

ASSOCIATE EDITOR: ERIC L. BARKER

# Vitamin D and Depression: Cellular and Regulatory Mechanisms

Michael J. Berridge

*Emeritus Babraham Fellow, The Babraham Institute, Cambridge, United Kingdom*

Abstract	80
I. Introduction	80
II. Dysfunctional Neural Circuits in Depression	81
III. Tonic Excitatory Drive and Depression	81
IV. Enhanced Neuronal Ca <sup>2+</sup> Signaling in Depression	84
V. Inflammation and Depression	86
VI. Vitamin D and Depression	87
VII. Depression and Alzheimer's Disease	88
VIII. Conclusion	88
References	89

**Abstract**—Depression is caused by a change in neural activity resulting from an increase in glutamate that drives excitatory neurons and may be responsible for the decline in the activity and number of the GABAergic inhibitory neurons. This imbalance between the excitatory and inhibitory neurons may contribute to the onset of depression. At the cellular level there is an increase in the concentration of intracellular Ca<sup>2+</sup> within the inhibitory neurons that is driven by an increase in entry through the NMDA receptors (NMDARs) and through activation of the phosphoinositide signaling pathway that generates inositol trisphosphate (InsP<sub>3</sub>) that releases Ca<sup>2+</sup> from the internal stores. The importance of these two pathways in driving the elevation of Ca<sup>2+</sup> is supported by the fact that depression can be

alleviated by ketamine that inhibits the NMDARs and scopolamine that inhibits the M1 receptors that drive InsP<sub>3</sub>/Ca<sup>2+</sup> pathway. This increase in Ca<sup>2+</sup> not only contributes to depression but it may also explain why individuals with depression have a strong likelihood of developing Alzheimer's disease. The enhanced levels of Ca<sup>2+</sup> may stimulate the formation of A $\beta$  to initiate the onset and progression of Alzheimer's disease. Just how vitamin D acts to reduce depression is unclear. The phenotypic stability hypothesis argues that vitamin D acts by reducing the increased neuronal levels of Ca<sup>2+</sup> that are driving depression. This action of vitamin D depends on its function to maintain the expression of the Ca<sup>2+</sup> pumps and buffers that reduce Ca<sup>2+</sup> levels, which may explain how it acts to reduce the onset of depression.

## I. Introduction

There are two forms of depression, unipolar depression and bipolar depression (BPD). In the case of BPD, there are alternating episodes of depression and mania. The depressive state in BPD resembles that in unipolar depression in that they both respond to antidepressants such as ketamine and the mood-stabilizer lithium (Li<sup>+</sup>), but it is still unclear whether they are caused by the same genetic and pathophysiological defects. In this review, it will be assumed that there are similarities in the depressive state that occurs in both BPD and unipolar depression such as major depressive disorder (MDD). Vitamin D deficiency has been linked to both

forms of depression but just how this occurs at the cellular level is unclear.

To describe how vitamin D functions, it is necessary to understand the properties of the vitamin D signaling pathway (Fig. 1). The active form of vitamin D is 1 $\alpha$ ,25-dihydroxy vitamin D<sub>3</sub> [1 $\alpha$ ,25(OH)<sub>2</sub>D<sub>3</sub>], which is formed by a series of reactions that take place in a number of different tissues. Sunlight acting on the skin initiates the formation of vitamin D<sub>3</sub> (cholecalciferol) through the photolysis of 7-dehydrocholesterol (Holick et al., 1980). The vitamin D<sub>3</sub> enters the blood and is transferred to the liver where a hydroxyl group is added to the C-25 position by a vitamin D-25 hydroxylase (encoded by the *CYP27A1* gene) to form 25-hydroxyvitamin

**Address correspondence to:** Michael J. Berridge, Emeritus Babraham Fellow, The Babraham Institute, Cambridge CB22 3AT, United Kingdom. E-mail: michael.berridge@babraham.ac.uk  
dx.doi.org/10.1124/pr.116.013227.

D<sub>3</sub> [25(OH)D<sub>3</sub>] that is the immediate precursor for active vitamin D. This 25(OH)D<sub>3</sub> is carried in the blood to enter multiple cell types where a 25(OH)D<sub>3</sub>-1 $\alpha$ -hydroxylase (encoded by the *CYP27B1* gene) adds another hydroxyl group to the 1 position to form the active 1,25(OH)<sub>2</sub>D<sub>3</sub>, which enters the nucleus to activate a large number of genes (Fig. 1). In this review, I will use the term vitamin D with the understanding that it refers to the vitamin D signaling pathway that contains a number of related components.

To understand the pathophysiology of depression and how vitamin D may act to prevent depression, it is necessary to explore what causes the alterations in neural function responsible for the change in mood. To explore how vitamin D might act to prevent depression, it is necessary to formulate a working hypothesis to explain the nature of the dysfunctional intracellular neuronal signaling systems. The hypothesis that is developed in the subsequent sections proposes that an increase in neuronal Ca<sup>2+</sup> levels is a major factor responsible for driving the onset of depression. Vitamin D normally acts to maintain Ca<sup>2+</sup> homeostasis (Berridge, 2015a,b), which suggest that the persistent increase in Ca<sup>2+</sup> caused by vitamin D deficiency may contribute to the onset of depression.

## II. Dysfunctional Neural Circuits in Depression

There is increasing evidence that depression occurs from alterations in the way different brain regions communicate with each other (Fitzgerald et al., 2008). Individuals with depression have a decline in neural activity in the frontal and temporal cortex and the insula. In addition, there is a decrease in activity in the cerebellum, subcortical, and limbic regions. This communication between brain regions is very dependent on the fact that neurons oscillate in synchrony with each other. An example of such oscillatory activity is the fast gamma oscillations (20–80 Hz). Such synchronous brain rhythms depend on an intimate mutual interaction between the excitatory and inhibitory neurons. Excitatory neurons release glutamate that not only excites its target neuron, but they also have collateral endings that activate the local inhibitory neurons, which release  $\gamma$ -aminobutyric acid (GABA) that then feeds back to inhibit the excitatory neurons. These tightly regulated feedback interactions between the excitatory and inhibitory neurons is an essential feature of neuronal communication within the brain, which may be altered in depression as a result of a change in the contribution of the inhibitory neurons. In individuals with

depression, there is a decline in GABA levels (Sanacora et al., 2004, Hasler et al., 2007) and this may be explained by the fact that the size and the number of inhibitory GABAergic neurons is reduced in the dorsal prefrontal cortex (Rajkowska et al., 2007) and in the occipital cortex (Maciag et al., 2010). These GABAergic inhibitory interneurons, which have an important role in coordinating the activity of the pyramidal neurons to generate brain rhythms (Klausberger et al., 2003) are altered in depression (Croarkin et al., 2011; Luscher et al., 2011; Ren et al., 2016). Such a deficit in the GABA-dependent inhibitory pathway may be responsible for the onset of major depressive disorder (MDD) (Levinson et al., 2010). The decline in the GABAergic neurons may be driven by an increase in the activity of the glutamatergic signaling pathway that occurs in depression (Deutschenbaur et al., 2016; Zhang et al., 2016a). For example, there is an increase in glutamate levels in various brain areas such as the anterior cingulate/medial prefrontal cortical region in patients with BPD (Paul and Skolnick 2003; Frye et al., 2007; Hashimoto et al., 2007; Gigante et al., 2012; Niciu et al., 2014; Zhang et al., 2016a). In individuals with depression, there is a decline in GABA levels (Sanacora et al., 2004; Hasler et al., 2007), and this may be explained by the fact that the size and the number of GABAergic neurons is reduced in the dorsal prefrontal cortex (Rajkowska et al., 2007) and in the occipital cortex (Maciag et al., 2010). High levels of glutamate will increase the intracellular level of Ca<sup>2+</sup>, resulting in two consequences. First, it will enhance the tonic excitatory drive responsible for regulating neuronal activity. Second, the elevated levels of Ca<sup>2+</sup> reduce protein synthesis, which may account for the decline in the function and number of GABAergic neurons as described later. There is increasing evidence that the onset and progression of depression may depend on an increase in Ca<sup>2+</sup> in neuronal cells.

