alzheimer disease: joint practice guidelines of the American College of Medical Genetics and the National Society of Genetic Counselors. Genetics. *Genet Med* **13**:597–605.
Gómez-Isla T, Price JL, McKeel DW, Morris JC, Growdon JH, and Hyman BT (1996) Profound loss of layer II entorhinal cortex neurons occurs in very mild Alzheimer's disease. *J Neurosci* **16**:4491–4500.
González A, Calfío C, Churruca M, and Maccioni RB (2022) Glucose metabolism and AD: evidence for a potential diabetes type 3. *Alzheimers Res Ther* **14**:56.
Gourmaud S, Shou H, Irwin DJ, Sansalone K, Jacobs LM, Lucas TH, Marsh ED, Davis KA, Jensen FE, and Talos DM (2020) Alzheimer-like amyloid and tau

alterations associated with cognitive deficit in temporal lobe epilepsy. *Brain* **143**:191–209.
Goutagny R, Gu N, Cavanagh C, Jackson J, Chabot J-G, Quirion R, Krantic S, and Williams S (2013) Alterations in hippocampal network oscillations and theta-gamma coupling arise before Abeta overproduction in a mouse model of Alzheimer's disease. *Eur J Neurosci* **37**:1896–1902.
Grant M, Alturaihi H, Jaquet P, Collier B, and Kumar U (2008) Cell growth inhibition and functioning of human somatostatin receptor type 2 are modulated by receptor heterodimerization. *Mol Endocrinol* **22**:2278–2292.
Grant M and Kumar U (2010) The role of G-proteins in the dimerisation of human somatostatin receptor types 2 and 5. *Regul Pept* **159**:3–8.
Griciuc A, Serrano-Pozo A, Parrado AR, Lesinski AN, Asselin CN, Mullin K, Hooli B, Choi SH, Hyman BT, and Tanzi RE (2013) Alzheimer's disease risk gene CD33 inhibits microglial uptake of amyloid beta. *Neuron* **78**:631–643.
Griffiths BJ and Jensen O (2023) Gamma oscillations and episodic memory. *Trends Neurosci* **46**:832–846.
Grilli M, Raiteri L, and Pittaluga A (2004) Somatostatin inhibits glutamate release from mouse cerebrocortical nerve endings through presynaptic sst2 receptors linked to the adenylyl cyclase-protein kinase A pathway. *Neuropharmacology* **46**:388–396.
Griñán-Ferré C, Corpas R, Puigoriol-Illamola D, Palomera-Ávalos V, Sanfeliu C, and Pallàs M (2018) Understanding Epigenetics in the Neurodegeneration of Alzheimer's Disease: SAMP8 Mouse Model. *J Alzheimers Dis* **62**:943–963.
Grosse G, Djalali S, Deng DR, Höltje M, Hinz B, Schwartzkopff K, Cygon M, Rothe T, Stroh T, Hellweg R, et al. (2005) Area-specific effects of brain-derived neurotrophic factor (BDNF) genetic ablation on various neuronal subtypes of the mouse brain. *Brain Res Dev Brain Res* **156**:111–126.
Grothe M, Zaborszky L, Atienza M, Gil-Neciga E, Rodriguez-Romero R, Teipel SJ, Amunts K, Suarez-Gonzalez A, and Cantero JL (2010) Reduction of basal forebrain cholinergic system parallels cognitive impairment in patients at high risk of developing Alzheimer's disease. *Cereb Cortex* **20**:1685–1695.
Grouselle D, Winsky-Sommerer R, David JP, Delacourte A, Dournaud P, and Epelbaum J (1998) Loss of somatostatin-like immunoreactivity in the frontal cortex of Alzheimer patients carrying the apolipoprotein epsilon 4 allele. *Neurosci Lett* **255**:21–24.
Guennewig B, Lim J, Marshall L, McCorkindale AN, Paasila PJ, Patrick E, Kril JJ, Halliday GM, Cooper AA, and Sutherland GT (2021) Defining early changes in Alzheimer's disease from RNA sequencing of brain regions differentially affected by pathology. *Sci Rep* **11**:4865.
Guilloux J-P, Douillard-Guilloux G, Kota R, Wang X, Gardier AM, Martinowich K, Tseng GC, Lewis DA, and Sibille E (2012) Molecular evidence for BDNF- and GABA-related dysfunctions in the amygdala of female subjects with major depression. *Mol Psychiatry* **17**:1130–1142.
Guillozet-Bongaarts AL, Hyde TM, Dalley RA, Hawrylycz MJ, Henry A, Hof PR, Hohmann J, Jones AR, Kuan CL, Royall J, et al. (2014) Altered gene expression in the dorsolateral prefrontal cortex of individuals with schizophrenia. *Mol Psychiatry* **19**:478–485.
Gullotta GS, Costantino G, Sortino MA, and Spampinato SF (2023) Microglia and the Blood-Brain Barrier: An External Player in Acute and Chronic Neuroinflammatory Conditions. *Int J Mol Sci* **24**:9144.
Gulyás AI, Hájos N, Katona I, and Freund TF (2003) Interneurons are the local targets of hippocampal inhibitory cells which project to the medial septum. *Eur J Neurosci* **17**:1861–1872.
Günther T, Tulipano G, Dournaud P, Bousquet C, Csaba Z, Kreienkamp H-J, Lupp A, Korbonits M, Castaño JP, Wester H-J, et al. (2018) International Union of Basic and Clinical Pharmacology. CV. Somatostatin Receptors: Structure, Function, Ligands, and New Nomenclature. *Pharmacol Rev* **70**:763–835.
Guo S, Wang H, and Yin Y (2022) Microglia Polarization From M1 to M2 in Neurodegenerative Diseases. *Front Aging Neurosci* **14**:815347.
Gyure KA, Durham R, Stewart WF, Smialek JE, and Troncoso JC (2001) Intraneuronal abeta-amyloid precedes development of amyloid plaques in Down syndrome. *Arch Pathol Lab Med* **125**:489–492.
Habeych ME, Falcone T, Dagar A, Ford L, and Castilla-Puentes R (2021) Dementia, Subtype of Seizures, and the Risk of New Onset Seizures: A Cohort Study. *J Alzheimers Dis* **81**:973–980.
Haenschel C, Bittner RA, Waltz J, Haertling F, Wibral M, Singer W, Linden DEJ, and Rodriguez E (2009) Cortical oscillatory activity is critical for working memory as revealed by deficits in early-onset schizophrenia. *J Neurosci* **29**:9481–9489.
Halliday MR, Rege SV, Ma Q, Zhao Z, Miller CA, Winkler EA, and Zlokovic BV (2016) Accelerated pericyte degeneration and blood-brain barrier breakdown in apolipoprotein E4 carriers with Alzheimer's disease. *J Cereb Blood Flow Metab* **36**:216–227.
Hama E, Shirotani K, Masumoto H, Sekine-Aizawa Y, Aizawa H, and Saido TC (2001) Clearance of extracellular and cell-associated amyloid beta peptide through viral expression of neprilysin in primary neurons. *J Biochem* **130**:721–726.
Hamel FG, Mahoney MJ, and Duckworth WC (1991) Degradation of intraendosomal insulin by insulin-degrading enzyme without acidification. *Diabetes* **40**:436–443.
Hampel H, Mesulam M-M, Cuello AC, Khachaturian AS, Vergallo A, Farlow MR, Snyder PJ, Giacobini E, and Khachaturian ZS (2019) Revisiting the Cholinergic Hypothesis in Alzheimer's Disease: Emerging Evidence from Translational and Clinical Research. *J Prev Alzheimers Dis* **6**:2–15.
Hardy JA and Higgins GA (1992) Alzheimer's disease: the amyloid cascade hypothesis. *Science* **256**:184–185.
Haroutunian V, Mantin R, Campbell GA, Tsuboyama GK, and Davis KL (1987) Cysteamine-induced depletion of central somatostatin-like immunoactivity: effects on behavior, learning, memory and brain neurochemistry. *Brain Res* **403**:234–242.
Hashimoto T, Arion D, Unger T, Maldonado-Avilés JG, Morris HM, Volk DW, Mirnics K, and Lewis DA (2008a) Alterations in GABA-related transcriptome in the dorsolateral prefrontal cortex of subjects with schizophrenia. *Mol Psychiatry* **13**:147–161.
Hashimoto T, Bazmi HH, Mirnics K, Wu Q, Sampson AR, and Lewis DA (2008b) Conserved regional patterns of GABA-related transcript expression in the neocortex of subjects with schizophrenia. *Am J Psychiatry* **165**:479–489.
Hashimoto M, Kazui H, Matsumoto K, Nakano Y, Yasuda M, and Mori E (2005) Does donepezil treatment slow the progression of hippocampal atrophy in patients with Alzheimer's disease? *Am J Psychiatry* **162**:676–682.
Hasselmo ME and Stern CE (2014) Theta rhythm and the encoding and retrieval of space and time. *Neuroimage* **85 Pt 2**:656–666.
Heinitz K, Beck M, Schliebs R, and Perez-Polo JR (2006) Toxicity mediated by soluble oligomers of beta-amyloid(1-42) on cholinergic SN56.B5.G4 cells. *J Neurochem* **98**:1930–1945.
Heise C, Taha E, Murru L, Ponzoni L, Cattaneo A, Guarnieri FC, Montani C, Mossa A, Vezzoli E, Ippolito G, et al. (2017) eEF2K/eEF2 Pathway Controls the Excitation/Inhibition Balance and Susceptibility to Epileptic Seizures. *Cereb Cortex* **27**:2226–2248.
Helyes Z, Pintér E, Németh J, Kéri G, Thán M, Oroszi G, Horváth A, and Szolcsányi J (2001) Anti-inflammatory effect of synthetic somatostatin analogues in the rat. *Br J Pharmacol* **134**:1571–1579.
Helyes Z, Pintér E, Németh J, Sándor K, Elekes K, Szabó A, Pozsgai G, Keszthelyi D, Kereskai L, Engström M, et al. (2006) Effects of the somatostatin receptor subtype 4 selective agonist J-2156 on sensory neuropeptide release and inflammatory reactions in rodents. *Br J Pharmacol* **149**:405–415.
Helyes Z, Pintér E, Sándor K, Elekes K, Bánvölgyi A, Keszthelyi D, Szoke E, Tóth DM, Sándor Z, Kereskai L, et al. (2009) Impaired defense mechanism against inflammation, hyperalgesia, and airway hyperreactivity in somatostatin 4 receptor gene-deleted mice. *Proc Natl Acad Sci USA* **106**:13088–13093.
Hernández C, Arroba AI, Bogdanov P, Ramos H, Simó-Servat O, Simó R, and Valverde AM (2020) Effect of Topical Administration of Somatostatin on Retinal Inflammation and Neurodegeneration in an Experimental Model of Diabetes. *J Clin Med* **9**:2579.
Hervás-Aguilar A, Puebla-Jiménez L, Burgos-Ramos E, Aguado-Llera D, and Arilla-Ferreiro E (2005) Effects of single and continuous administration of amyloid beta-peptide (25-35) on adenylyl cyclase activity and the somatostatinergic system in the rat frontal and parietal cortex. *Neuroscience* **135**:181–190.
Hong S, Ostaszewski BL, Yang T, O'Malley TT, Jin M, Yanagisawa K, Li S, Bartels T, and Selkoe DJ (2014) Soluble Abeta oligomers are rapidly sequestered from brain ISF in vivo and bind GM1 ganglioside on cellular membranes. *Neuron* **82**:308–319.
Honoré E, Khlaifia A, Bosson A, and Lacaille J-C (2021) Hippocampal Somatostatin Interneurons, Long-Term Synaptic Plasticity and Memory. *Front Neural Circuits* **15**:687558.
Hou Z-H and Yu X (2013) Activity-regulated somatostatin expression reduces dendritic spine density and lowers excitatory synaptic transmission via postsynaptic somatostatin receptor 4. *J Biol Chem* **288**:2501–2509.
Houser CR (2014) Do structural changes in GABA neurons give rise to the epileptic state? *Adv Exp Med Biol* **813**:151–160.
Howard R, McShane R, Lindesay J, Ritchie C, Baldwin A, Barber R, Burns A, Dening T, Findlay D, Holmes C, et al. (2015) Nursing home placement in the Donepezil and Memantine in Moderate to Severe Alzheimer's Disease (DOMINO-AD) trial: secondary and post-hoc analyses. *Lancet Neurol* **14**:1171–1181.
Huang S-M, Mouri A, Kokubo H, Nakajima R, Suemoto T, Higuchi M, Staufenbiel M, Noda Y, Yamaguchi H, Nabeshima T, et al. (2006) Neprilysin-sensitive synapse-associated amyloid-beta peptide oligomers impair neuronal plasticity and cognitive function. *J Biol Chem* **281**:17941–17951.
Hukovic N, Panetta R, Kumar U, and Patel YC (1996) Agonist-dependent regulation of cloned human somatostatin receptor types 1-5 (hSSTR1-5): subtype selective internalization or upregulation. *Endocrinology* **137**:4046–4049.
Hulette CM, Welsh-Bohmer KA, Murray MG, Saunders AM, Mash DC, and McIntyre LM (1998) Neuropathological and neuropsychological changes in "normal" aging: evidence for preclinical Alzheimer disease in cognitively normal individuals. *J Neuropathol Exp Neurol* **57**:1168–1174.
Iaccarino HF, Singer AC, Martorell AJ, Rudenko A, Gao F, Gillingham TZ, Mathys H, Seo J, Kritskiy O, Abdurrob F, et al. (2016) Gamma frequency entrainment attenuates amyloid load and modifies microglia. *Nature* **540**:230–235.
Imfeld P, Bodmer M, Schuerch M, Jick SS, and Meier CR (2013) Seizures in patients with Alzheimer's disease or vascular dementia: a population-based nested case-control analysis. *Epilepsia* **54**:700–707.
Ittner AA, Gladbach A, Bertz J, Suh LS, and Ittner LM (2014) p38 MAP kinase-mediated NMDA receptor-dependent suppression of hippocampal hypersynchronicity in a mouse model of Alzheimer's disease. *Acta Neuropathol Commun* **2**:149.
Iwasawa C, Narita M, and Tamura H (2019) Regional and temporal regulation and role of somatostatin receptor subtypes in the mouse brain following systemic kainate-induced acute seizures. *Neurosci Res* **149**:38–49.
Iwata N, Higuchi M, and Saido TC (2005) Metabolism of amyloid-beta peptide and Alzheimer's disease. *Pharmacol Ther* **108**:129–148.
Iwata N, Tsubuki S, Takaki Y, Shirotani K, Lu B, Gerard NP, Gerard C, Hama E, Lee HJ, and Saido TC (2001) Metabolic regulation of brain Abeta by neprilysin. *Science* **292**:1550–1552.
Iwata N, Tsubuki S, Takaki Y, Watanabe K, Sekiguchi M, Hosoki E, Kawashima-Morishima M, Lee HJ, Hama E, Sekine-Aizawa Y, et al. (2000) Identification of the major Abeta1-42-degrading catabolic pathway in brain parenchyma: suppression leads to biochemical and pathological deposition. *Nat Med* **6**:143–150.
Jack CR, Wiste HJ, Vemuri P, Weigand SD, Senjem ML, Zeng G, Bernstein MA, Gunter JL, Pankratz VS, Aisen PS, et al.; Disease Neuroimaging Initiative (2010) Brain beta-amyloid measures and magnetic resonance imaging atrophy both predict time-to-progression from mild cognitive impairment to Alzheimer's disease. *Brain* **133**:3336–3348.

Jaehde U, Masereeuw R, De Boer AG, Fricker G, Nagelkerke JF, Vonderscher J, and Breimer DD (1994) Quantification and visualization of the transport of octreotide, a somatostatin analogue, across monolayers of cerebrovascular endothelial cells. *Pharm Res* **11**:442–448.
Jansen IE, Savage JE, Watanabe K, Bryois J, Williams DM, Steinberg S, Sealock J, Karlsson IK, Hägg S, Athanasiu L, et al. (2019) Genome-wide meta-analysis identifies new loci and functional pathways influencing Alzheimer's disease risk. *Nat Genet* **51**:404–413.
Janssen JC, Beck JA, Campbell TA, Dickinson A, Fox NC, Harvey RJ, Houlden H, Rossor MN, and Collinge J (2003) Early onset familial Alzheimer's disease: Mutation frequency in 31 families. *Neurology* **60**:235–239.
Jayadev S, Leverenz JB, Steinbart E, Stahl J, Klunk W, Yu C-E, and Bird TD (2010) Alzheimer's disease phenotypes and genotypes associated with mutations in presenilin 2. *Brain* **133**:1143–1154.
Jiang T, Yu J-T, Hu N, Tan M-S, Zhu X-C, and Tan L (2014) CD33 in Alzheimer's disease. *Mol Neurobiol* **49**:529–535.
Jimenez S, Baglietto-Vargas D, Caballero C, Moreno-Gonzalez I, Torres M, Sanchez-Varo R, Ruano D, Vizuete M, Gutierrez A, and Vitorica J (2008) Inflammatory response in the hippocampus of PS1M146L/APP751SL mouse model of Alzheimer's disease: age-dependent switch in the microglial phenotype from alternative to classic. *J Neurosci* **28**:11650–11661.
Jin S, Kedia N, Illes-Toth E, Haralampiev I, Prisner S, Herrmann A, Wanker EE, and Bieschke J (2016) Amyloid-beta(1-42) Aggregation Initiates Its Cellular Uptake and Cytotoxicity. *J Biol Chem* **291**:19590–19606.
Jinno S, Klausberger T, Marton LF, Dalezios Y, Roberts JDB, Fuentealba P, Bushong EA, Henze D, Buzsáki G, and Somogyi P (2007) Neuronal diversity in GABAergic long-range projections from the hippocampus. *J Neurosci* **27**:8790–8804.
Johnson RD, Schauerte JA, Chang C-C, Wisser KC, Althaus JC, Carruthers CJL, Sutton MA, Steel DG, and Gafni A (2013) Single-molecule imaging reveals abeta42:abeta40 ratio-dependent oligomer growth on neuronal processes. *Biophys J* **104**:894–903.
Johnson RD, Schauerte JA, Wisser KC, Gafni A, and Steel DG (2011) Direct observation of single amyloid-beta(1-40) oligomers on live cells: binding and growth at physiological concentrations. *PLoS One* **6**:e23970.
Jolkkonen J, Kähkönen K, and Pitkänen A (1997) Cholinergic deafferentation exacerbates seizure-induced loss of somatostatin-immunoreactive neurons in the rat hippocampus. *Neuroscience* **80**:401–411.
Jucker M and Walker LC (2018) Propagation and spread of pathogenic protein assemblies in neurodegenerative diseases. *Nat Neurosci* **21**:1341–1349.
Justice NJ (2018) The relationship between stress and Alzheimer's disease. *Neurobiol Stress* **8**:127–133.
Kam MK, Kim B, Lee DG, Lee HJ, Park Y-H, and Lee D-S (2022) Amyloid beta oligomers-induced parkin aggravates ER stress-mediated cell death through a positive feedback loop. *Neurochem Int* **155**:105312.
Kane J, Cavanagh JF, and Dillon DG (2019) Reduced Theta Power During Memory Retrieval in Depressed Adults. *Biol Psychiatry Cogn Neurosci Neuroimaging* **4**:636–643.
Kanemitsu H, Tomiyama T, and Mori H (2003) Human neprilysin is capable of degrading amyloid beta peptide not only in the monomeric form but also the pathological oligomeric form. *Neurosci Lett* **350**:113–116.
Kang J-E, Cirrito JR, Dong H, Csernansky JG, and Holtzman DM (2007) Acute stress increases interstitial fluid amyloid-beta via corticotropin-releasing factor and neuronal activity. *Proc Natl Acad Sci USA* **104**:10673–10678.
Kanigowski D, Bogaj K, Barth AL, and Urban-Ciecko J (2023) Somatostatin-expressing interneurons modulate neocortical network through GABAb receptors in a synapse-specific manner. *Sci Rep* **13**:8780.
Katzman R, Terry R, DeTeresa R, Brown T, Davies P, Fuld P, Renbing X, and Peck A (1988) Clinical, pathological, and neurochemical changes in dementia: a subgroup with preserved mental status and numerous neocortical plaques. *Ann Neurol* **23**:138–144.
Keskin AD, Kekuš M, Adelsberger H, Neumann U, Shimshek DR, Song B, Zott B, Peng T, Förstl H, Staufenbiel M, et al. (2017) BACE inhibition-dependent repair of Alzheimer's pathophysiology. *Proc Natl Acad Sci USA* **114**:8631–8636.
Kim H-J, Chae S-C, Lee D-K, Chromy B, Lee SC, Park Y-C, Klein WL, Krafft GA, and Hong S-T (2003) Selective neuronal degeneration induced by soluble oligomeric amyloid beta protein. *FASEB J* **17**:118–120.
Kim SJ, Chung WH, Rhim H, Eun S-Y, Jung SJ, and Kim J (2002) Postsynaptic action mechanism of somatostatin on the membrane excitability in spinal substantia gelatinosa neurons of juvenile rats. *Neuroscience* **114**:1139–1148.
Kisler K, Nelson AR, Rege SV, Ramanathan A, Wang Y, Ahuja A, Lazic D, Tsai PS, Zhao Z, Zhou Y, et al. (2017) Pericyte degeneration leads to neurovascular uncoupling and limits oxygen supply to brain. *Nat Neurosci* **20**:406–416.
Kitiyanant N, Kitiyanant Y, Svendsen CN, and Thangnipon W (2012) BDNF-, IGF-1- and GDNF-secreting human neural progenitor cells rescue amyloid beta-induced toxicity in cultured rat septal neurons. *Neurochem Res* **37**:143–152.
Kling MA, Rubinow DR, Doran AR, Roy A, Davis CL, Calabrese JR, Nieman LK, Post RM, Chrousos GP, and Gold PW (1993) Cerebrospinal fluid immunoreactive somatostatin concentrations in patients with Cushing's disease and major depression: relationship to indices of corticotropin-releasing hormone and cortisol secretion. *Neuroendocrinology* **57**:79–88.
Kluge C, Stoppel C, Szinyei C, Stork O, and Pape H-C (2008) Role of the somatostatin system in contextual fear memory and hippocampal synaptic plasticity. *Learn Mem* **15**:252–260.
Klyubin I, Betts V, Welzel AT, Blennow K, Zetterberg H, Wallin A, Lemere CA, Cullen WK, Peng Y, Wisniewski T, et al. (2008) Amyloid beta protein dimer-containing human CSF disrupts synaptic plasticity: prevention by systemic passive immunization. *J Neurosci* **28**:4231–4237.
Knoferle J, Yoon SY, Walker D, Leung L, Gillespie AK, Tong LM, Bien-Ly N, and Huang Y (2014) Apolipoprotein E4 produced in GABAergic interneurons causes learning and memory deficits in mice. *J Neurosci* **34**:14069–14078.
Köhler C, Eriksson LG, Davies S, and Chan-Palay V (1987) Co-localization of neuropeptide tyrosine and somatostatin immunoreactivity in neurons of individual subfields of the rat hippocampal region. *Neurosci Lett* **78**:1–6.
Komoltsev IG, Frankevich SO, Shirobokova NI, Volkova AA, Onufriev MV, Moiseeva JV, Novikova MR, and Gulyaeva NV (2021) Neuroinflammation and Neuronal Loss in the Hippocampus Are Associated with Immediate Posttraumatic Seizures and Corticosterone Elevation in Rats. *Int J Mol Sci* **22**:5883.
Konradi C, Yang CK, Zimmerman EI, Lohmann KM, Gresch P, Pantazopoulos H, Berretta S, and Heckers S (2011a) Hippocampal interneurons are abnormal in schizophrenia. *Schizophr Res* **131**:165–173.
Konradi C, Zimmerman EI, Yang CK, Lohmann KM, Gresch P, Pantazopoulos H, Berretta S, and Heckers S (2011b) Hippocampal interneurons in bipolar disorder. *Arch Gen Psychiatry* **68**:340–350.
Konstantoulea K, Guerreiro P, Ramakers M, Louros N, Aubrey LD, Houben B, Michiels E, De Vleeschouwer M, Lampi Y, Ribeiro LF, et al. (2022) Heterotypic Amyloid beta interactions facilitate amyloid assembly and modify amyloid structure. *EMBO J* **41**:e108591.
Kook S-Y, Hong HS, Moon M, Ha CM, Chang S, and Mook-Jung I (2012) Abeta(1)(-)(4)(2)-RAGE interaction disrupts tight junctions of the blood-brain barrier via Ca(2)(+)-calcineurin signaling. *J Neurosci* **32**:8845–8854.
Kozhemyakin M, Rajasekaran K, Todorovic MS, Kowalski SL, Balint C, and Kapur J (2013) Somatostatin type-2 receptor activation inhibits glutamate release and prevents status epilepticus. *Neurobiol Dis* **54**:94–104.
Krantic S, Robitaille Y, and Quirion R (1992) Deficits in the somatostatin SS1 receptor sub-type in frontal and temporal cortices in Alzheimer's disease. *Brain Res* **573**:299–304.
Kreienkamp HJ, Roth A, and Richter D (1998) Rat somatostatin receptor subtype 4 can be made sensitive to agonist-induced internalization by mutation of a single threonine (residue 331). *DNA Cell Biol* **17**:869–878.
Kröger E, Mouls M, Wilchesky M, Berkers M, Carmichael P-H, van Marum R, Souverein P, Egberts T, and Laroche M-L (2015) Adverse Drug Reactions Reported With Cholinesterase Inhibitors: An Analysis of 16 Years of Individual Case Safety Reports From VigiBase. *Ann Pharmacother* **49**:1197–1206.
Kubota Y, Shigematsu N, Karube F, Sekigawa A, Kato S, Yamaguchi N, Hirai Y, Morishima M, and Kawaguchi Y (2011) Selective coexpression of multiple chemical markers defines discrete populations of neocortical GABAergic neurons. *Cereb Cortex* **21**:1803–1817.
Kumar U (2005) Expression of somatostatin receptor subtypes (SSTR1-5) in Alzheimer's disease brain: an immunohistochemical analysis. *Neuroscience* **134**:525–538.
Kumar U (2013) G-Protein Coupled Receptors Dimerization: Diversity in Somatostatin Receptors Subtypes. *J Pharmacogenomics Pharmacoproteomics* **4**:2.
Kurochkin IV, Guarnera E, and Berezovsky IN (2018) Insulin-Degrading Enzyme in the Fight against Alzheimer's Disease. *Trends Pharmacol Sci* **39**:49–58.
Kvitsiani D, Ranade S, Hangya B, Taniguchi H, Huang JZ, and Kepecs A (2013) Distinct behavioural and network correlates of two interneuron types in prefrontal cortex. *Nature* **498**:363–366.
Kwak S-E, Kim J-E, Choi H-C, Song H-K, Kim Y-I, Jo S-M, and Kang T-C (2008) The expression of somatostatin receptors in the hippocampus of pilocarpine-induced rat epilepsy model. *Neuropeptides* **42**:569–583.
Lacor PN, Buniel MC, Chang L, Fernandez SJ, Gong Y, Viola KL, Lambert MP, Velasco PT, Bigio EH, Finch CE, et al. (2004) Synaptic targeting by Alzheimer's-related amyloid beta oligomers. *J Neurosci* **24**:10191–10200.
Lacor PN, Buniel MC, Furlow PW, Clemente AS, Velasco PT, Wood M, Viola KL, and Klein WL (2007) Abeta oligomer-induced aberrations in synapse composition, shape, and density provide a molecular basis for loss of connectivity in Alzheimer's disease. *J Neurosci* **27**:796–807.
Lambert MP, Barlow AK, Chromy BA, Edwards C, Freed R, Liosatos M, Morgan TE, Rozovsky I, Trommer B, Viola KL, et al. (1998) Diffusible, nonfibrillar ligands derived from Abeta1-42 are potent central nervous system neurotoxins. *Proc Natl Acad Sci USA* **95**:6448–6453.
Larner AJ (2010) Epileptic seizures in AD patients. *Neuromolecular Med* **12**:71–77.
Leão RN, Mikulovic S, Leão KE, Munguba H, Gezelius H, Enjin A, Patra K, Eriksson A, Loew LM, Tort ABL, et al. (2012) OLM interneurons differentially modulate CA3 and entorhinal inputs to hippocampal CA1 neurons. *Nat Neurosci* **15**:1524–1530.
Lee J, Lee KJ, and Kim H (2017) Gender differences in behavioral and psychological symptoms of patients with Alzheimer's disease. *Asian J Psychiatr* **26**:124–128.
Lehmann L, Lo A, Knox KM, and Barker-Haliski M (2021) Alzheimer's Disease and Epilepsy: A Perspective on the Opportunities for Overlapping Therapeutic Innovation. *Neurochem Res* **46**:1895–1912.
Lei S, Cheng T, Guo Y, Li C, Zhang W, and Zhi F (2014) Somatostatin ameliorates lipopolysaccharide-induced tight junction damage via the ERK-MAPK pathway in Caco2 cells. *Eur J Cell Biol* **93**:299–307.
Leissring MA, Farris W, Chang AY, Walsh DM, Wu X, Sun X, Frosch MP, and Selkoe DJ (2003) Enhanced proteolysis of beta-amyloid in APP transgenic mice prevents plaque formation, secondary pathology, and premature death. *Neuron* **40**:1087–1093.
Leissring MA, Farris W, Wu X, Christodoulou DC, Haigis MC, Guarente L, and Selkoe DJ (2004) Alternative translation initiation generates a novel isoform of insulin-degrading enzyme targeted to mitochondria. *Biochem J* **383**:439–446.
Leng F and Edison P (2021) Neuroinflammation and microglial activation in Alzheimer disease: where do we go from here? *Nat Rev Neurol* **17**:157–172.
Lepousez G, Mouret A, Loudes C, Epelbaum J, and Viollet C (2010) Somatostatin contributes to in vivo gamma oscillation modulation and odor discrimination in the olfactory bulb. *J Neurosci* **30**:870–875.
Leung L, Andrews-Zwilling Y, Yoon SY, Jain S, Ring K, Dai J, Wang MM, Tong L, Walker D, and Huang Y (2012) Apolipoprotein E4 causes age- and sex-dependent impairments of hilar GABAergic interneurons and learning and memory deficits in mice. *PLoS One* **7**:e53569.