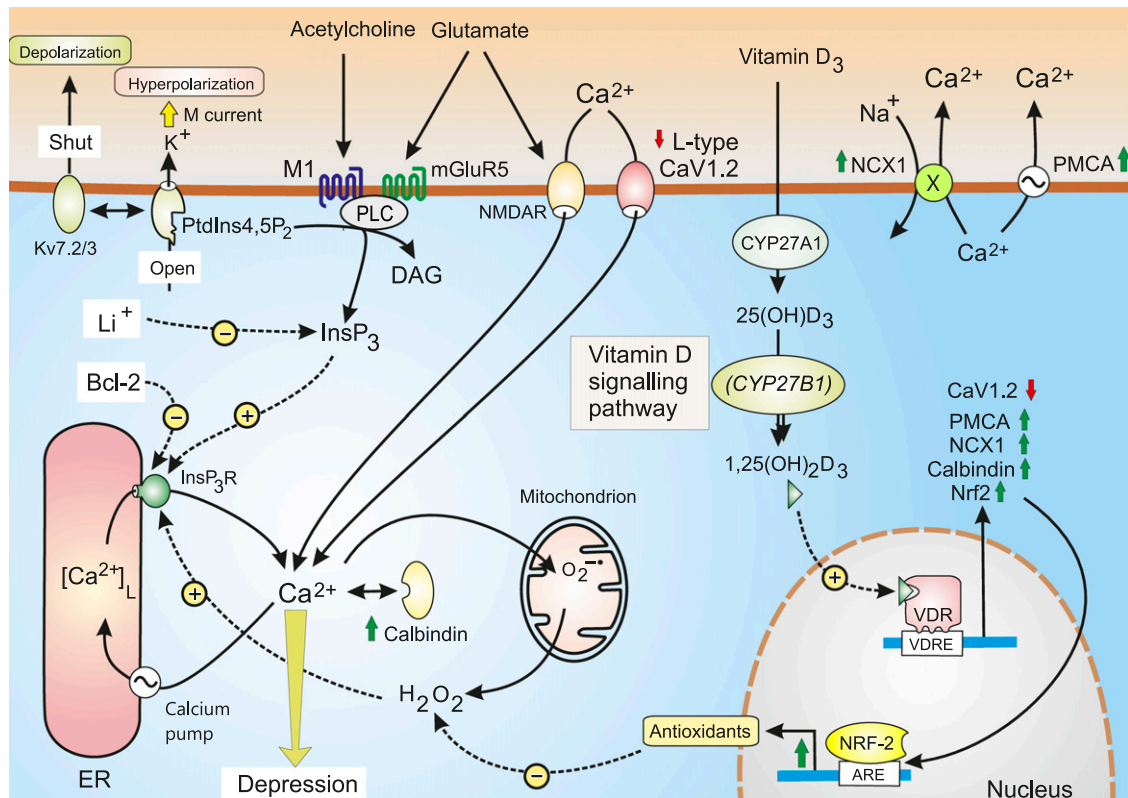
## III. Tonic Excitatory Drive and Depression

Abnormal activation of the tonic excitatory drive that functions to regulate neuronal activity may contribute to the elevation of Ca<sup>2+</sup> that occurs in depression. The rhythmical neuronal oscillations that occur synchronously in the brain have varied frequencies during the sleep/wake cycle. During the wake period there are fast gamma (20–80 Hz) and theta (4–10 Hz) oscillations, which then decline to the much slower delta (1–4 Hz) and slow oscillations (<1 Hz) that occur during sleep (Berridge, 2014a,b). This range of frequencies is

---

**ABBREVIATIONS:** ACh, acetylcholine; AD, Alzheimer's disease; BPD, bipolar depression; E-I, excitation-inhibition; ER, endoplasmic reticulum; GABA,  $\gamma$ -aminobutyric acid; GSH, glutathione; 5-HT, 5-hydroxytryptamine; InsP<sub>3</sub>, inositol 1,4,5-trisphosphate; Li<sup>+</sup>, lithium; MDD, major depressive disorder; mGluR, metabotropic glutamatergic receptor; M1, muscarinic acetylcholine receptor; NCS-1, neuronal calcium sensor 1; NCX1, Na<sup>+</sup>/Ca<sup>2+</sup> exchanger 1; NMDAR, NMDA receptor; PMCA, plasma membrane Ca<sup>2+</sup>-ATPase; PtdIns4,5P<sub>2</sub>, phosphatidylinositol 4,5-bisphosphate; ROS, reactive oxygen species; RYRs, ryanodine receptors; TNF- $\alpha$ , tumor necrosis factor- $\alpha$ .

---



**Fig. 1.** The role of Ca<sup>2+</sup> signaling in depression. Increased glutamate that occurs during depression enhances Ca<sup>2+</sup> through the activation of NMDAR Ca<sup>2+</sup> channels and by activation of the metabotropic glutamatergic receptor 5 (mGluR5) that is coupled to phospholipase C (PLC) to hydrolyze phosphatidylinositol 4,5-bisphosphate (PtdIns4,5P<sub>2</sub>) to form inositol 1,4,5-trisphosphate (InsP<sub>3</sub>) that releases Ca<sup>2+</sup> from the endoplasmic reticulum (ER). Acetylcholine acting through the muscarinic 1 (M1) receptor also stimulates the formation of InsP<sub>3</sub>. The hydrolysis of PIP<sub>2</sub>, which normally acts to open the Kv7 2/3 channels that hyperpolarizes the neuronal membrane, acts to close these K<sup>+</sup> channels and the membrane depolarizes, resulting in enhanced neuronal excitability. Vitamin D acts to reduce Ca<sup>2+</sup> signaling by acting through the vitamin D receptor (VDR) to increase the expression of the Ca<sup>2+</sup> buffer calbindin and it increases expression of the plasma membrane Ca<sup>2+</sup> pump (PMCA) and the sodium/Ca<sup>2+</sup> exchanger 1 (NCX1). Vitamin D also reduces the level of Ca<sup>2+</sup> by reducing the expression of the L-type CaV1.2 channel.

regulated by the ascending arousal system that consists of a number of different neurons located mainly in the brain stem, midbrain, basal forebrain, and hypothalamus. In addition to arousing the brain from sleep, it also is responsible for maintaining the wake state and can adjust the frequency of the oscillating neural circuits as they participate in different types of behavior. This ascending arousal system regulates the sleep/wake cycle by releasing transmitters such as acetylcholine (ACh), dopamine, histamine, noradrenaline, orexin, and serotonin. Some of these transmitters such as serotonin, dopamine, and acetylcholine feature significantly in depression (Manji et al., 2003).