Li G, Bien-Ly N, Andrews-Zwilling Y, Xu Q, Bernardo A, Ring K, Halabisky B, Deng C, Mahley RW, and Huang Y (2009a) GABAergic interneuron dysfunction impairs hippocampal neurogenesis in adult apolipoprotein E4 knockin mice. *Cell Stem Cell* **5**:634–645.

Li Y, Du X-F, Liu C-S, Wen Z-L, and Du J-L (2012) Reciprocal regulation between resting microglial dynamics and neuronal activity in vivo. *Dev Cell* **23**:1189–1202.

Li S, Hong S, Shepardson NE, Walsh DM, Shankar GM, and Selkoe D (2009b) Soluble oligomers of amyloid Beta protein facilitate hippocampal long-term depression by disrupting neuronal glutamate uptake. *Neuron* **62**:788–801.

Li S, Jin M, Koeglsperger T, Shepardson NE, Shankar GM, and Selkoe DJ (2011) Soluble Abeta oligomers inhibit long-term potentiation through a mechanism involving excessive activation of extrasynaptic NR2B-containing NMDA receptors. *J Neurosci* **31**:6627–6638.

Li N, Lee B, Liu R-J, Banasr M, Dwyer JM, Iwata M, Li X-Y, Aghajanian G, and Duman RS (2010) mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. *Science* **329**:959–964.

Liebner S, Dijkhuizen RM, Reiss Y, Plate KH, Agalliu D, and Constantin G (2018) Functional morphology of the blood-brain barrier in health and disease. *Acta Neuropathol* **135**:311–336.

Liguz-Lecznar M, Urban-Ciecko J, and Kossut M (2016) Somatostatin and Somatostatin-Containing Neurons in Shaping Neuronal Activity and Plasticity. *Front Neural Circuits* **10**:48.

Lin L-C and Sibille E (2013) Reduced brain somatostatin in mood disorders: a common pathophysiological substrate and drug target? *Front Pharmacol* **4**:110.

Lin LC and Sibille E (2015) Somatostatin, neuronal vulnerability and behavioral emotionality. *Mol Psychiatry* **20**:377–387.

Lindquist SG, Nielsen JE, Stokholm J, Schwartz M, Batbayli M, Ballegaard M, Erdal J, Krabbe K, and Waldemar G (2008) Atypical early-onset Alzheimer's disease caused by the Iranian APP mutation. *J Neurol Sci* **268**:124–130.

Liu Y, Lu D, Zhang Y, Li S, Liu X, and Lin H (2010) The evolution of somatostatin in vertebrates. *Gene* **463**:21–28.

Long JM and Holtzman DM (2019) Alzheimer Disease: An Update on Pathobiology and Treatment Strategies. *Cell* **179**:312–339.

Lopez-Pigozzi D, Laurent F, Brotons-Mas JR, Valderrama M, Valero M, Fernandez-Lamo I, Cid E, Gomez-Dominguez D, Gal B, and Menendez de la Prida L (2016) Altered Oscillatory Dynamics of CA1 Parvalbumin Basket Cells during Theta-Gamma Rhythmopathies of Temporal Lobe Epilepsy. *eNeuro* ***3*** **3**:

Lourenco MV, Clarke JR, Frozza RL, Bomfim TR, Forny-Germano L, Batista AF, Sathler LB, Brito-Moreira J, Amaral OB, Silva CA, et al. (2013) TNF-alpha mediates PKR-dependent memory impairment and brain IRS-1 inhibition induced by Alzheimer's beta-amyloid oligomers in mice and monkeys. *Cell Metab* **18**:831–843.

Lovett-Barron M, Kaifosh P, Kheirbek MA, Danielson N, Zaremba JD, Reardon TR, Turi GF, Hen R, Zemelman BV, and Losonczy A (2014) Dendritic inhibition in the hippocampus supports fear learning. *Science* **343**:857–863.

Löw K, Crestani F, Keist R, Benke D, Brünig I, Benson JA, Fritschy JM, Rülicke T, Bluethmann H, Möhler H, et al. (2000) Molecular and neuronal substrate for the selective attenuation of anxiety. *Science* **290**:131–134.

Ludwig M and Pittman QJ (2003) Talking back: dendritic neurotransmitter release. *Trends Neurosci* **26**:255–261.

Ma T (2023) Roles of eukaryotic elongation factor 2 kinase (eEF2K) in neuronal plasticity, cognition, and Alzheimer disease. *J Neurochem* **166**:47–57.

Ma Y, Hu H, Berrebi AS, Mathers PH, and Agmon A (2006) Distinct subtypes of somatostatin-containing neocortical interneurons revealed in transgenic mice. *J Neurosci* **26**:5069–5082.

Ma T, Trinh MA, Wexler AJ, Bourbon C, Gatti E, Pierre P, Cavener DR, and Klann E (2013) Suppression of eIF2alpha kinases alleviates Alzheimer's disease-related plasticity and memory deficits. *Nat Neurosci* **16**:1299–1305.

Ma Q-L, Yang F, Rosario ER, Ubeda OJ, Beech W, Gant DJ, Chen PP, Hudspeth B, Chen C, Zhao Y, et al. (2009) Beta-amyloid oligomers induce phosphorylation of tau and inactivation of insulin receptor substrate via c-Jun N-terminal kinase signaling: suppression by omega-3 fatty acids and curcumin. *J Neurosci* **29**:9078–9089.

Mably AJ and Colgin LL (2018) Gamma oscillations in cognitive disorders. *Curr Opin Neurobiol* **52**:182–187.

Mably AJ, Gereke BJ, Jones DT, and Colgin LL (2017) Impairments in spatial representations and rhythmic coordination of place cells in the 3xTg mouse model of Alzheimer's disease. *Hippocampus* **27**:378–392.

Maezawa I, Zimin PI, Wulff H, and Jin L-W (2011) Amyloid-beta protein oligomer at low nanomolar concentrations activates microglia and induces microglial neurotoxicity. *J Biol Chem* **286**:3693–3706.

Maji SK, Perrin MH, Sawaya MR, Jessberger S, Vadodaria K, Rissman RA, Singru PS, Nilsson KPR, Simon R, Schubert D, et al. (2009) Functional amyloids as natural storage of peptide hormones in pituitary secretory granules. *Science* **325**:328–332.

Malkov A, Shevkova L, Latyshkova A, and Kitchigina V (2022) Theta and gamma hippocampal-neocortical oscillations during the episodic-like memory test: Impairment in epileptogenic rats. *Exp Neurol* **354**:114110.

Mancillas JR, Siggins GR, and Bloom FE (1986) Somatostatin selectively enhances acetylcholine-induced excitations in rat hippocampus and cortex. *Proc Natl Acad Sci USA* **83**:7518–7521.

Marcon G, Giaccone G, Cupidi C, Balestrieri M, Beltrami CA, Finato N, Bergonzi P, Sorbi S, Bugiani O, and Tagliavini F (2004) Neuropathological and clinical phenotype of an Italian Alzheimer family with M239V mutation of presenilin 2 gene. *J Neuropathol Exp Neurol* **63**:199–209.

Martel G, Dutar P, Epelbaum J, and Viollet C (2012) Somatostatinergic systems: an update on brain functions in normal and pathological aging. *Front Endocrinol (Lausanne)* **3**:154.

Marti M, Bregola G, Binaschi A, Gemignani A, and Simonato M (2000a) Kindled seizure-evoked somatostatin release in the hippocampus: inhibition by MK-801. *Neuroreport* **11**:3209–3212.

Marti M, Bregola G, Morari M, Gemignani A, and Simonato M (2000b) Somatostatin release in the hippocampus in the kindling model of epilepsy: a microdialysis study. *J Neurochem* **74**:2497–2503.

Martin E, Boucher C, Fontaine B, and Delarasse C (2017) Distinct inflammatory phenotypes of microglia and monocyte-derived macrophages in Alzheimer's disease models: effects of aging and amyloid pathology. *Aging Cell* **16**:27–38.

Maruyama M, Higuchi M, Takaki Y, Matsuba Y, Tanji H, Nemoto M, Tomita N, Matsui T, Iwata N, Mizukami H, et al. (2005) Cerebrospinal fluid neprilysin is reduced in prodromal Alzheimer's disease. *Ann Neurol* **57**:832–842.

Masliah E, Alford M, DeTeresa R, Mallory M, and Hansen L (1996) Deficient glutamate transport is associated with neurodegeneration in Alzheimer's disease. *Ann Neurol* **40**:759–766.

Mathys H, Peng Z, Boix CA, Victor MB, Leary N, Babu S, Abdelhady G, Jiang X, Ng AP, Ghafari K, et al. (2023) Single-cell atlas reveals correlates of high cognitive function, dementia, and resilience to Alzheimer's disease pathology. *Cell* **186**:4365–4385 e4327.

Matos M, Bosson A, Riebe I, Reynell C, Vallée J, Laplante I, Panatier A, Robitaille R, and Lacaille J-C (2018) Astrocytes detect and upregulate transmission at inhibitory synapses of somatostatin interneurons onto pyramidal cells. *Nat Commun* **9**:4254.

Matsuoka N and Aigner TG (1997) FK960 [N-(4-acetyl-1-piperazinyl)-p-fluorobenzamide monohydrate], a novel potential antidementia drug, improves visual recognition memory in rhesus monkeys: comparison with physostigmine. *J Pharmacol Exp Ther* **280**:1201–1209.

Matsuoka N, Maeda N, Yamaguchi I, and Satoh M (1994) Possible involvement of brain somatostatin in the memory formation of rats and the cognitive enhancing action of FR121196 in passive avoidance task. *Brain Res* **642**:11–19.

Matsuoka N and Satoh M (1998) FK960, a novel potential anti-dementia drug, augments long-term potentiation in mossy fiber-CA3 pathway of guinea-pig hippocampal slices. *Brain Res* **794**:248–254.

Mattson MP and Arumugam TV (2018) Hallmarks of Brain Aging: Adaptive and Pathological Modification by Metabolic States. *Cell Metab* **27**:1176–1199.

Mawuenyega KG, Sigurdson W, Ovod V, Munsell L, Kasten T, Morris JC, Yarasheski KE, and Bateman RJ (2010) Decreased clearance of CNS beta-amyloid in Alzheimer's disease. *Science* **330**:1774.

Mazzeo A, Arroba AI, Beltramo E, Valverde AM, and Porta M (2017) Somatostatin protects human retinal pericytes from inflammation mediated by microglia. *Exp Eye Res* **164**:46–54.

Magariños AM, Verdugo JM, and McEwen BS (1997) Chronic stress alters synaptic terminal structure in hippocampus. *Proc Natl Acad Sci USA* **94**:14002–14008.

McBain CJ, DiChiara TJ, and Kauer JA (1994) Activation of metabotropic glutamate receptors differentially affects two classes of hippocampal interneurons and potentiates excitatory synaptic transmission. *J Neurosci* **14**:4433–4445.

McCarthy AD, Owens IJ, Bansal AT, McTighe SM, Bussey TJ, and Saksida LM (2011) FK962 and donepezil act synergistically to improve cognition in rats: potential as an add-on therapy for Alzheimer's disease. *Pharmacol Biochem Behav* **98**:76–80.

McEwen BS (1999) Stress and the aging hippocampus. *Front Neuroendocrinol* **20**:49–70.

McEwen BS, Nasca C, and Gray JD (2016) Stress Effects on Neuronal Structure: Hippocampus, Amygdala, and Prefrontal Cortex. *Neuropsychopharmacology* **41**:3–23.

McGeer PL, Itagaki S, Tago H, and McGeer EG (1987) Reactive microglia in patients with senile dementia of the Alzheimer type are positive for the histocompatibility glycoprotein HLA-DR. *Neurosci Lett* **79**:195–200.

McShane R, Westby MJ, Roberts E, Minakaran N, Schneider L, Farrimond LE, Maayan N, Ware J, and Debarros J (2019) Memantine for dementia. *Cochrane Database Syst Rev* **3**:CD003154.

Medina-Rodriguez EM and Beurel E (2022) Blood brain barrier and inflammation in depression. *Neurobiol Dis* **175**:105926.

Melzer S, Michael M, Caputi A, Eliava M, Fuchs EC, Whittington MA, and Monyer H (2012) Long-range-projecting GABAergic neurons modulate inhibition in hippocampus and entorhinal cortex. *Science* **335**:1506–1510.

Mesulam M (1976) A horseradish peroxidase method for the identification of the efferents of acetyl cholinesterase-containing neurons. *J Histochem Cytochem* **24**:1281–1285.

Mesulam M, Shaw P, Mash D, and Weintraub S (2004) Cholinergic nucleus basalis tauopathy emerges early in the aging-MCI-AD continuum. *Ann Neurol* **55**:815–828.

Mikulovic S, Restrepo CE, Siwani S, Bauer P, Pupe S, Tort ABL, Kullander K, and Leão RN (2018) Ventral hippocampal OLM cells control type 2 theta oscillations and response to predator odor. *Nat Commun* **9**:3638.

Milligan Armstrong A, Porter T, Quek H, White A, Haynes J, Jackaman C, Villemagne V, Munyard K, Laws SM, Verdile G, et al. (2021) Chronic stress and Alzheimer's disease: the interplay between the hypothalamic-pituitary-adrenal axis, genetics and microglia. *Biol Rev Camb Philos Soc* **96**:2209–2228.

Miners JS, Van Helmond Z, Chalmers K, Wilcock G, Love S, and Kehoe PG (2006) Decreased expression and activity of neprilysin in Alzheimer disease are associated with cerebral amyloid angiopathy. *J Neuropathol Exp Neurol* **65**:1012–1021.

Minkeviciene R, Rheims S, Dobszay MB, Zilberter M, Hartikainen J, Fülöp L, Penke B, Zilberter Y, Harkany T, Pitkänen A, et al. (2009) Amyloid beta-induced neuronal hyperexcitability triggers progressive epilepsy. *J Neurosci* **29**:3453–3462.

Mizuseki K, Sirota A, Pastalkova E, and Buzsáki G (2009) Theta oscillations provide temporal windows for local circuit computation in the entorhinal-hippocampal loop. *Neuron* **64**:267–280.

Molchan SE, Hill JL, Martinez RA, Lawlor BA, Mellow AM, Rubinow DR, Bissette G, Nemeroff CB, and Sunderland T (1993) CSF somatostatin in Alzheimer's

disease and major depression: relationship to hypothalamic-pituitary-adrenal axis and clinical measures. *Psychoneuroendocrinology* **18**:509–519.
Momiyama T and Zaborszky L (2006) Somatostatin presynaptically inhibits both GABA and glutamate release onto rat basal forebrain cholinergic neurons. *J Neurophysiol* **96**:686–694.
Mondragón-Rodríguez S, Salas-Gallardo A, González-Pereyra P, Macías M, Ordaz B, Peña-Ortega F, Aguilar-Vázquez A, Orta-Salazar E, Díaz-Cintra S, Perry G, et al. (2018) Phosphorylation of Tau protein correlates with changes in hippocampal theta oscillations and reduces hippocampal excitability in Alzheimer's model. *J Biol Chem* **293**:8462–8472.
Moneta D, Richichi C, Aliprandi M, Dournaud P, Dutar P, Billard JM, Carlo AS, Viollet C, Hannon JP, Fehlmann D, et al. (2002) Somatostatin receptor subtypes 2 and 4 affect seizure susceptibility and hippocampal excitatory neurotransmission in mice. *Eur J Neurosci* **16**:843–849.
Montagne A, Zhao Z, and Zlokovic BV (2017) Alzheimer's disease: A matter of blood-brain barrier dysfunction? *J Exp Med* **214**:3151–3169.
Monteggia LM, Gideons E, and Kavalali ET (2013) The role of eukaryotic elongation factor 2 kinase in rapid antidepressant action of ketamine. *Biol Psychiatry* **73**:1199–1203.
Moon SL, Sonenberg N, and Parker R (2018) Neuronal Regulation of eIF2alpha Function in Health and Neurological Disorders. *Trends Mol Med* **24**:575–589.
Moore SD, Madamba SG, Joëls M, and Siggins GR (1988) Somatostatin augments the M-current in hippocampal neurons. *Science* **239**:278–280.
Moreno-Gonzalez I, Baglietto-Vargas D, Sanchez-Varo R, Jimenez S, Trujillo-Estrada L, Sanchez-Mejias E, Del Rio JC, Torres M, Romero-Acebal M, Ruano D, et al. (2009) Extracellular amyloid-beta and cytotoxic glial activation induce significant entorhinal neuron loss in young PS1(M146L)/APP(751SL) mice. *J Alzheimers Dis* **18**:755–776.
Mores KL, Cassell RJ, and van Rijn RM (2018) Arrestin recruitment and signaling by G protein-coupled receptor heteromers. *Neuropharmacology* **152**:15–21.
Morimoto M, Morita N, Ozawa H, Yokoyama K, and Kawata M (1996) Distribution of glucocorticoid receptor immunoreactivity and mRNA in the rat brain: an immunohistochemical and in situ hybridization study. *Neurosci Res* **26**:235–269.
Morita M, Kurochkin IV, Motojima K, Goto S, Takano T, Okamura S, Sato R, Yokota S, and Imanaka T (2000) Insulin-degrading enzyme exists inside of rat liver peroxisomes and degrades oxidized proteins. *Cell Struct Funct* **25**:309–315.
Morley JE, Armbrecht HJ, Farr SA, and Kumar VB (2012) The senescence accelerated mouse (SAMP8) as a model for oxidative stress and Alzheimer's disease. *Biochim Biophys Acta* **1822**:650–656.
Morris HM, Hashimoto T, and Lewis DA (2008) Alterations in somatostatin mRNA expression in the dorsolateral prefrontal cortex of subjects with schizophrenia or schizoaffective disorder. *Cereb Cortex* **18**:1575–1587.
Mortensen EL and Høgh P (2001) A gender difference in the association between APOE genotype and age-related cognitive decline. *Neurology* **57**:89–95.
Mouradian MM, Blin J, Giuffra M, Heuser IJ, Baronti F, Ownby J, and Chase TN (1991) Somatostatin replacement therapy for Alzheimer dementia. *Ann Neurol* **30**:610–613.
Moyse E, Szigethy E, Danger JM, Vaudry H, Wenk GL, Beaudet A, and Epelbaum J (1993) Short- and long-term effects of nucleus basalis magnocellularis lesions on cortical levels of somatostatin and its receptors in the rat. *Brain Res* **607**:154–160.
Müller C and Remy S (2018) Septo-hippocampal interaction. *Cell Tissue Res* **373**:565–575.
Muller JF, Mascagni F, and McDonald AJ (2007) Postsynaptic targets of somatostatin-containing interneurons in the rat basolateral amygdala. *J Comp Neurol* **500**:513–529.
Murakami S, Imbe H, Morikawa Y, Kubo C, and Senba E (2005) Chronic stress, as well as acute stress, reduces BDNF mRNA expression in the rat hippocampus but less robustly. *Neurosci Res* **53**:129–139.
Nag S and Tang F (2001) The effect of age on the response of the rat brains to continuous beta-amyloid infusion. *Brain Res* **889**:303–307.
Nag S, Yee BK, and Tang F (1999) Reduction in somatostatin and substance P levels and choline acetyltransferase activity in the cortex and hippocampus of the rat after chronic intracerebroventricular infusion of beta-amyloid (1-40). *Brain Res Bull* **50**:251–262.
Nagarajan R, Lyu J, Kambali M, Wang M, Courtney CD, Christian-Hinman CA, and Rudolph U (2023) Genetic Ablation of Dentate Hilar Somatostatin-Positive GABAergic Interneurons is Sufficient to Induce Cognitive Impairment. *Mol Neurobiol* **61**:567–580.
Nakata A, Saito H, and Nishiyama N (1996) Facilitatory role of somatostatin via muscarinic cholinergic system in the generation of long-term potentiation in the rat dentate gyrus in vivo. *Brain Res* **723**:135–140.
Nalivaeva NN and Turner AJ (2019) Targeting amyloid clearance in Alzheimer's disease as a therapeutic strategy. *Br J Pharmacol* **176**:3447–3463.
Nawa H, Pelleymounter MA, and Carnahan J (1994) Intraventricular administration of BDNF increases neuropeptide expression in newborn rat brain. *J Neurosci* **14**:3751–3765.
Negrete-Díaz JV, Falcón-Moya R, and Rodríguez-Moreno A (2022) Kainate receptors: from synaptic activity to disease. *FEBS J* **289**:5074–5088.
Nelson AR, Sweeney MD, Sagare AP, and Zlokovic BV (2016) Neurovascular dysfunction and neurodegeneration in dementia and Alzheimer's disease. *Biochim Biophys Acta* **1862**:887–900.
Nemeroff CB, Youngblood WW, Manberg PJ, Prange AJ, and Kizer JS (1983) Regional brain concentrations of neuropeptides in Huntington's chorea and schizophrenia. *Science* **221**:972–975.
Neske GT, Patrick SL, and Connors BW (2015) Contributions of diverse excitatory and inhibitory neurons to recurrent network activity in cerebral cortex. *J Neurosci* **35**:1089–1105.
Neumann WL, Sandoval KE, Mobayen S, Minaeian M, Kukielski SG, Srabony KN, Frare R, Slater O, Farr SA, Niehoff ML, et al. (2021) Synthesis and structure-activity relationships of 3,4,5-trisubstituted-1,2,4-triazoles: high affinity and selective somatostatin receptor-4 agonists for Alzheimer's disease treatment. *RSC Med Chem* **12**:1352–1365.
Nilsson CL, Brinkmalm A, Minthon L, Blennow K, and Ekman R (2001) Processing of neuropeptide Y, galanin, and somatostatin in the cerebrospinal fluid of patients with Alzheimer's disease and frontotemporal dementia. *Peptides* **22**:2105–2112.
Nilsson P, Sörgjerd K, Kakiya N, Sasaguri H, Watamura N, Shimozawa M, Tsubuki S, Zhou Z, Loera-Valencia R, Takamura R, et al. (2020) Somatostatin receptor subtypes 1 and 4 redundantly regulate neprilysin, the major amyloid-beta degrading enzyme in brain. *BioRxiv*
Nishitsuji K, Tomiyama T, Ishibashi K, Ito K, Teraoka R, Lambert MP, Klein WL, and Mori H (2009) The E693Delta mutation in amyloid precursor protein increases intracellular accumulation of amyloid beta oligomers and causes endoplasmic reticulum stress-induced apoptosis in cultured cells. *Am J Pathol* **174**:957–969.
Nocera S, Simon A, Fiquet O, Chen Y, Gascuel J, Datiche F, Schneider N, Epelbaum J, and Viollet C (2019) Somatostatin Serves a Modulatory Role in the Mouse Olfactory Bulb: Neuroanatomical and Behavioral Evidence. *Front Behav Neurosci* **13**:61.
Nosyreva E and Kavalali ET (2010) Activity-dependent augmentation of spontaneous neurotransmission during endoplasmic reticulum stress. *J Neurosci* **30**:7358–7368.
Nuñez A and Buño W (2021) The Theta Rhythm of the Hippocampus: From Neuronal and Circuit Mechanisms to Behavior. *Front Cell Neurosci* **15**:649262.
Obermayer J, Heistek TS, Kerkhofs A, Goriounova NA, Kroon T, Baayen JC, Idema S, Testa-Silva G, Couey JJ, and Mansvelder HD (2018) Lateral inhibition by Martinotti interneurons is facilitated by cholinergic inputs in human and mouse neocortex. *Nat Commun* **9**:4101.
Oh ES, Rosenberg PB, Rattinger GB, Stuart EA, Lyketsos CG, and Leoutsakos J-MS (2021) Psychotropic Medication and Cognitive, Functional, and Neuropsychiatric Outcomes in Alzheimer's Disease (AD). *J Am Geriatr Soc* **69**:955–963.
Oh MM, Simkin D, and Disterhoft JF (2016) Intrinsic Hippocampal Excitability Changes of Opposite Signs and Different Origins in CA1 and CA3 Pyramidal Neurons Underlie Aging-Related Cognitive Deficits. *Front Syst Neurosci* **10**:52.
Okonogi T and Sasaki T (2021) Theta-Range Oscillations in Stress-Induced Mental Disorders as an Oscillotherapeutic Target. *Front Behav Neurosci* **15**:698753.
Oliveira MM and Klann E (2022) eIF2-dependent translation initiation: Memory consolidation and disruption in Alzheimer's disease. *Semin Cell Dev Biol* **125**:101–109.
Opal MD, Klenotich SC, Morais M, Bessa J, Winkle J, Doukas D, Kay LJ, Sousa N, and Dulawa SM (2014) Serotonin 2C receptor antagonists induce fast-onset antidepressant effects. *Mol Psychiatry* **19**:1106–1114.
Paik S, Somvanshi RK, and Kumar U (2019) Somatostatin Maintains Permeability and Integrity of Blood-Brain Barrier in beta-Amyloid Induced Toxicity. *Mol Neurobiol* **56**:292–306.
Palmer K, Di Iulio F, Varsi AE, Gianni W, Sancesario G, Caltagirone C, and Spalletta G (2010) Neuropsychiatric predictors of progression from amnestic-mild cognitive impairment to Alzheimer's disease: the role of depression and apathy. *J Alzheimers Dis* **20**:175–183.
Palop JJ, Chin J, Roberson ED, Wang J, Thwin MT, Bien-Ly N, Yoo J, Ho KO, Yu G-Q, Kreitzer A, et al. (2007) Aberrant excitatory neuronal activity and compensatory remodeling of inhibitory hippocampal circuits in mouse models of Alzheimer's disease. *Neuron* **55**:697–711.
Palop JJ and Mucke L (2016) Network abnormalities and interneuron dysfunction in Alzheimer disease. *Nat Rev Neurosci* **17**:777–792.
Pantazopoulos H, Wiseman JT, Markota M, Ehrenfeld L, and Berretta S (2017) Decreased Numbers of Somatostatin-Expressing Neurons in the Amygdala of Subjects With Bipolar Disorder or Schizophrenia: Relationship to Circadian Rhythms. *Biol Psychiatry* **81**:536–547.
Park K, Lee J, Jang HJ, Richards BA, Kohl MM, and Kwag J (2020) Optogenetic activation of parvalbumin and somatostatin interneurons selectively restores theta-nested gamma oscillations and oscillation-induced spike timing-dependent long-term potentiation impaired by amyloid beta oligomers. *BMC Biol* **18**:7.
Paspalas CD and Papadopoulos GC (1999) Noradrenergic innervation of peptidergic interneurons in the rat visual cortex. *Cereb Cortex* **9**:844–853.
Patel YC, Greenwood MT, Warszynska A, Panetta R, and Srikant CB (1994) All five cloned human somatostatin receptors (hSSTR1-5) are functionally coupled to adenylyl cyclase. *Biochem Biophys Res Commun* **198**:605–612.
Patel YC and Wheatley T (1983) In vivo and in vitro plasma disappearance and metabolism of somatostatin-28 and somatostatin-14 in the rat. *Endocrinology* **112**:220–225.
Perianes-Cachero A, Canelles S, Aguado-Llera D, Frago LM, Toledo-Lobo MV, Carrera I, Cacabelos R, Chowen JA, Argente J, Arilla-Ferreiro E, et al. (2015) Reduction in Abeta-induced cell death in the hippocampus of 17beta-estradiol-treated female rats is associated with an increase in IGF-I signaling and somatostatinergic tone. *J Neurochem* **135**:1257–1271.
Perrenoud Q, Geoffroy H, Gauthier B, Rancillac A, Alfonsi F, Kessaris N, Rossier J, Vitalis T, and Gallopin T (2012) Characterization of Type I and Type II nNOS-Expressing Interneurons in the Barrel Cortex of Mouse. *Front Neural Circuits* **6**:36.
Pigino G, Morfini G, Atagi Y, Deshpande A, Yu C, Jungbauer L, LaDu M, Busciglio J, and Brady S (2009) Disruption of fast axonal transport is a pathogenic mechanism for intraneuronal amyloid beta. *Proc Natl Acad Sci USA* **106**:5907–5912.
Pitt J, Wilcox KC, Tortelli V, Diniz LP, Oliveira MS, Dobbins C, Yu X-W, Nandamuri S, Gomes FCA, DiNunno N, et al. (2017) Neuroprotective astrocyte-derived insulin/insulin-like growth factor 1 stimulates endocytic processing and extracellular release of neuron-bound Abeta oligomers. *Mol Biol Cell* **28**:2623–2636.
Poon WW, Blurton-Jones M, Tu CH, Feinberg LM, Chabrier MA, Harris JW, Jeon NL, and Cotman CW (2011) beta-Amyloid impairs axonal BDNF retrograde trafficking. *Neurobiol Aging* **32**:821–833.