The serotonergic neurons in the dorsal raphe, which synthesize serotonin [5-hydroxytryptamine (5-HT)], extend throughout the brain to release serotonin in the hippocampus, prefrontal cortex, substantia nigra, nucleus accumbens, amygdala, and lateral habenula. The serotonin hypothesis, which was one of the first attempts to explain depression, proposed that depression may result from a deficiency in serotonin (Schildkraut 1965; Jacobsen et al., 2012). The selective serotonin reuptake inhibitors such as fluoxetine, paroxetine, and citalopram, relieve the symptoms of depression by

bringing about an increase in serotonin levels that have two important actions in the brain (Kobayashi et al., 2008; Thompson et al., 2015). First, the elevated serotonin activates neurogenesis by increasing the proliferation of progenitor cells in the hippocampal dentate gyrus (Malberg et al., 2000) and is the basis of the neurogenesis hypothesis that proposes that a decrease in neurogenesis causes the onset of depression (Jacobs et al., 2000; Miller and Hen, 2015).

Neurogenesis is a process whereby new functional neurons are generated from precursor cells (Ming and Song 2011; Kempermann et al., 2015). Second, serotonin controls excitatory synaptic transmission in the hippocampus and prefrontal cortex (Cai et al., 2013; Thompson et al., 2015), perhaps operating through the tonic excitatory drive. The decline in serotonin may be caused by inflammation that is associated with depression as described later. A reduction in serotonin levels thus seems to be one of the causes of depression as described later.

The transmitters, such as serotonin and acetylcholine (ACh) discussed above, are released globally and are responsible for activating the tonic excitatory drive using a variety of signaling mechanisms to control the

activity of the excitatory and inhibitory neurons that interact with each other to generate the synchronous brain rhythms (Berridge, 2014a,b). For example, ACh acts through M1 receptors to stimulate phosphatidylinositol 4,5-bisphosphate (PtdIns4,5P<sub>2</sub>) hydrolysis, which contributes to depolarization by decreasing the permeability of K<sub>v</sub>7.2 and K<sub>v</sub>7.3 that are delayed rectifier potassium channels that regulate neuronal excitability by controlling the M current (Fig. 1). In addition, the inositol 1,4,5-trisphosphate (InsP<sub>3</sub>) released after the hydrolysis of PtdIns4,5P<sub>2</sub> promotes the release of Ca<sup>2+</sup> that stimulates the Ca<sup>2+</sup>-activated nonselective cation current. The importance of ACh has been highlighted by the fact that scopolamine, which inhibits muscarinic receptors, functions as an antidepressant (Furey and Drevets, 2006; Drevets et al., 2013; Navarria et al., 2015). In the hippocampal CA1 region, the GABAergic interneurons respond to serotonin through 5-HT<sub>2A</sub> receptors (5-HT<sub>2A</sub>Rs) that stimulate phospholipase C $\beta$  that hydrolyzes PtdIns4,5P<sub>2</sub>, resulting in closure of the hyperpolarizing M current. Serotonin also induces membrane depolarization by producing InsP<sub>3</sub> to increase Ca<sup>2+</sup> that stimulates the Ca<sup>2+</sup>-activated nonselective cation current, resulting in membrane excitability (Wyskiel and Andrade, 2016). Dopamine acts through both the D1 and D2 receptors to regulate the formation of cyclic AMP, which also regulates neuronal excitability. Inactivation of the D2 receptors in the dorsolateral prefrontal cortex is prevented by neuronal calcium sensor 1 (NCS-1). It is of interest, therefore, to find that the levels of NCS-1 are markedly elevated in BPD (Koh et al., 2003). It is also of interest that NCS-1 enhances the release of Ca<sup>2+</sup> by the InsP<sub>3</sub> receptor 1 (InsP<sub>3</sub>R1), which explains how NCS-1 may contribute to the elevation in Ca<sup>2+</sup> that occurs in depression (Schlecker et al., 2006). The antimanic drug lithium (Li<sup>+</sup>) inhibits this stimulatory action of NCS-1, further supporting the concept that an elevation in the InsP<sub>3</sub>/Ca<sup>2+</sup> signaling pathway contributes to depression pathology (Schlecker et al., 2006).

Another reason for considering a possible role for changes in the tonic excitatory drive in BPD, is the finding that two of the genes that have consistently been linked to BPD play a role in regulating neuronal activity. One of these genes is *CACNA1C*, which encodes the  $\alpha$  subunit of the Ca<sub>v</sub>1.2 L-type voltage-sensitive Ca<sup>2+</sup> channels (Ferreira et al., 2008; Tesli et al., 2013; Heyes et al., 2015; Kabir et al., 2016). Opening of this channel generates a Ca<sup>2+</sup> signal that contributes to the tonic excitatory drive by activating the HCN channel. Neuronal Ca<sup>2+</sup> levels are enhanced by an increase in the activity of this Ca<sub>v</sub>1.2 L-type voltage-sensitive Ca<sup>2+</sup> channel, which is encoded by the *CACNA1C* gene. Polymorphisms located within the *CACNA1C* gene, which is associated with both depression and bipolar disorder (Zhang et al., 2013), result in an increase in the level of Ca<sup>2+</sup> (Perrier et al., 2011; Ou

et al., 2015; Uemura et al., 2015; Harrison 2016). Such an increase in the activity of the Ca<sub>v</sub>1.2 L-type channels is of interest because it may help to explain the relationship between vitamin D deficiency and depression as described later. This role of enhanced Ca<sub>v</sub>1.2 L-type Ca<sup>2+</sup> channels causing depression has led to a proposal that the inhibition of these channels may act to improve mood disorders (Boal et al., 2016). Such a possibility is supported by the observation that the Ca<sup>2+</sup> channel blocker isradipine is able to treat bipolar depression (Ostacher et al., 2014). The other gene is *ANK3* that encodes ankyrin-G, which plays a role in positioning the K<sub>v</sub>7.2/K<sub>v</sub>7.3 channels to the correct location in the neuronal membrane. K<sub>v</sub>7.2 and K<sub>v</sub>7.3 are delayed rectifier channels that contribute to the regulation of neuronal excitability by controlling the M current (Fig. 1).

An important feature of this tonic excitatory drive is that it normally is applied equally to both the excitatory and inhibitory neurons and this excitation-inhibition (E-I) balance is essential for proper brain function (Tao et al., 2014). Through a process of homeostatic plasticity, the excitatory and inhibitory neurons adjust their synaptic strength so as to maintain this E-I balance (McClung and Nestler, 2008; Turrigiano 2008; Ren et al., 2016). The idea that depression may be caused by an E-I imbalance is supported by the observation that depression is associated with a decline in the number of the GABAergic inhibitory interneurons (Klausberger et al., 2003), which may be driven by the increase in the glutamatergic signaling pathway that occurs in BPD (Paul and Skolnick, 2003; Frye et al., 2007; Gigante et al., 2012). For example, there is an increase in glutamate levels in various brain areas such as the anterior cingulate/medial prefrontal cortical region in patients with depression (Frye et al., 2007; Gigante et al., 2012). In addition to distorting the E-I balance, this increase in glutamate levels could also contribute to the increase in the levels of both Ca<sup>2+</sup> and reactive oxygen species (ROS) levels that are associated with depression as described below.

Depression seems to occur as a result of a decline in both the number and connectivity of spine synapses particularly in the GABAergic neurons (Duman and Duman, 2015; Calabrese et al., 2016). Ketamine, which inhibits the Ca<sup>2+</sup> entry through the NMDARs, and scopolamine that inhibits muscarinic receptors can restore this decline in synaptogenesis that occurs during depression (Duman and Aghajanian, 2012; Raab-Graham et al., 2016; Ren et al., 2016; Wohleb et al., 2017). This restoration of normal synaptic connections may be mediated through the ability of ketamine to reduce the elevated levels of Ca<sup>2+</sup> that are a feature of depression. Similarly, the antidepressant action of scopolamine (Furey and Drevets, 2006; Drevets et al., 2013; Navarria et al., 2015) may depend on its ability to reduce Ca<sup>2+</sup> levels by inhibiting the

muscarinic receptors that act through the  $\text{InsP}_3/\text{Ca}^{2+}$  signaling pathway. This may explain why the activation of KCNQ channels, which will hyperpolarize the membrane to reduce neuronal hyperactivity and intracellular  $\text{Ca}^{2+}$  levels, can also alleviate depression (Friedman et al., 2016). High levels of calcium that occur in depression activate eukaryotic elongation factor 2 kinase, which phosphorylates and inhibits eukaryotic elongation factor 2, resulting in less dendritic protein synthesis and negatively affecting synapse formation (Sutton et al., 2007). The persistent elevation in  $\text{Ca}^{2+}$  may thus be a key pathologic factor responsible for the decline in synapses that occur during depression.