Poon WW, Carlos AJ, Aguilar BL, Berchtold NC, Kawano CK, Zograbyan V, Yaopruke T, Shelanski M, and Cotman CW (2013) beta-Amyloid (Abeta) oligomers impair brain-derived neurotrophic factor retrograde trafficking by down-regulating ubiquitin C-terminal hydrolase, UCH-L1. *J Biol Chem* **288**:16937–16948.

Prévot T and Sibille E (2021) Altered GABA-mediated information processing and cognitive dysfunctions in depression and other brain disorders. *Mol Psychiatry* **26**:151–167.

Prévôt TD, Gastambide F, Viollet C, Henkous N, Martel G, Epelbaum J, Béracochéa D, and Guillou J-L (2017) Roles of Hippocampal Somatostatin Receptor Subtypes in Stress Response and Emotionality. *Neuropsychopharmacology* **42**:1647–1656.

Price BR, Johnson LA, and Norris CM (2021) Reactive astrocytes: The nexus of pathological and clinical hallmarks of Alzheimer's disease. *Ageing Res Rev* **68**:101335.

Price JL and Morris JC (1999) Tangles and plaques in nondemented aging and "preclinical" Alzheimer's disease. *Ann Neurol* **45**:358–368.

Prusiner SB (1984) Some speculations about prions, amyloid, and Alzheimer's disease. *N Engl J Med* **310**:661–663.

Puig E, Tolchard J, Riera A, and Carulla N (2020) Somatostatin, an In Vivo Binder to Abeta Oligomers, Binds to betaPFO(Abeta(1-42)) Tetramers. *ACS Chem Neurosci* **11**:3358–3365.

Qiu C, Zeyda T, Johnson B, Hochgeschwender U, de Lecea L, and Tallent MK (2008) Somatostatin receptor subtype 4 couples to the M-current to regulate seizures. *J Neurosci* **28**:3567–3576.

Racine A-S, Michon F-X, Laplante I, and Lacaille J-C (2021) Somatostatin contributes to long-term potentiation at excitatory synapses onto hippocampal somatostatinergic interneurons. *Mol Brain* **14**:130.

Ramos B, Baglietto-Vargas D, del Rio JC, Moreno-Gonzalez I, Santa-Maria C, Jimenez S, Caballero C, Lopez-Tellez JF, Khan ZU, Ruano D, et al. (2006) Early neuropathology of somatostatin/NPY GABAergic cells in the hippocampus of a PS1xAPP transgenic model of Alzheimer's disease. *Neurobiol Aging* **27**:1658–1672.

Ramser EM, Gan KJ, Decker H, Fan EY, Suzuki MM, Ferreira ST, and Silverman MA (2013) Amyloid-beta oligomers induce tau-independent disruption of BDNF axonal transport via calcineurin activation in cultured hippocampal neurons. *Mol Biol Cell* **24**:2494–2505.

Rana A and Musto AE (2018) The role of inflammation in the development of epilepsy. *J Neuroinflammation* **15**:144.

Reiner A and Levitz J (2018) Glutamatergic Signaling in the Central Nervous System: Ionotropic and Metabotropic Receptors in Concert. *Neuron* **98**:1080–1098.

Reinikainen KJ, Koponen H, Jolkkonen J, and Riekkinen PJ (1990) Decreased somatostatin-like immunoreactivity in the cerebrospinal fluid of chronic schizophrenic patients with cognitive impairment. *Psychiatry Res* **33**:307–312.

Reisberg B, Doody R, Stöffler A, Schmitt F, Ferris S, and Möbius HJ; Memantine Study Group (2003) Memantine in moderate-to-severe Alzheimer's disease. *N Engl J Med* **348**:1333–1341.

Riedemann T (2019) Diversity and Function of Somatostatin-Expressing Interneurons in the Cerebral Cortex. *Int J Mol Sci* **20**:2952.

Robertson MJ, Meyerowitz JG, Panova O, Borrelli K, and Skiniotis G (2022) Plasticity in ligand recognition at somatostatin receptors. *Nat Struct Mol Biol* **29**:210–217.

Robinson SL and Thiele TE (2020) A role for the neuropeptide somatostatin in the neurobiology of behaviors associated with substances abuse and affective disorders. *Neuropharmacology* **167**:107983.

Roceri M, Cirulli F, Pessina C, Peretto P, Racagni G, and Riva MA (2004) Postnatal repeated maternal deprivation produces age-dependent changes of brain-derived neurotrophic factor expression in selected rat brain regions. *Biol Psychiatry* **55**:708–714.

Rofo F, Ugur Yilmaz C, Metzendorf N, Gustavsson T, Beretta C, Erlandsson A, Sehlin D, Syvänen S, Nilsson P, and Hultqvist G (2021) Enhanced neprilysin-mediated degradation of hippocampal Abeta42 with a somatostatin peptide that enters the brain. *Theranostics* **11**:789–804.

Rogers SL, Doody RS, Pratt RD, and Ieni JR (2000) Long-term efficacy and safety of donepezil in the treatment of Alzheimer's disease: final analysis of a US multicentre open-label study. *Eur Neuropsychopharmacol* **10**:195–203.

Rohrer SP and Schaeffer JM (2000) Identification and characterization of subtype selective somatostatin receptor agonists. *J Physiol Paris* **94**:211–215.

Romoli M, Sen A, Parnetti L, Calabresi P, and Costa C (2021) Amyloid-beta: a potential link between epilepsy and cognitive decline. *Nat Rev Neurol* **17**:469–485.

Rossom R, Dysken, and M, Adityanjee (2004) Efficacy and tolerability of memantine in the treatment of dementia. *Am J Geriatr Pharmacother* **2**:303–312.

Rossor MN, Emson PC, Mountjoy CQ, Roth M, and Iversen LL (1980) Reduced amounts of immunoreactive somatostatin in the temporal cortex in senile dementia of Alzheimer type. *Neurosci Lett* **20**:373–377.

Ruangritchankul S, Chantharit P, Srisuma S, and Gray LC (2021) Adverse Drug Reactions of Acetylcholinesterase Inhibitors in Older People Living with Dementia: A Comprehensive Literature Review. *Ther Clin Risk Manag* **17**:927–949.

Rudy B, Fishell G, Lee S, and Hjerling-Leffler J (2011) Three groups of interneurons account for nearly 100% of neocortical GABAergic neurons. *Dev Neurobiol* **71**:45–61.

Russo R, Borghi R, Markesbery W, Tabaton M, and Piccini A (2005) Neprylisin decreases uniformly in Alzheimer's disease and in normal aging. *FEBS Lett* **579**:6027–6030.

Saito T, Iwata N, Tsubuki S, Takaki Y, Takano J, Huang S-M, Suemoto T, Higuchi M, and Saido TC (2005) Somatostatin regulates brain amyloid beta peptide Abeta42 through modulation of proteolytic degradation. *Nat Med* **11**:434–439.

Saiz-Sanchez D, Ubeda-Bañon I, de la Rosa-Prieto C, Argandoña-Palacios L, Garcia-Muñozguren S, Insausti R, and Martinez-Marcos A (2010) Somatostatin, tau, and beta-amyloid within the anterior olfactory nucleus in Alzheimer disease. *Exp Neurol* **223**:347–350.

Sakai A, Ujike H, Nakata K, Takehisa Y, Imamura T, Uchida N, Kanzaki A, Yamamoto M, Fujisawa Y, Okumura K, et al. (2004) Association of the Neprilysin gene with susceptibility to late-onset Alzheimer's disease. *Dement Geriatr Cogn Disord* **17**:164–169.

Salpekar JA and Mula M (2019) Common psychiatric comorbidities in epilepsy: How big of a problem is it? *Epilepsy Behav* **98**:293–297.

Salvadores N, Moreno-Gonzalez I, Gamez N, Quiroz G, Vegas-Gomez L, Escandón M, Jimenez S, Vitorica J, Gutierrez A, Soto C, et al. (2022) Abeta oligomers trigger necroptosis-mediated neurodegeneration via microglia activation in Alzheimer's disease. *Acta Neuropathol Commun* **10**:31.

Samanta SR and Ramesh M (2022) Alzheimer's is a multifactorial disease, in *Alzheimer's Disease: Recent Findings in Pathophysiology, Diagnostic and Therapeutic Modalities* (Govindaraju T, ed) pp 1–34, Royal Society of Chemistry Publishing, Cambridge, UK.

Samson WK, Zhang JV, Avsian-Kretchmer O, Cui K, Yosten GLC, Klein C, Lyu R-M, Wang YX, Chen XQ, Yang J, et al. (2008) Neuronostatin encoded by the somatostatin gene regulates neuronal, cardiovascular, and metabolic functions. *J Biol Chem* **283**:31949–31959.

Sánchez-Muñoz I, Sánchez-Franco F, Vallejo M, Fernández A, Palacios N, Fernández M, Sánchez-Grande M, and Cacicedo L (2011) Regulation of somatostatin gene expression by brain derived neurotrophic factor in fetal rat cerebrocortical cells. *Brain Res* **1375**:28–40.

Sandoval KE, Farr SA, Banks WA, Crider AM, Morley JE, and Witt KA (2012) Somatostatin receptor subtype-4 agonist NNC 26-9100 decreases extracellular and intracellular Abeta(1-42) trimers. *Eur J Pharmacol* **683**:116–124.