#### IV. Enhanced Neuronal $\text{Ca}^{2+}$ Signaling in Depression

A number of mechanisms contribute to the abnormal elevation of neuronal  $\text{Ca}^{2+}$  that seems to be responsible for the onset of depression (Berridge, 2012; 2014b). Again a key aspect of depression appears to be an elevation in glutamate that will elevate  $\text{Ca}^{2+}$  by acting on both ionotropic and metabotropic receptors (Fig. 1). For example, the NMDA receptor (NMDAR) is an ionotropic channel that responds to glutamate by increasing the entry of external  $\text{Ca}^{2+}$ . The antidepressant drug ketamine acts by inhibiting the NMDARs, thus reducing the influx of external  $\text{Ca}^{2+}$  (Miller et al., 2014). One of the consequences of ketamine acting to reduce the intracellular level of  $\text{Ca}^{2+}$  is to promote the protein synthesis necessary to restore the synaptic connections that are reduced in depression as described above (Sutton et al., 2007).

The enhanced glutamate levels may also contribute to the elevation in  $\text{Ca}^{2+}$  by activating metabotropic glutamatergic receptors such as the mGluR2/3 and mGluR5 (Chaki et al., 2013; Pałucha-Poniewiera et al., 2013; Newell and Matosin, 2014). The function of mGluR5 is facilitated by the protein S100A10 (p11) that binds to the cytoplasmic tail of this receptor (Lee et al., 2015). Knockout of p11 in GABAergic neurons has an antidepressant effect supporting the idea that the function of the mGluR5s is closely related to p11. The significance of the mGluRs is also supported by studies on the scaffolding protein Homer, which has three members Homer1, Homer2, and Homer3. An alteration in the function of these Homer proteins has been implicated in a number of neurologic diseases (Szumlinski et al., 2006; Luo et al., 2012). Genome-wide association studies have established that single nucleotide polymorphisms in Homer1 are linked to major depression (Rietschel et al., 2010). In the medial prefrontal cortex, the expression of Homer1a is increased by various antidepressant treatments, whereas a decrease in its expression increased depressive-like behavior (Serchov et al., 2015; 2016).

One of the primary locations of Homer1 is in the postsynaptic density where it acts as an adaptor protein to regulate a number of  $\text{Ca}^{2+}$  signaling components (Serchov et al., 2016). For example, Homer1 functions to link the NMDA receptor (NMDAR) to the metabotropic receptors (mGluR1 and mGluR5) (Bertaso et al., 2010). The interaction between these two receptors is functionally important in that there is a reciprocal inhibition operating between the NMDAR and mGluR5 receptors (Perroy et al., 2008). This would imply that if Homer1 is defective then the two receptors would separate and would become more active to enhance  $\text{Ca}^{2+}$  signaling. This is of interest in that the mGluR5 and NMDARs have been implicated in the pathophysiology of depression (Newell and Matosin 2014). The significance of NMDARs in depression is evident by the fact that ketamine, which is a potent inhibitor of this receptor, has antidepressant effects (Miller et al., 2014). Homer proteins also provide a link between metabotropic glutamate receptors (mGluRs), which generate  $\text{InsP}_3$ , and the underlying  $\text{InsP}_3$ Rs (Tu et al., 1998). Antidepressant responses have been observed after inhibition of metabotropic glutamate receptors (mGluRs) such as mGluR2 and mGluR5 (Krystal et al., 2010). Homer can also provide a link between the  $\text{InsP}_3$ Rs in the endoplasmic reticulum (ER) and the TRPC1  $\text{Ca}^{2+}$  channels in the plasma membrane, thereby promoting an increase in the entry of external  $\text{Ca}^{2+}$  (Yuan et al., 2003). The activity of ryanodine receptors (RYRs), which can contribute to depression by releasing  $\text{Ca}^{2+}$  from the internal stores (Galeotti et al., 2008a,b), can also be regulated by Homer proteins (Feng et al., 2002; Hwang et al., 2003; Pouliquin and Dulhanty, 2009).

The mGluRs act by stimulating the phosphoinositide signaling pathway, which generates the  $\text{InsP}_3$  that releases  $\text{Ca}^{2+}$  from internal stores and thus contributes to the increase in neuronal  $\text{Ca}^{2+}$  levels. Such a mechanism could account for the elevated levels of  $\text{Ca}^{2+}$  that have been described in a large number of cell types taken from patients with BPD (Dubovsky et al., 1992; Warsh et al., 2004). Lithium ( $\text{Li}^+$ ) reduces this increase in phosphoinositide signaling by reducing the supply of inositol as described in the inositol depletion hypothesis (Berridge et al., 1989). This inositol depletion hypothesis is based on the idea that depression arises through overactive phosphoinositide signaling pathways (as described above) that can be corrected by drugs such as  $\text{Li}^+$  and valproate. The excessive phosphoinositide signaling may contribute to depression by increasing the intracellular level of  $\text{Ca}^{2+}$  by altering the tonic excitatory drive that alters the E-I balance within the central nervous system. The inositol depletion hypothesis emerged from the observation that  $\text{Li}^+$  is a potent inhibitor of the inositol monophosphatase responsible for hydrolyzing inositol monophosphates ( $\text{Ins1P}$ ,  $\text{Ins3P}$ , and  $\text{Ins4P}$ ) to free inositol. By inhibiting the formation

of inositol,  $\text{Li}^+$  reduces the supply of the free inositol required to resynthesize the PtdIns necessary to provide the PtdIns4,5P<sub>2</sub> required for this signaling pathway. There is now considerable support for this inositol depletion hypothesis (Lubrich and van Calker, 1999; Harwood, 2005; Deraniew and Greenberg, 2009; Kim and Thayer, 2009). Further support for the hypothesis comes from the observation that  $\text{Li}^+$  can inhibit the sodium *myo*-inositol transporter-1 (SMIT1) responsible for taking up inositol from the plasma (Lubrich and van Calker, 1999). This inositol depletion hypothesis was strengthened further when it was discovered that valproate has a similar action in that it too will deplete internal inositol (Eickholt et al., 2005) by inhibiting both the uptake of external inositol by SMIT and by inhibiting the inositol synthase responsible for the de novo synthesis of inositol from glucose 6-phosphate.

The inositol depletion hypothesis suggests that depression may arise through excessive elevation of the neuronal phosphoinositide signaling pathway that alters the tonic excitatory drive. Such a conclusion is supported by the observation that the levels of G $\alpha$ q/11 and phospholipase C (PLC)-beta 1, which are key components of the phosphoinositide signaling pathway, are elevated in the occipital cortex from patients with BPD (Mathews et al., 1997). The consequence of this change will depend on whether this increase in signaling is functionally important in either the excitatory or inhibitory neurons. Changes in the activity of either the excitatory or inhibitory neurons result in subtle alterations in the neuronal circuits that control behavior. The basic idea is that the periodic switching between depression and mania, which is a characteristic feature of BPD (Salvadore et al., 2010), is caused by an alteration in the E-I balance that controls neuronal activity. During the generation of brain rhythms, it is essential for the excitatory and inhibitory neurons to be activated equally.

The onset of both BPD and major depressive disorder (MDD) has also been linked to dysfunction of the mitochondria (Kato, 2007; Andreazza et al., 2010;2013; Jou et al., 2009; Clay et al., 2011; Callaly et al., 2015; Morris and Berk, 2015; Bansal and Kuhad, 2016). There is a decline in the nuclear mRNA molecules and proteins that contribute to mitochondrial respiration (Scaini et al., 2016; Kim et al., 2014). In particular, there is a decline in the function of complex I of the electron transport chain responsible for ATP formation. A decline in the efficiency of this electron transport chain also results in an increase in the formation of reactive oxygen species (ROS) that induces oxidative stress. Such oxidative stress arising from increased levels of ROS plays an important role in the pathophysiology of BPD (Steckert et al., 2010; Andreazza et al., 2013; Brown et al., 2014; Callaly et al., 2015). The elevation of ROS is enhanced by the fact that neurons from patients with depression have much reduced antioxidants such

as glutathione (GSH) (Gawryluk et al., 2011; Kulak et al., 2013). The  $\text{Ca}^{2+}$  buffering role of the mitochondria is also compromised, resulting in an increase in the intracellular level of  $\text{Ca}^{2+}$ , which is a feature of neurons in both BPD and MDD.

A particularly interesting aspect of this decrease in mitochondrial function in depression is that it may result from a decline in vitamin D. Vitamin D acts to maintain the normal mitochondrial control of cellular bioenergetics (Calton et al., 2015). Vitamin D regulates the activity of the mitochondrial respiratory chain (Consiglio et al., 2015). In skeletal muscle, fatigue and a decline in muscle strength are alleviated by vitamin D acting to enhance mitochondrial respiration and oxidative phosphorylation, thereby increasing the formation of ATP (Bouillon and Verstuyf, 2013; Sinha et al., 2013; Ryan et al., 2016). Vitamin D regulates mitochondrial function through two actions. First, it acts on the nucleus to increase the expression of many of the components responsible for mitochondrial function. Second, the VDR enters the mitochondrion where it may act directly to regulate mitochondrial function, but exactly what it does is still not clear. In human platelets, the VDR is located in the mitochondria (Silvagno et al., 2010). In keratinocytes, the VDR enters the mitochondria through the permeability transition pore (Silvagno et al., 2013). The role of vitamin D in maintaining normal mitochondria may be one explanation for the link between vitamin D deficiency and depression. When vitamin D is low, mitochondrial function will be compromised, resulting in an elevation of ROS and a reduction in the formation of ATP, which will have a major impact on  $\text{Ca}^{2+}$  homeostasis. The formation of ROS facilitates the release of  $\text{Ca}^{2+}$  from the ER by the  $\text{InsP}_3$ Rs and the RYRs, whereas the decline in ATP will reduce the ability of neurons to extrude  $\text{Ca}^{2+}$  from the cell. Both these effects will contribute to the abnormal elevation in neuronal  $\text{Ca}^{2+}$  levels that have been linked to the onset of depression as described earlier.

Hyperactivity of the  $\text{InsP}_3/\text{Ca}^{2+}$  pathway contributes to BPD. This is supported by studies showing that depression is associated with single nucleotide polymorphisms in the Bcl-2 gene, which reduce Bcl-2 expression that results in an increase in  $\text{InsP}_3$ -induced  $\text{Ca}^{2+}$  release (Machado-Vieira et al., 2011; Uemura et al., 2011;2015; Soeiro-de-Souza et al., 2013). This  $\text{Ca}^{2+}$  release by  $\text{InsP}_3$  is normally suppressed by Bcl-2 (Fig. 1) (Distelhorst and Bootman, 2011). One of the actions of the antidepressant drug  $\text{Li}^+$  is to increase the expression of Bcl-2 (Chen et al., 1999; Manji et al., 2000; Corson et al., 2004). Studies on mice have revealed that the blockade of both  $\text{InsP}_3$ Rs and RyRs, through inhibition or deletion, induces an antidepressant-like effect (Galeotti et al., 2006). An antidepressive state in mice was obtained by either inhibiting the RYRs or by deleting them (Galeotti et al., 2008a). A similar decline in depression was observed when the  $\text{InsP}_3$ Rs were



either inhibited or deleted (Galeotti et al., 2008b). On the other hand, depressant-like responses were observed upon stimulation of these  $\text{Ca}^{2+}$ -mobilizing channels, thus confirming the hypothesis outlined earlier that an elevation of  $\text{Ca}^{2+}$  plays a role in depression. An increase in the activity of the  $\text{CaV1.2}$  L-type  $\text{Ca}^{2+}$  channel also contributes to this dysregulation of  $\text{Ca}^{2+}$  as described earlier (section III).

All this evidence suggests that an increase in neuronal  $\text{Ca}^{2+}$  may be a primary driver of depression. This conclusion may also explain the close relationship between inflammation and depression as described below.

## V. Inflammation and Depression

There is a close association between inflammation and depression (Maes, 1995; 2011; Dantzer et al., 2008; Miller et al., 2009; Barbosa et al., 2014a,b; Swardfager et al., 2016; Berk et al., 2013b; Najjar et al., 2013; Brites and Fernandes, 2015; Wohleb et al., 2016). The bidirectional link between inflammation and depression has emerged from studies showing that major depressive disorders are associated with individuals with chronic inflammation and with diseases such as cardiovascular diseases, type 2 diabetes, and rheumatoid arthritis. The proinflammatory cytokines interleukin- $1\alpha$  and  $\beta$ , tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ), and interleukin-6 have been implicated in the onset of depression (Maes, 2011; Dantzer et al., 2008; Najjar et al., 2013; Swardfager et al., 2016; Zhang et al., 2016b). The TNF- $\alpha$  protein levels were significantly increased in those areas of the brain such as the dorsolateral prefrontal and anterior cingulate cortex that play a significant role in regulating both mood and cognition (Dean et al., 2013). The microglia plays a major role in releasing these cytokines within the brain (Barbosa et al., 2014b). A part of the therapeutic action of  $\text{Li}^+$ , which is used to treat BPD, is to reduce inflammation by altering the expression of a number of cytokines (Nassar and Azab, 2014).