Sandoval KE, Farr SA, Banks WA, Crider AM, Morley JE, and Witt KA (2013) Somatostatin receptor subtype-4 agonist NNC 26-9100 mitigates the effect of soluble Abeta(42) oligomers via a metalloproteinase-dependent mechanism. *Brain Res* **1520**:145–156.

Sandoval K, Umbaugh D, House A, Crider A, and Witt K (2019) Somatostatin Receptor Subtype-4 Regulates mRNA Expression of Amyloid-Beta Degrading Enzymes and Microglia Mediators of Phagocytosis in Brains of 3xTg-AD Mice. *Neurochem Res* **44**:2670–2680.

Savonenko A, Xu GM, Melnikova T, Morton JL, Gonzales V, Wong MPF, Price DL, Tang F, Markowska AL, and Borchelt DR (2005) Episodic-like memory deficits in the APPswe/PS1dE9 mouse model of Alzheimer's disease: relationships to beta-amyloid deposition and neurotransmitter abnormalities. *Neurobiol Dis* **18**:602–617.

Scharfman H, Goodman J, Macleod A, Phani S, Antonelli C, and Croll S (2005) Increased neurogenesis and the ectopic granule cells after intrahippocampal BDNF infusion in adult rats. *Exp Neurol* **192**:348–356.

Scharfman HE and Schwartzkroin PA (1989) Selective depression of GABA-mediated IPSPs by somatostatin in area CA1 of rabbit hippocampal slices. *Brain Res* **493**:205–211.

Scheich B, Gaszner B, Kormos V, László K, Ádori C, Borbély É, Hajna Z, Tékus V, Bölcskei K, Ábrahám I, et al. (2016) Somatostatin receptor subtype 4 activation is involved in anxiety and depression-like behavior in mouse models. *Neuropharmacology* **101**:204–215.

Schettini G, Florio T, Magri G, Grimaldi M, Meucci O, Landolfi E, and Marino A (1988) Somatostatin and SMS 201-995 reverse the impairment of cognitive functions induced by cysteamine depletion of brain somatostatin. *Eur J Pharmacol* **151**:399–407.

Schmid LC, Mittag M, Poll S, Steffen J, Wagner J, Geis H-R, Schwarz I, Schmidt B, Schwarz MK, Remy S, et al. (2016) Dysfunction of Somatostatin-Positive Interneurons Associated with Memory Deficits in an Alzheimer's Disease Model. *Neuron* **92**:114–125.

Schober J, Polina J, Walters F, Scott N, Lodholz E, Crider A, Sandoval K, and Witt K (2021) NNC 26-9100 increases Abeta1-42 phagocytosis, inhibits nitric oxide production and decreases calcium in BV2 microglia cells. *PLoS One* **16**:e0254242.

Schreff M, Schulz S, Händel M, Keilhoff G, Braun H, Pereira G, Klutzny M, Schmidt H, Wolf G, and Höllt V (2000) Distribution, targeting, and internalization of the sst4 somatostatin receptor in rat brain. *J Neurosci* **20**:3785–3797.

Schulz S, Händel M, Schreff M, Schmidt H, and Höllt V (2000) Localization of five somatostatin receptors in the rat central nervous system using subtype-specific antibodies. *J Physiol Paris* **94**:259–264.

Schweitzer P, Madamba SG, and Siggins GR (1998) Somatostatin increases a voltage-insensitive K+ conductance in rat CA1 hippocampal neurons. *J Neurophysiol* **79**:1230–1238.

Scott L, Feng J, Kiss T, Needle E, Atchison K, Kawabe TT, Milici AJ, Hajos-Korcsok E, Riddell D, and Hajos M (2012) Age-dependent disruption in hippocampal theta oscillation in amyloid-beta overproducing transgenic mice. *Neurobiol Aging* **33**:1481.e1413–1423.

Scott HA, Gebhardt FM, Mitrovic AD, Vandenberg RJ, and Dodd PR (2011) Glutamate transporter variants reduce glutamate uptake in Alzheimer's disease. *Neurobiol Aging* **32**:553–e551-511.

Selkoe DJ (2008) Soluble oligomers of the amyloid beta-protein impair synaptic plasticity and behavior. *Behav Brain Res* **192**:106–113.

Selkoe DJ (2019) Early network dysfunction in Alzheimer's disease. *Science* **365**:540–541.

Selkoe DJ and Hardy J (2016) The amyloid hypothesis of Alzheimer's disease at 25 years. *EMBO Mol Med* **8**:595–608.

Sen A, Nelson TJ, and Alkon DL (2015) ApoE4 and Abeta Oligomers Reduce BDNF Expression via HDAC Nuclear Translocation. *J Neurosci* **35**:7538–7551.

Seney ML, Tripp A, McCune S, Lewis DA, and Sibille E (2015) Laminar and cellular analyses of reduced somatostatin gene expression in the subgenual anterior cingulate cortex in major depression. *Neurobiol Dis* **73**:213–219.

Sengillo JD, Winkler EA, Walker CT, Sullivan JS, Johnson M, and Zlokovic BV (2013) Deficiency in mural vascular cells coincides with blood-brain barrier disruption in Alzheimer's disease. *Brain Pathol* **23**:303–310.

Shankar GM, Bloodgood BL, Townsend M, Walsh DM, Selkoe DJ, and Sabatini BL (2007) Natural oligomers of the Alzheimer amyloid-beta protein induce reversible synapse loss by modulating an NMDA-type glutamate receptor-dependent signaling pathway. *J Neurosci* **27**:2866–2875.

Shankar GM, Li S, Mehta TH, Garcia-Munoz A, Shepardson NE, Smith I, Brett FM, Farrell MA, Rowan MJ, Lemere CA, et al. (2008) Amyloid-beta protein dimers isolated directly from Alzheimer's brains impair synaptic plasticity and memory. *Nat Med* **14**:837–842.
Sharma V, Sood R, Khlaifia A, Eslamizade MJ, Hung T-Y, Lou D, Asgarihafshejani A, Lalzar M, Kiniry SJ, Stokes MP, et al. (2020) eIF2alpha controls memory consolidation via excitatory and somatostatin neurons. *Nature* **586**:412–416.
Shen W, Li Z, Tang Y, Han P, Zhu F, Dong J, Ma T, Zhao K, Zhang X, Xie Y, et al. (2022) Somatostatin interneurons inhibit excitatory transmission mediated by astrocytic GABA(B) and presynaptic GABA(B) and adenosine A(1) receptors in the hippocampus. *J Neurochem* **163**:310–326.
Sherman MA, LaCroix M, Amar F, Larson ME, Forster C, Aguzzi A, Bennett DA, Ramsden M, and Lesné SE (2016) Soluble Conformers of Abeta and Tau Alter Selective Proteins Governing Axonal Transport. *J Neurosci* **36**:9647–9658.
Shi M, Chu F, Zhu F, and Zhu J (2022) Impact of Anti-amyloid-beta Monoclonal Antibodies on the Pathology and Clinical Profile of Alzheimer's Disease: A Focus on Aducanumab and Lecanemab. *Front Aging Neurosci* **14**:870517.
Shi A, Petrache AL, Shi J, and Ali AB (2020) Preserved Calretinin Interneurons in an App Model of Alzheimer's Disease Disrupt Hippocampal Inhibition via Upregulated P2Y1 Purinoreceptors. *Cereb Cortex* **30**:1272–1290.
Shirotani K, Tsubuki S, Iwata N, Takaki Y, Harigaya W, Maruyama K, Kiryu-Seo S, Kiyama H, Iwata H, Tomita T, et al. (2001) Neprilysin degrades both amyloid beta peptides 1-40 and 1-42 most rapidly and efficiently among thiorphan- and phosphoramidon-sensitive endopeptidases. *J Biol Chem* **276**:21895–21901.
Sibille E, Morris HM, Kota RS, and Lewis DA (2011) GABA-related transcripts in the dorsolateral prefrontal cortex in mood disorders. *Int J Neuropsychopharmacol* **14**:721–734.
Siegle JH and Wilson MA (2014) Enhancement of encoding and retrieval functions through theta phase-specific manipulation of hippocampus. *Elife* **3**:e03061.
Siehler S, Nunn C, Hannon J, Feuerbach D, and Hoyer D (2008) Pharmacological profile of somatostatin and cortistatin receptors. *Mol Cell Endocrinol* **286**:26–34.
Silwal A, House A, Sandoval K, Vijeth S, Umbaugh D, Crider A, Mobayen S, Neumann W, and Witt KA (2021) Novel Somatostatin Receptor-4 Agonist SM-I-26 Mitigates Lipopolysaccharide-Induced Inflammatory Gene Expression in Microglia. *Neurochem Res* **47**:768–780.
Sjöstedt E, Zhong W, Fagerberg L, Karlsson M, Mitsios N, Adori C, Oksvold P, Edfors F, Limiszewska A, Hikmet F, et al. (2020) An atlas of the protein-coding genes in the human, pig, and mouse brain. *Science* **367**:eaay5947.
Sloviter RS (1987) Decreased hippocampal inhibition and a selective loss of interneurons in experimental epilepsy. *Science* **235**:73–76.
Smalley KS, Koenig JA, Feniuk W, and Humphrey PP (2001) Ligand internalization and recycling by human recombinant somatostatin type 4 (h sst(4)) receptors expressed in CHO-K1 cells. *Br J Pharmacol* **132**:1102–1110.
Smith PA, Sellers LA, and Humphrey PP (2001) Somatostatin activates two types of inwardly rectifying K+ channels in MIN-6 cells. *J Physiol* **532**:127–142.
Snider BJ, Norton J, Coats MA, Chakraverty S, Hou CE, Jervis R, Lendon CL, Goate AM, McKeel DW, and Morris JC (2005) Novel presenilin 1 mutation (S170F) causing Alzheimer disease with Lewy bodies in the third decade of life. *Arch Neurol* **62**:1821–1830.
Soininen HS, Jolkkonen JT, Reinikainen KJ, Halonen TO, and Riekkinen PJ (1984) Reduced cholinesterase activity and somatostatin-like immunoreactivity in the cerebrospinal fluid of patients with dementia of the Alzheimer type. *J Neurol Sci* **63**:167–172.
Solarski M, Wang H, Wille H, and Schmitt-Ulms G (2018) Somatostatin in Alzheimer's disease: A new Role for an Old Player. *Prion* **12**:1–8.
Sondag CM, Dhawan G, and Combs CK (2009) Beta amyloid oligomers and fibrils stimulate differential activation of primary microglia. *J Neuroinflammation* **6**:1.
Soumier A and Sibille E (2014) Opposing effects of acute versus chronic blockade of frontal cortex somatostatin-positive inhibitory neurons on behavioral emotionality in mice. *Neuropsychopharmacology* **39**:2252–2262.
Spalletta G, Caltagirone C, Girardi P, Gianni W, Casini AR, and Palmer K (2012) The role of persistent and incident major depression on rate of cognitive deterioration in newly diagnosed Alzheimer's disease patients. *Psychiatry Res* **198**:263–268.
Spalletta G, Long JD, Robinson RG, Trequattrini A, Pizzoli S, Caltagirone C, and Orfei MD (2015) Longitudinal Neuropsychiatric Predictors of Death in Alzheimer's Disease. *J Alzheimers Dis* **48**:627–636.
Spalletta G, Musicco M, Padovani A, Rozzini L, Perri R, Fadda L, Canonico V, Trequattrini A, Pettenati C, Caltagirone C, et al. (2010) Neuropsychiatric symptoms and syndromes in a large cohort of newly diagnosed, untreated patients with Alzheimer disease. *Am J Geriatr Psychiatry* **18**:1026–1035.
Speers LJ and Bilkey DK (2021) Disorganization of Oscillatory Activity in Animal Models of Schizophrenia. *Front Neural Circuits* **15**:741767.
Spijker AT and van Rossum EFC (2012) Glucocorticoid sensitivity in mood disorders. *Neuroendocrinology* **95**:179–186.
Sponne I, Fifre A, Drouet B, Klein C, Koziel V, Pinçon-Raymond M, Olivier J-L, Chambaz J, and Pillot T (2003) Apoptotic neuronal cell death induced by the non-fibrillar amyloid-beta peptide proceeds through an early reactive oxygen species-dependent cytoskeleton perturbation. *J Biol Chem* **278**:3437–3445.
Stargardt A, Gillis J, Kamphuis W, Wiemhoefer A, Kooijman L, Raspe M, Benckhuijsen W, Drijfhout JW, Hol EM, and Reits E (2013) Reduced amyloid-beta degradation in early Alzheimer's disease but not in the APPswePS1dE9 and 3xTg-AD mouse models. *Aging Cell* **12**:499–507.
Stengel A and Taché YF (2017) Activation of Brain Somatostatin Signaling Suppresses CRF Receptor-Mediated Stress Response. *Front Neurosci* **11**:231.
Strowski MZ, Dashkevicz MP, Parmar RM, Wilkinson H, Kohler M, Schaeffer JM, and Blake AD (2002) Somatostatin receptor subtypes 2 and 5 inhibit corticotropin-releasing hormone-stimulated adrenocorticotropin secretion from AtT-20 cells. *Neuroendocrinology* **75**:339–346.
Subedi S, Sasidharan S, Nag N, Saudagar P, and Tripathi T (2022) Amyloid Cross-Seeding: Mechanism, Implication, and Inhibition. *Molecules* **27**:1776.
Sun LY, Al-Regaiey K, Masternak MM, Wang J, and Bartke A (2005) Local expression of GH and IGF-1 in the hippocampus of GH-deficient long-lived mice. *Neurobiol Aging* **26**:929–937.
Suzuki N and Bekkers JM (2010) Distinctive classes of GABAergic interneurons provide layer-specific phasic inhibition in the anterior piriform cortex. *Cereb Cortex* **20**:2971–2984.
Swaab DF, Bao A-M, and Lucassen PJ (2005) The stress system in the human brain in depression and neurodegeneration. *Ageing Res Rev* **4**:141–194.
Szabo S and Reichlin S (1981) Somatostatin in rat tissues is depleted by cysteamine administration. *Endocrinology* **109**:2255–2257.
Szatloczki G, Hoffmann I, Vincze V, Kalman J, and Pakaski M (2015) Speaking in Alzheimer's Disease, is That an Early Sign? Importance of Changes in Language Abilities in Alzheimer's Disease. *Front Aging Neurosci* **7**:195.
Szepesi Z, Manouchehrian O, Bachiller S, and Deierborg T (2018) Bidirectional Microglia-Neuron Communication in Health and Disease. *Front Cell Neurosci* **12**:323.
Tabner BJ, El-Agnaf OMA, Turnbull S, German MJ, Paleologou KE, Hayashi Y, Cooper LJ, Fullwood NJ, and Allsop D (2005) Hydrogen peroxide is generated during the very early stages of aggregation of the amyloid peptides implicated in Alzheimer disease and familial British dementia. *J Biol Chem* **280**:35789–35792.
Takahashi RH, Nagao T, and Gouras GK (2017) Plaque formation and the intraneuronal accumulation of beta-amyloid in Alzheimer's disease. *Pathol Int* **67**:185–193.
Takaki Y, Iwata N, Tsubuki S, Taniguchi S, Toyoshima S, Lu B, Gerard NP, Gerard C, Lee HJ, Shirotani K, et al. (2000) Biochemical identification of the neutral endopeptidase family member responsible for the catabolism of amyloid beta peptide in the brain. *J Biochem* **128**:897–902.
Takata F, Nakagawa S, Matsumoto J, and Dohgu S (2021) Blood-Brain Barrier Dysfunction Amplifies the Development of Neuroinflammation: Understanding of Cellular Events in Brain Microvascular Endothelial Cells for Prevention and Treatment of BBB Dysfunction. *Front Cell Neurosci* **15**:661838.
Tallent MK and Qiu C (2008) Somatostatin: an endogenous antiepileptic. *Mol Cell Endocrinol* **286**:96–103.
Tallent MK and Siggins GR (1997) Somatostatin depresses excitatory but not inhibitory neurotransmission in rat CA1 hippocampus. *J Neurophysiol* **78**:3008–3018.
Tallent MK and Siggins GR (1999) Somatostatin acts in CA1 and CA3 to reduce hippocampal epileptiform activity. *J Neurophysiol* **81**:1626–1635.
Tapia-Arancibia L and Astier H (1989) Actions of excitatory amino acids on somatostatin release from cortical neurons in primary cultures. *J Neurochem* **53**:1134–1141.
Tariot PN, Farlow MR, Grossberg GT, Graham SM, McDonald S, and Gergel I; Memantine Study Group (2004) Memantine treatment in patients with moderate to severe Alzheimer disease already receiving donepezil: a randomized controlled trial. *JAMA* **291**:317–324.
Tokita K, Inoue T, Yamazaki S, Wang F, Yamaji T, Matsuoka N, and Mutoh S (2005) FK962, a novel enhancer of somatostatin release, exerts cognitive-enhancing actions in rats. *Eur J Pharmacol* **527**:111–120.
Tokita K, Yamazaki S, Yamazaki M, Matsuoka N, and Mutoh S (2002) Combination of a novel antidementia drug FK960 with donepezil synergistically improves memory deficits in rats. *Pharmacol Biochem Behav* **73**:511–519.
Tolchin B, Hirsch LJ, and LaFrance WC (2020) Neuropsychiatric Aspects of Epilepsy. *Psychiatr Clin North Am* **43**:275–290.
Tomiyama T, Matsuyama S, Iso H, Umeda T, Takuma H, Ohnishi K, Ishibashi K, Teraoka R, Sakama N, Yamashita T, et al. (2010) A mouse model of amyloid beta oligomers: their contribution to synaptic alteration, abnormal tau phosphorylation, glial activation, and neuronal loss in vivo. *J Neurosci* **30**:4845–4856.
Tomoda T, Sumitomo A, Newton D, and Sibille E (2022) Molecular origin of somatostatin-positive neuron vulnerability. *Mol Psychiatry* **27**:2304–2314.
Tooyama I, Kimura H, Akiyama H, and McGeer PL (1990) Reactive microglia express class I and class II major histocompatibility complex antigens in Alzheimer's disease. *Brain Res* **523**:273–280.
Topolnik L and Tamboli S (2022) The role of inhibitory circuits in hippocampal memory processing. *Nat Rev Neurosci* **23**:476–492.
Townsend M, Shankar GM, Mehta T, Walsh DM, and Selkoe DJ (2006) Effects of secreted oligomers of amyloid beta-protein on hippocampal synaptic plasticity: a potent role for trimers. *J Physiol* **572**:477–492.
Tripp A, Kota RS, Lewis DA, and Sibille E (2011) Reduced somatostatin in subgenual anterior cingulate cortex in major depression. *Neurobiol Dis* **42**:116–124.
Tripp A, Oh H, Guilloux J-P, Martinowich K, Lewis DA, and Sibille E (2012) Brain-derived neurotrophic factor signaling and subgenual anterior cingulate cortex dysfunction in major depressive disorder. *Am J Psychiatry* **169**:1194–1202.
Troubat R, Barone P, Leman S, Desmidt T, Cressant A, Atanasova B, Brizard B, El Hage W, Surget A, Belzung C, et al. (2021) Neuroinflammation and depression: A review. *Eur J Neurosci* **53**:151–171.
Tsai Z-R, Zhang H-W, Tseng C-H, Peng H-C, Kok VC, Li GP, Hsiung CA, and Hsu C-Y (2021) Late-onset epilepsy and subsequent increased risk of dementia. *Aging (Albany NY)* **13**:3573–3587.
Tundo G, Ciaccio C, Sbardella D, Boraso M, Viviani B, Coletta M, and Marini S (2012) Somatostatin modulates insulin-degrading-enzyme metabolism: implications for the regulation of microglia activity in AD. *PLoS One* **7**:e34376.
Tundo GR, Di Muzio E, Ciaccio C, Sbardella D, Di Pierro D, Polticelli F, Coletta M, and Marini S (2016) Multiple allosteric sites are involved in the modulation of insulin-degrading-enzyme activity by somatostatin. *FEBS J* **283**:3755–3770.
Tundo GR, Sbardella D, Ciaccio C, Grasso G, Gioia M, Coletta A, Polticelli F, Di Pierro D, Milardi D, Van Endert P, et al. (2017) Multiple functions of insulin-degrading enzyme: a metabolic crosslight? *Crit Rev Biochem Mol Biol* **52**:554–582.
Uddin MS, Rahman MM, Jakaria M, Rahman MS, Hossain MS, Islam A, Ahmed M, Mathew B, Omar UM, Barreto GE, et al. (2020) Estrogen Signaling in Alzheimer's Disease: Molecular Insights and Therapeutic Targets for Alzheimer's Dementia. *Mol Neurobiol* **57**:2654–2670.