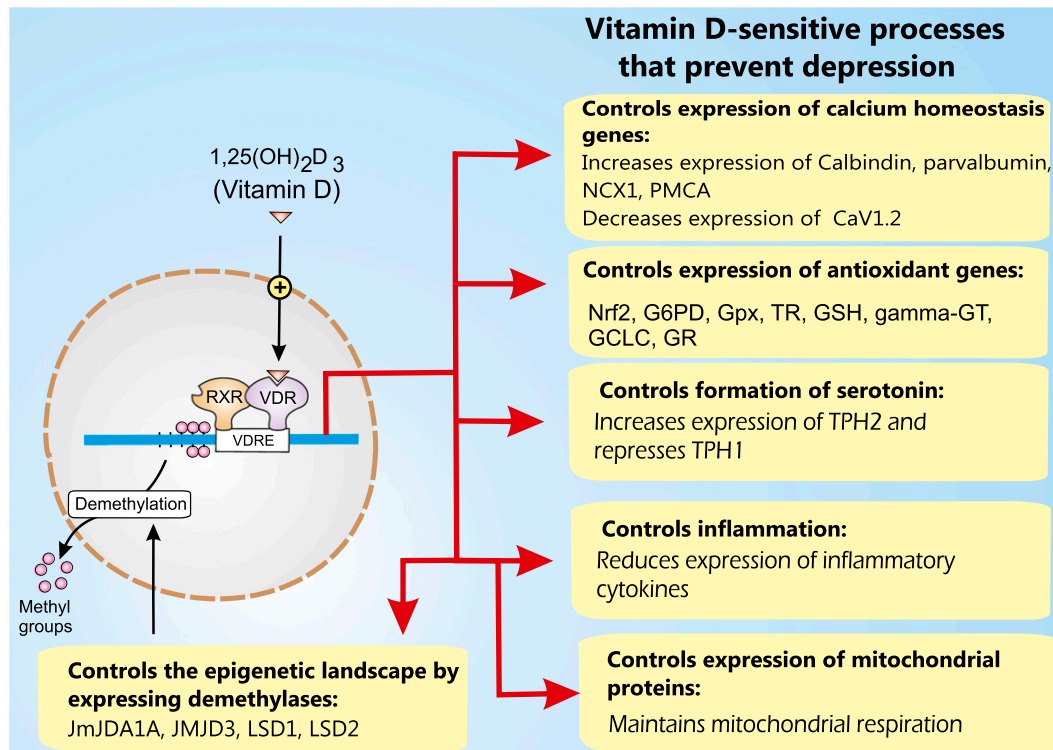
One of the consequences of inflammation is a decline in the plasma level of tryptophan, which is an essential amino acid that is transported into the brain where it functions in the synthesis of serotonin (Catena-Dell'Osso et al., 2011). Depression is associated with a decline in the level of serotonin. Interleukin-6 appears to be one of the major cytokines associated with depression (Sukoff Rizzo et al., 2012; Money et al., 2016). Depression induced by cytokines may also result from changes in the activity of the hippocampus, extended amygdala, and hypothalamus. In patients suffering from depression, there is an increased activation of microglia in the anterior cingulate cortex, prefrontal cortex, and insula (Swardfager et al., 2016). The alterations in neural function during depression are also reflected in alterations in sleep patterns

(Turek, 2005; Franzen and Buysse, 2008; Bower et al., 2010).

There are a number of ways whereby inflammation might act to alter the neural activity responsible for depression. An increase in the formation of reactive oxygen species (ROS), which can exert a profound effect on neuronal function, has been observed in depression (Kunz et al., 2008; Wang et al., 2009; Leonard and Maes 2012; Berk et al., 2013b; Najjar et al., 2013; Barbosa et al., 2014b). Much of the ROS is generated by mitochondria (Zorov et al., 2014) and there is evidence that depression is associated with an increase in mitochondrial function (Berk et al., 2013b). This evidence is supported by the fact that mood disorders have been linked to genetically mediated alterations in mitochondrial function (Anglin et al., 2012). A role for ROS is supported by the observation that the level of glutathione (GSH), which is one of the major antioxidants in neurons (Dean et al., 2009), is depleted in depression (Gawryluk et al., 2011; Berk et al., 2013a). The mood-stabilizing drug  $\text{Li}^+$  may reduce oxidative damage by increasing the expression of genes (*GCL* and *GST*) that are responsible for generating GSH (Cui et al., 2007; Shao et al., 2008). In addition, treatment with *N*-acetylcysteine, which acts to restore neuronal GSH levels, is also proving to be an effective treatment of depression (Dean et al., 2011; Berk et al., 2013a).

The increase in ROS that occurs during inflammation may induce depression through a number of mechanisms such as an alteration in the formation of key transmitters such as serotonin and an increase in  $\text{Ca}^{2+}$  signaling. One of the actions of cytokines and the associated increase in ROS formation is inhibition of serotonin synthesis (Catena-Dell'Osso et al., 2011; Leonard and Maes, 2012), which is a component of the serotonin hypothesis of depression described earlier. Tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ), which is one of the cytokines, that contributes to depression, acts through the specificity protein 1 to increase the transcription of  $\text{InsP}_3\text{Rs}$  that will enhance  $\text{Ca}^{2+}$  signaling (Park et al., 2009; Xia et al., 2012). There is a crosstalk between  $\text{Ca}^{2+}$  and redox signaling in that ROS enhances  $\text{Ca}^{2+}$ , which then feeds back to enhance ROS (Hidalgo and Donoso, 2008; Paula-Lima et al., 2014; Berridge 2015b). An important action of ROS is to enhance  $\text{Ca}^{2+}$  signaling by increasing the sensitivity of the inositol 1,4,5-trisphosphate receptors ( $\text{InsP}_3\text{Rs}$ ) (Fig. 1) (Missiaen et al., 1991; Bootman et al., 1992; Bird et al., 1993; Bánsághi et al., 2014) and ryanodine receptors (RYRs) (Terentyev et al., 2008; Donoso et al., 2011) to increase the release of  $\text{Ca}^{2+}$  from the endoplasmic reticulum (ER). The increase of ROS can also elevate intracellular  $\text{Ca}^{2+}$  levels by inhibiting the PMCA pump on the plasma membrane (Lock et al., 2011).

One of the important actions of vitamin D is to reduce inflammation (Hewison, 2010; Berk et al., 2013b) (Fig. 2). One way it does this is to reduce the expression of



**Fig. 2.** Vitamin D prevents the onset of depression by activating a number of processes that are critical to maintain normal healthy neurons. Vitamin D enters the nucleus where it associates with the retinoid X receptor (RXR) and then binds to the vitamin D response element (VDRE), which is located on a large number of genes. It maintains  $\text{Ca}^{2+}$  homeostasis by inducing the expression of calbindin, parvalbumin,  $\text{Na}^+/\text{Ca}^{2+}$  exchanger 1 (NCX1), and the plasma membrane  $\text{Ca}^{2+}$ -ATPase (PMCA) pump. It also regulates  $\text{Ca}^{2+}$  by reducing the expression of the CaV1.2 calcium channel. It activates expression of many antioxidant genes such as the nuclear factor-erythroid-2-related factor 2 (NRF2),  $\gamma$ -glutamyl transpeptidase ( $\gamma$ -GT), glutamate cysteine ligase (GCLC), glutathione reductase (GR), glutathione peroxidase (Gpx). It controls the formation of serotonin by increasing the level of tryptophan hydroxylase 2 (TPH2) while repressing tryptophan hydroxylase 1 (TPH1). It reduces inflammation by reducing the expression of inflammatory cytokines. It regulates the expression of many mitochondrial proteins that maintain normal mitochondrial respiration. Finally, it regulates the epigenetic landscape by promoting the expression of DNA demethylases such as Jumonji domain-containing protein 1A and 3 (JMJD1A, JMJD3) and lysine-specific demethylase 1 and 2 (LSD1, LSD2).

inflammatory cytokines (Beilfuss et al., 2012; Grossmann et al., 2012; Wei and Christakos, 2015), which is a prominent feature of how inflammatory responses lead to depression.

## VI. Vitamin D and Depression

There is increasing evidence to show that vitamin D deficiency is associated with depression. Individuals with normal levels of vitamin D have a much lower probability of developing depression (Hoogendijk et al., 2008; Stewart and Hirani, 2010; Chan et al., 2011; Gracious et al., 2012; Anglin et al., 2013; Black et al., 2014; Grudet et al., 2014; von Känel et al., 2015; Kerr et al., 2015; Brouwer-Brolsma et al., 2016; Moy et al., 2016). In patients with heart failure and cancer, depression has been associated with vitamin D deficiency (Björkhem-Bergman and Bergman, 2016; Johansson et al., 2016). Depression in the young has also been linked to vitamin D deficiency (Polak et al., 2014; Kerr et al., 2015). There are indications that depression in younger people has increased in the United Kingdom. Because this may be caused by a deficiency in vitamin D, there is an imperative to measure the levels of

vitamin D in school children. A deficiency in vitamin D is also a risk factor for late-life depression (Okereke and Singh, 2016). It has been suggested that vitamin D deficiency may set the stage for both the onset and the progression of depression by acting synergistically with other factors (Cui et al., 2015). The risk of developing depression is reduced in those individuals that have high serum vitamin D levels (Jääskeläinen et al., 2015). Mood symptoms in depression were improved after treatment with vitamin D (Sikoglu et al., 2015; Stokes et al., 2016). There is increasing evidence that one of the main functions of vitamin D is to maintain  $\text{Ca}^{2+}$  homeostasis as outlined in the phenotypic stability hypothesis (Fig. 2).

The phenotypic stability hypothesis attempts to explain how vitamin D functions to maintain healthy cells to prevent the onset of the many diseases that have been linked to vitamin D deficiency such as depression (Berridge, 2014b; 2015a,b). One of the primary functions of vitamin D is to regulate the expression of those  $\text{Ca}^{2+}$  signaling toolkit components that function to maintain low cytosolic resting levels of  $\text{Ca}^{2+}$  (Fig. 2). The phenotypic stability hypothesis explains how vitamin D acts to maintain both  $\text{Ca}^{2+}$  and redox



homeostasis (Berridge, 2015a,b). For example, vitamin D can increase expression of the plasma membrane  $\text{Ca}^{2+}$ -ATPase (PMCA) and  $\text{Na}^+/\text{Ca}^{2+}$  exchanger 1 (NCX1) that extrude  $\text{Ca}^{2+}$  and the calbindin D-9k, calbindin D-28k, and parvalbumin that buffer  $\text{Ca}^{2+}$  (de Viragh et al., 1989; Alexianu et al., 1998; Perez et al., 2008; Wasserman, 2004). Both the calbindins and parvalbumin are significant  $\text{Ca}^{2+}$  buffers in the cytoplasm of neurons. Vitamin D can also reduce the expression of the L-type  $\text{CaV}1.2$  and  $\text{CaV}1.3$  channels in hippocampal (Brewer et al., 2001) and cortical neurons (Gezen-Ak et al., 2011). If vitamin D is deficient, the expression of the  $\text{CaV}1.2$  and  $\text{CaV}1.3$  channels will be increased and the  $\text{Ca}^{2+}$  pumps and buffers will be reduced and these changes will contribute to the elevated levels of  $\text{Ca}^{2+}$  that occur in BPD.  $\text{Ca}^{2+}$  channel blockers can reduce depression (Dubovsky 1993) and there is increasing interest in the possibility that such  $\text{Ca}^{2+}$  channel antagonists could be developed to treat depression (Cipriani et al., 2016).

Another important function of vitamin D is to control the formation of serotonin and this is another feature of the link between vitamin D deficiency and depression (Patrick and Ames, 2015). It has been shown that one of the actions of vitamin D is to induce the expression of the serotonin-synthesizing gene tryptophan hydroxylase 2 while repressing the expression of tryptophan hydroxylase 1 (Fig. 2). Both tryptophan hydroxylase 1 and tryptophan hydroxylase 2 play a role in serotonin synthesis. Vitamin D may thus prevent depression by maintaining normal serotonin levels.

The basis of the phenotypic stability hypothesis is that vitamin D controls the expression of those genes that are responsible for maintaining both  $\text{Ca}^{2+}$  and reactive oxygen species (ROS) homeostasis. There is evidence that vitamin D may prevent depression by reducing neural  $\text{Ca}^{2+}$  levels (Kalueff et al., 2004). The elevation in both  $\text{Ca}^{2+}$  and ROS levels in neuronal cells that occurs during vitamin D deficiency (Berridge, 2015b) may explain the link to depression. Another important function of vitamin D is to prevent the hypermethylation of gene promoters (Fig. 2). Such epigenetic alterations that lead to a decline in the expression of key signaling proteins are a feature of many neural diseases including depression (Tsankova et al., 2007; Guidotti et al., 2011; Dogra et al., 2016; Saavedra et al., 2016). One of the main functions of vitamin D is to maintain the expression of the DNA demethylases (Fig. 2), such as Jumonji domain-containing protein 1A and 3 (JMJD1A, JMJD3) and lysine-specific demethylase 1 and 2 (LSD1, LSD2) that act to prevent the hypermethylation of promoter regions that are responsible for reducing gene transcription (Pereira et al., 2012). Some of these genes play an important role in the function of GABAergic neurons (Guidotti et al., 2011), which may account for the decline in the size and number of GABAergic neurons that

occurs during depression (Rajkowska et al., 2007; Maciag et al., 2010).

## VII. Depression and Alzheimer's Disease

Older adults that suffer from depression, especially when associated with mild cognitive impairment, have a strong risk of developing Alzheimer's disease (AD) (Van der Mussele et al., 2014; Mourao et al., 2016; Kaup et al., 2016; Kida et al., 2016; Mirza et al., 2016). What is interesting about both depression and AD is that they both display an increase in  $\text{Ca}^{2+}$  that has been linked to vitamin D deficiency (Darwish et al., 2015). There also is evidence that a deficiency in vitamin D is linked to a decline in cognition (Annweiler, 2016). Such a decline in cognition is often associated with depression (Dong et al., 2016). Such vitamin D deficiency will result in an elevation of  $\text{Ca}^{2+}$  that not only induces the decline in cognition and the onset of depression, but it may also set the stage for the initiation of AD. The onset of AD may occur in those individuals who are deficient in vitamin D and thus have abnormally elevated levels of  $\text{Ca}^{2+}$  that may induce the formation of the pathologic  $\text{A}\beta$  oligomers that then initiates the onset of AD (Berridge 2016a). Such a possibility is based on the fact that  $\text{Ca}^{2+}$  acts to stimulate the formation of  $\text{A}\beta$  (Querfurth and Selkoe, 1994; Green and LaFerla, 2008; Itkin et al., 2011). Such a mechanism would explain how the increase in  $\text{Ca}^{2+}$  that occurs in depression may trigger the formation of  $\text{A}\beta$  and thus initiate the onset and progression of AD. In addition to AD, depression may also be associated with the onset of other neurodegenerative diseases such as Parkinson's disease (PD), Huntington's disease, and amyotrophic lateral sclerosis (Réus et al., 2016) that are induced by a dysregulation of  $\text{Ca}^{2+}$  signaling (Berridge, 2016b).

## VIII. Conclusion

Depression arises through a change in neural activity. Normal brain function depends on a fine balance between the activity of the excitatory and inhibitory neurons (E-I balance). There are indications that there is an increase in the levels of glutamate that results in an increase in the activity of the excitatory neurons, whereas there is a decline in the activity and number of the GABAergic inhibitory neurons. This alteration in neural activity is associated with a marked increase in the intracellular level of  $\text{Ca}^{2+}$ , which may account for the decline in the inhibitory neurons through the inhibition of protein synthesis in the synapses. The increase in glutamate levels may contribute to the increase in  $\text{Ca}^{2+}$  levels in that glutamate activates both the ionotropic NMDARs that gate  $\text{Ca}^{2+}$  and the metabotropic glutamatergic receptors such as the mGluR5s and the muscarinic M1 receptors that are coupled to the phosphoinositide signaling pathway that generates

InsP<sub>3</sub> that releases Ca<sup>2+</sup> from the internal stores. The significance of these two pathways is supported by the fact that depression can be alleviated by ketamine that inhibits the NMDARs and scopolamine that inhibits the M1 receptors. The increase in Ca<sup>2+</sup> may also help to explain why depression is such a strong risk factor for the onset of Alzheimer's disease (AD). It is conceivable that the increase in Ca<sup>2+</sup> that occurs in depression may act to trigger the activation of amyloid formation that then initiates the onset of AD.