Umeda T, Tomiyama T, Sakama N, Tanaka S, Lambert MP, Klein WL, and Mori H (2011) Intraneuronal amyloid beta oligomers cause cell death via endoplasmic reticulum stress, endosomal/lysosomal leakage, and mitochondrial dysfunction in vivo. *J Neurosci Res* **89**:1031–1042.
Unterberger I, Trinka E, Ransmayr G, Scherfler C, and Bauer G (2021) Epileptic aphasia - A critical appraisal. *Epilepsy Behav* **121**:108064.
Urban-Ciecko J and Barth AL (2016) Somatostatin-expressing neurons in cortical networks. *Nat Rev Neurosci* **17**:401–409.
Urban-Ciecko J, Jouhanneau J-S, Myal SE, Poulet JFA, and Barth AL (2018) Precisely Timed Nicotinic Activation Drives SST Inhibition in Neocortical Circuits. *Neuron* **97**:611–625.e5.
van Dalen JW, Caan MWA, van Gool WA, and Richard E (2017) Neuropsychiatric symptoms of cholinergic deficiency occur with degradation of the projections from the nucleus basalis of Meynert. *Brain Imaging Behav* **11**:1707–1719.
van den Berg MT, Wester VL, Vreeker A, Koenders MA, Boks MP, van Rossum EFC, and Spijker AT (2020) Higher cortisol levels may proceed a manic episode and are related to disease severity in patients with bipolar disorder. *Psychoneuroendocrinology* **119**:104658.
van Grondelle W, Iglesias CL, Coll E, Artzner F, Paternostre M, Lacombe F, Cardus M, Martinez G, Montes M, Cherif-Cheikh R, et al. (2007) Spontaneous fibrillation of the native neuropeptide hormone Somatostatin-14. *J Struct Biol* **160**:211–223.
Van Op den Bosch J, Torfs P, De Winter BY, De Man JG, Pelckmans PA, Van Marck E, Grundy D, Van Nassauw L, and Timmermans J-P (2009) Effect of genetic SSTR4 ablation on inflammatory peptide and receptor expression in the non-inflamed and inflamed murine intestine. *J Cell Mol Med* **13**:3283–3295.
van Vliet EA and Marchi N (2022) Neurovascular unit dysfunction as a mechanism of seizures and epilepsy during aging. *Epilepsia* **63**:1297–1313.
Vanetti M, Kouba M, Wang X, Vogt G, and Höllt V (1992) Cloning and expression of a novel mouse somatostatin receptor (SSTR2B). *FEBS Lett* **311**:290–294.
Vécsei L and Widerlöv E (1988) Effects of intracerebroventricularly administered somatostatin on passive avoidance, shuttle-box behaviour and open-field activity in rats. *Neuropeptides* **12**:237–242.
Vécsei L, Alling C, and Widerlöv E (1990) Comparative studies of intracerebroventricularly administered cysteamine and pantethine in different behavioral tests and on brain catecholamines in rats. *Arch Int Pharmacodyn Ther* **305**:140–151.
Vécsei L, Bollók I, and Telegdy G (1983a) Comparative studies with cyclic and linear somatostatin on active avoidance behaviour and open-field activity in rats. *Acta Physiol Hung* **61**:43–49.
Vécsei L, Bollók I, and Telegdy G (1983b) The effect of linear somatostatin on the active avoidance behaviour and open-field activity on haloperidol, phenoxybenzamine and atropine pretreated rats. *Acta Physiol Hung* **62**:205–211.
Vécsei L, Bollók I, and Telegdy G (1983c) Intracerebroventricular somatostatin attenuates electroconvulsive shock-induced amnesia in rats. *Peptides* **4**:293–295.
Vécsei L, Bollók I, Varga J, Penke B, and Telegdy G (1984a) The effects of somatostatin, its fragments and an analog on electroconvulsive shock-induced amnesia in rats. *Neuropeptides* **4**:137–143.
Vécsei L, Király C, Bollók I, Nagy A, Varga J, Penke B, and Telegdy G (1984b) Comparative studies with somatostatin and cysteamine in different behavioral tests on rats. *Pharmacol Biochem Behav* **21**:833–837.
Vécsei L, Pavo I, Zsigo J, Penke B, and Widerlöv E (1989) Comparative studies of somatostatin-14 and some of its fragments on passive avoidance behavior, open field activity and on barrel rotation phenomenon in rats. *Peptides* **10**:1153–1157.
Vepsäläinen S, Helisalmi S, Koivisto AM, Tapaninen T, Hiltunen M, and Soininen H (2007a) Somatostatin genetic variants modify the risk for Alzheimer's disease among Finnish patients. *J Neurol* **254**:1504–1508.
Vepsäläinen S, Parkinson M, Helisalmi S, Mannermaa A, Soininen H, Tanzi RE, Bertram L, and Hiltunen M (2007b) Insulin-degrading enzyme is genetically associated with Alzheimer's disease in the Finnish population. *J Med Genet* **44**:606–608.
Vermunt L, Sikkes SAM, van den Hout A, Handels R, Bos I, van der Flier WM, Kern S, Ousset PJ, Maruff P, Skoog I, et al.; Alzheimer Disease Neuroimaging Initiative (2019) Duration of preclinical, prodromal, and dementia stages of Alzheimer's disease in relation to age, sex, and APOE genotype. *Alzheimers Dement* **15**:888–898.
Versele R, Sevin E, Gosselet F, Fenart L, and Candela P (2022) TNF-alpha and IL-1beta Modulate Blood-Brain Barrier Permeability and Decrease Amyloid-beta Peptide Efflux in a Human Blood-Brain Barrier Model. *Int J Mol Sci* **23**:10235.
Vezzani A, Monno A, Rizzi M, Galli A, Barrios M, and Samanin R (1992) Somatostatin release is enhanced in the hippocampus of partially and fully kindled rats. *Neuroscience* **51**:41–46.
Vezzani A, Ravizza T, Bedner P, Aronica E, Steinhäuser C, and Boison D (2022) Astrocytes in the initiation and progression of epilepsy. *Nat Rev Neurol* **18**:707–722.
Vezzani A, Serafini R, Stasi MA, Viganò G, Rizzi M, and Samanin R (1991) A peptidase-resistant cyclic octapeptide analogue of somatostatin (SMS 201-995) modulates seizures induced by quinolinic and kainic acids differently in the rat hippocampus. *Neuropharmacology* **30**:345–352.
Viana F and Hille B (1996) Modulation of high voltage-activated calcium channels by somatostatin in acutely isolated rat amygdaloid neurons. *J Neurosci* **16**:6000–6011.
Villette V, Poindessous-Jazat F, Simon A, Léna C, Roullot E, Bellessort B, Epelbaum J, Dutar P, and Stéphan A (2010) Decreased rhythmic GABAergic septal activity and memory-associated theta oscillations after hippocampal amyloid-beta pathology in the rat. *J Neurosci* **30**:10991–11003.
Villuendas G, Sánchez-Franco F, Palacios N, Fernández M, and Cacicedo L (2001) Involvement of VIP on BDNF-induced somatostatin gene expression in cultured fetal rat cerebral cortical cells. *Brain Res Mol Brain Res* **94**:59–66.
Viollet C, Lepousez G, Loudes C, Videau C, Simon A, and Epelbaum J (2008) Somatostatinergic systems in brain: networks and functions. *Mol Cell Endocrinol* **286**:75–87.
Viollet C, Vaillend C, Videau C, Bluet-Pajot MT, Ungerer A, L'Héritier A, Kopp C, Potier B, Billard J, Schaeffer J, et al. (2000) Involvement of sst2 somatostatin receptor in locomotor, exploratory activity and emotional reactivity in mice. *Eur J Neurosci* **12**:3761–3770.
Vöglein J, Ricard I, Noachtar S, Kukull WA, Dieterich M, Levin J, and Danek A (2020) Seizures in Alzheimer's disease are highly recurrent and associated with a poor disease course. *J Neurol* **267**:2941–2948.
Voineskos D, Daskalakis ZJ, and Blumberger DM (2020) Management of Treatment-Resistant Depression: Challenges and Strategies. *Neuropsychiatr Dis Treat* **16**:221–234.
Vossel KA, Beagle AJ, Rabinovici GD, Shu H, Lee SE, Naasan G, Hegde M, Cornes SB, Henry ML, Nelson AB, et al. (2013) Seizures and epileptiform activity in the early stages of Alzheimer disease. *JAMA Neurol* **70**:1158–1166.
Vossel KA, Ranasinghe KG, Beagle AJ, Mizuiri D, Honma SM, Dowling AF, Darwish SM, Van Berlo V, Barnes DE, Mantle M, et al. (2016) Incidence and impact of subclinical epileptiform activity in Alzheimer's disease. *Ann Neurol* **80**:858–870.
Vossel KA, Tartaglia MC, Nygaard HB, Zeman AZ, and Miller BL (2017) Epileptic activity in Alzheimer's disease: causes and clinical relevance. *Lancet Neurol* **16**:311–322.
Wakeman DR, Weed MR, Perez SE, Cline EN, Viola KL, Wilcox KC, Moddrelle DS, Nisbett EZ, Kurian AM, Bell AF, et al. (2022) Intrathecal amyloid-beta oligomer administration increases tau phosphorylation in the medial temporal lobe in the African green monkey: A nonhuman primate model of Alzheimer's disease. *Neuropathol Appl Neurobiol* **48**:e12800.
Waller R, Mandeya M, Viney E, Simpson JE, and Wharton SB (2020) Histological characterization of interneurons in Alzheimer's disease reveals a loss of somatostatin interneurons in the temporal cortex. *Neuropathology* **40**:336–346.
Wan W, Cao L, Liu L, Zhang C, Kalionis B, Tai X, LY, and Xia S (2015) Abeta(1-42) oligomer-induced leakage in an in vitro blood-brain barrier model is associated with up-regulation of RAGE and metalloproteinases, and down-regulation of tight junction scaffold proteins. *J Neurochem* **134**:382–393.
Wang AY, Lohmann KM, Yang CK, Zimmerman EI, Pantazopoulos H, Herring N, Berretta S, Heckers S, and Konradi C (2011) Bipolar disorder type 1 and schizophrenia are accompanied by decreased density of parvalbumin- and somatostatin-positive interneurons in the parahippocampal region. *Acta Neuropathol* **122**:615–626.
Wang F, Shu C, Jia L, Zuo X, Zhang Y, Zhou A, Qin W, Song H, Wei C, Zhang F, et al. (2012) Exploration of 16 candidate genes identifies the association of IDE with Alzheimer's disease in Han Chinese. *Neurobiol Aging* **33**:1014.e1–9.
Wang H, Muiznieks LD, Ghosh P, Williams D, Solarski M, Fang A, Ruiz-Riquelme A, Pomès R, Watts JC, Chakrabartty A, et al. (2017) Somatostatin binds to the human amyloid beta peptide and favors the formation of distinct oligomers. *Elife* **6**:e28401.
Wang J, Ikonen S, Gurevicius K, van Groen T, and Tanila H (2002) Alteration of cortical EEG in mice carrying mutated human APP transgene. *Brain Res* **943**:181–190.
Wang Q, Van Heerikhuize J, Aronica E, Kawata M, Seress L, Joels M, Swaab DF, and Lucassen PJ (2013) Glucocorticoid receptor protein expression in human hippocampus; stability with age. *Neurobiol Aging* **34**:1662–1673.
Wang S, Wang R, Chen L, Bennett DA, Dickson DW, and Wang D-S (2010) Expression and functional profiling of neprilysin, insulin-degrading enzyme, and endothelin-converting enzyme in prospectively studied elderly and Alzheimer's brain. *J Neurochem* **115**:47–57.
Wang Y, Wang Y, Xu C, Wang S, Tan N, Chen C, Chen L, Wu X, Fei F, Cheng H, et al. (2020) Direct Septum-Hippocampus Cholinergic Circuit Attenuates Seizure Through Driving Somatostatin Inhibition. *Biol Psychiatry* **87**:843–856.
Watson GS, Baker LD, Cholerton BA, Rhoads KW, Merriam GR, Schellenberg GD, Asthana S, Cherrier M, and Craft S (2009) Effects of insulin and octreotide on memory and growth hormone in Alzheimer's disease. *J Alzheimers Dis* **18**:595–602.
Weekman EM and Wilcock DM (2016) Matrix Metalloproteinase in Blood-Brain Barrier Breakdown in Dementia. *J Alzheimers Dis* **49**:893–903.
Wei Z, Koya J, and Reznik SE (2021) Insulin Resistance Exacerbates Alzheimer Disease via Multiple Mechanisms. *Front Neurosci* **15**:687157.
Welcome MO (2020) Cellular mechanisms and molecular signaling pathways in stress-induced anxiety, depression, and blood-brain barrier inflammation and leakage. *Inflammopharmacology* **28**:643–665.
Welikovitch LA, Do Carmo S, Maglóczky Z, Szocsics P, Lőke J, Freund T, and Cuello AC (2018) Evidence of intraneuronal Abeta accumulation preceding tau pathology in the entorhinal cortex. *Acta Neuropathol* **136**:901–917.
Whitehouse PJ, Price DL, Clark AW, Coyle JT, and DeLong MR (1981) Alzheimer disease: evidence for selective loss of cholinergic neurons in the nucleus basalis. *Ann Neurol* **10**:122–126.
Wiels WA, Wittens MMJ, Zeeuws D, Baeken C, and Engelborghs S (2021) Neuropsychiatric Symptoms in Mild Cognitive Impairment and Dementia Due to AD: Relation With Disease Stage and Cognitive Deficits. *Front Psychiatry* **12**:707580.
Wood LS, Pickering EH, McHale D, and Dechairo BM (2007) Association between neprilysin polymorphisms and sporadic Alzheimer's disease. *Neurosci Lett* **427**:103–106.
Xu H, Garcia-Ptacek S, Jönsson L, Wimo A, Nordström P, and Eriksdotter M (2021) Long-term Effects of Cholinesterase Inhibitors on Cognitive Decline and Mortality. *Neurology* **96**:e2220–e2230.
Xu X, Roby KD, and Callaway EM (2006) Mouse cortical inhibitory neuron type that coexpresses somatostatin and calretinin. *J Comp Neurol* **499**:144–160.
Xue S, Jia L, and Jia J (2009) Association between somatostatin gene polymorphisms and sporadic Alzheimer's disease in Chinese population. *Neurosci Lett* **465**:181–183.
Yan P, Xue Z, Li D, Ni S, Wang C, Jin X, Zhou D, Li X, Zhao X, Chen X, et al. (2021) Dysregulated CRTC1-BDNF signaling pathway in the hippocampus

contributes to Abeta oligomer-induced long-term synaptic plasticity and memory impairment. *Exp Neurol* **345**:113812.
Yang T, Li S, Xu H, Walsh DM, and Selkoe DJ (2017) Large Soluble Oligomers of Amyloid beta-Protein from Alzheimer Brain Are Far Less Neuroactive Than the Smaller Oligomers to Which They Dissociate. *J Neurosci* **37**:152–163.
Yasojima K, Akiyama H, McGeer EG, and McGeer PL (2001a) Reduced neprilysin in high plaque areas of Alzheimer brain: a possible relationship to deficient degradation of beta-amyloid peptide. *Neurosci Lett* **297**:97–100.
Yasojima K, McGeer EG, and McGeer PL (2001b) Relationship between beta amyloid peptide generating molecules and neprilysin in Alzheimer disease and normal brain. *Brain Res* **919**:115–121.
Yassa MA, Lacy JW, Stark SM, Albert MS, Gallagher M, and Stark CEL (2011) Pattern separation deficits associated with increased hippocampal CA3 and dentate gyrus activity in nondemented older adults. *Hippocampus* **21**:968–979.
Yeung M and Treit D (2012) The anxiolytic effects of somatostatin following intra-septal and intra-amygdalar microinfusions are reversed by the selective sst2 antagonist PRL2903. *Pharmacol Biochem Behav* **101**:88–92.
Yeung M, Engin E, and Treit D (2011) Anxiolytic-like effects of somatostatin isoforms SST 14 and SST 28 in two animal models (Rattus norvegicus) after intra-amygdalar and intra-septal microinfusions. *Psychopharmacology (Berl)* **216**:557–567.
Yin Z, Geng X, Zhang Z, Wang Y, and Gao X (2021) Rhein Relieves Oxidative Stress in an Abeta1-42 Oligomer-Burdened Neuron Model by Activating the SIRT1/PGC-1alpha-Regulated Mitochondrial Biogenesis. *Front Pharmacol* **12**:746711.
Yu L, Liu Y, Yang H, Zhu X, Cao X, Gao J, Zhao H, and Xu Y (2017) PSD-93 Attenuates Amyloid-beta-Mediated Cognitive Dysfunction by Promoting the Catabolism of Amyloid-beta. *J Alzheimers Dis* **59**:913–927.
Yunusa I, Rashid N, Abler V, and Rajagopalan K (2021) Comparative Efficacy, Safety, Tolerability, and Effectiveness of Antipsychotics in The Treatment of Dementia-Related Psychosis (DRP): A Systematic Literature Review. *J Prev Alzheimers Dis* **8**:520–533.
Zelano J, Brigo F, and Garcia-Patek S (2020) Increased risk of epilepsy in patients registered in the Swedish Dementia Registry. *Eur J Neurol* **27**:129–135.
Zempel H, Thies E, Mandelkow E, and Mandelkow E-M (2010) Abeta oligomers cause localized Ca(2+) elevation, missorting of endogenous Tau into dendrites, Tau phosphorylation, and destruction of microtubules and spines. *J Neurosci* **30**:11938–11950.
Zepa L, Frenkel M, Belinson H, Kariv-Inbal Z, Kayed R, Masliah E, and Michaelson DM (2011) ApoE4-Driven Accumulation of Intraneuronal Oligomerized Abeta42 following Activation of the Amyloid Cascade In Vivo Is Mediated by a Gain of Function. *Int J Alzheimers Dis* **2011**:792070.
Zhang H, Liu D, Wang Y, Huang H, Zhao Y, and Zhou H (2017) Meta-analysis of expression and function of neprilysin in Alzheimer's disease. *Neurosci Lett* **657**:69–76.
Zhang ZJ, Lappi DA, Wrenn CC, Milner TA, and Wiley RG (1998) Selective lesion of the cholinergic basal forebrain causes a loss of cortical neuropeptide Y and somatostatin neurons. *Brain Res* **800**:198–206.
Zhao Q-F, Tan L, Wang H-F, Jiang T, Tan M-S, Tan L, Xu W, Li J-Q, Wang J, Lai T-J, et al. (2016) The prevalence of neuropsychiatric symptoms in Alzheimer's disease: Systematic review and meta-analysis. *J Affect Disord* **190**:264–271.
Zhao W, Han S, Qiu N, Feng W, Lu M, Zhang W, Wang M, Zhou Q, Chen S, Xu W, et al. (2022) Structural insights into ligand recognition and selectivity of somatostatin receptors. *Cell Res* **32**:761–772.
Zhao W-Q, De Felice FG, Fernandez S, Chen H, Lambert MP, Quon MJ, Krafft GA, and Klein WL (2008) Amyloid beta oligomers induce impairment of neuronal insulin receptors. *FASEB J* **22**:246–260.
Zhao W-Q, Lacor PN, Chen H, Lambert MP, Quon MJ, Krafft GA, and Klein WL (2009) Insulin receptor dysfunction impairs cellular clearance of neurotoxic oligomeric a{beta}. *J Biol Chem* **284**:18742–18753.
Zhou L, Wei C, Huang W, Bennett DA, Dickson DW, Wang R, and Wang D (2013) Distinct subcellular patterns of neprilysin protein and activity in the brains of Alzheimer's disease patients, transgenic mice and cultured human neuronal cells. *Am J Transl Res* **5**:608–621.
Zolochevska O and Taglialatela G (2016) Non-Demented Individuals with Alzheimer's Disease Neuropathology: Resistance to Cognitive Decline May Reveal New Treatment Strategies. *Curr Pharm Des* **22**:4063–4068.
Zott B, Simon MM, Hong W, Unger F, Chen-Engerer H-J, Frosch MP, Sakmann B, Walsh DM, and Konnerth A (2019) A vicious cycle of beta amyloid-dependent neuronal hyperactivation. *Science* **365**:559–565.