A role for this increase in neuronal Ca<sup>2+</sup> levels in driving depression may also explain why vitamin D deficiency is a risk factor for depression. Vitamin D functions normally to maintain low intracellular Ca<sup>2+</sup> levels, but when vitamin D levels decline the levels of Ca<sup>2+</sup> begin to rise within the cell and this may enhance the onset of depression. This elevation of Ca<sup>2+</sup> is enhanced by the fact that vitamin D plays an important role in maintain normal mitochondrial respiration. In addition, vitamin D acts to reduce inflammation, it maintains the synthesis of serotonin, and it induces the expression of DNA demethylases that controls the epigenetic landscape, thus enabling gene transcription to continue to maintain normal neuronal activity and to prevent depression.

#### Authorship Contributions

Wrote or contributed to the writing of the manuscript: Berridge.

#### References

- Alexianu ME, Robbins E, Carswell S, and Appel SH (1998) 1 $\alpha$ , 25 dihydroxyvitamin D<sub>3</sub>-dependent up-regulation of calcium-binding proteins in motoneuron cells. *J Neurosci Res* 51:58–66.
- Andreazza AC, Shao L, Wang JF, and Young LT (2010) Mitochondrial complex I activity and oxidative damage to mitochondrial proteins in the prefrontal cortex of patients with bipolar disorder. *Arch Gen Psychiatry* 67:360–368.
- Andreazza AC, Wang JF, Salmasi F, Shao L, and Young LT (2013) Specific sub-cellular changes in oxidative stress in prefrontal cortex from patients with bipolar disorder. *J Neurochem* 127:552–561.
- Anglin RE, Garside SL, Tarnopolsky MA, Mazurek MF, and Rosebush PI (2012) The psychiatric manifestations of mitochondrial disorders: a case and review of the literature. *J Clin Psychiatry* 73:506–512.
- Anglin RE, Samaan Z, Walter SD, and McDonald SD (2013) Vitamin D deficiency and depression in adults: systematic review and meta-analysis. *Br J Psychiatry* 202:100–107.
- Anweiler C (2016) Vitamin D in dementia prevention. *Ann N Y Acad Sci* 1367:57–63.
- Bánásághi S, Golenár T, Madesh M, Csordás G, RamachandraRao S, Sharma K, Yule DI, Joseph SK, and Hajnóczky G (2014) Isoform- and species-specific control of inositol 1,4,5-trisphosphate (IP<sub>3</sub>) receptors by reactive oxygen species. *J Biol Chem* 289:8170–8181.
- Bansal Y and Kuhad A (2016) Mitochondrial dysfunction in depression. *Curr Neuropharmacol* 14:610–618.
- Barbosa IG, Bauer ME, Machado-Vieira R, and Teixeira AL (2014a) Cytokines in bipolar disorder: paving the way for neuroprogression. *Neural Plast* 2014:360481.
- Barbosa IG, Machado-Vieira R, Soares JC, and Teixeira AL (2014b) The immunology of bipolar disorder. *Neuroimmunomodulation* 21:117–122.
- Beilfuss J, Berg V, Sneve M, Jorde R, and Kamycheva E (2012) Effects of a 1-year supplementation with cholecalciferol on interleukin-6, tumor necrosis factor- $\alpha$  and insulin resistance in overweight and obese subjects. *Cytokine* 60:870–874.
- Berk M, Malhi GS, Gray LJ, and Dean OM (2013a) The promise of N-acetylcysteine in neuropsychiatry. *Trends Pharmacol Sci* 34:167–177.
- Berk M, Williams LJ, Jacka FN, O'Neil A, Pasco JA, Moylan S, Allen NB, Stuart AL, Hayley AC, Byrne ML, et al. (2013b) So depression is an inflammatory disease, but where does the inflammation come from? *BMC Med* 11:200.
- Berridge MJ (2012) Dysregulation of neural calcium signalling in Alzheimer disease, bipolar disorder and schizophrenia. *Prion* 6:1–12.
- Berridge MJ (2014a) Calcium regulation of neural rhythms, memory and Alzheimer's disease. *J Physiol* 592:281–293.
- Berridge MJ (2014b) Calcium signalling and psychiatric disease: bipolar disorder and schizophrenia. *Cell Tissue Res* 357:477–492.
- Berridge MJ (2015a) Vitamin D: a custodian of cell signalling stability in health and disease. *Biochem Soc Trans* 43:349–358.
- Berridge MJ (2015b) Vitamin D cell signalling in health and disease. *Biochem Biophys Res Commun* 460:53–71.
- Berridge MJ (2016a) Vitamin D, reactive oxygen species and calcium signalling in ageing and disease. *Philos Trans R Soc Lond B Biol Sci* 371:20150434.
- Berridge MJ (2016b) The inositol trisphosphate/calcium signaling pathway in health and disease. *Physiol Rev* 96:1261–1296.
- Berridge MJ, Downes CP, and Hanley MR (1989) Neural and developmental actions of lithium: a unifying hypothesis. *Cell* 59:411–419.
- Bertaso F, Roussignol G, Worley P, Bockaert J, Fagni L, and Ango F (2010) Homer1a-dependent crosstalk between NMDA and metabotropic glutamate receptors in mouse neurons. *PLoS One* 5:e9755.
- Bird GS, Burgess GM, and Putney JW Jr (1993) Sulfhydryl reagents and cAMP-dependent kinase increase the sensitivity of the inositol 1,4,5-trisphosphate receptor in hepatocytes. *J Biol Chem* 268:17917–17923.
- Björkhem-Bergman L and Bergman P (2016) Vitamin D and patients with palliative cancer. *BMJ Support Palliat Care* 6:287–291.
- Black LJ, Jacoby P, Allen KL, Trapp GS, Hart PH, Byrne SM, Mori TA, Beilin LJ, and Oddy WH (2014) Low vitamin D levels are associated with symptoms of depression in young adult males. *Aust N Z J Psychiatry* 48:464–471.
- Boal AH, Smith DJ, McCallum L, Muir S, Touyz RM, Dominiczak AF, and Padmanabhan S (2016) Monotherapy with major antihypertensive drug classes and risk of hospital admissions for mood disorders. *Hypertension* 68:1132–1138.
- Bootman MD, Taylor CW, and Berridge MJ (1992) The thiol reagent, thimerosal, evokes Ca<sup>2+</sup> spikes in HeLa cells by sensitizing the inositol 1,4,5-trisphosphate receptor. *J Biol Chem* 267:25113–25119.
- Bouillon R and Verstuyf A (2013) Vitamin D, mitochondria, and muscle. *J Clin Endocrinol Metab* 98:961–963.
- Bower B, Bylsma LM, Morris BH, and Rottenberg J (2010) Poor reported sleep quality predicts low positive affect in daily life among healthy and mood-disordered persons. *J Sleep Res* 19:323–332.
- Brewer LD, Thibault V, Chen KC, Langub MC, Landfield PW, and Porter NM (2001) Vitamin D hormone confers neuroprotection in parallel with downregulation of L-type calcium channel expression in hippocampal neurons. *J Neurosci* 21:98–108.
- Brites D and Fernandes A (2015) Neuroinflammation and depression: Microglia activation, extracellular microvesicles and microRNA Dysregulation. *Front Cell Neurosci* 9:476.
- Brouwer-Brolsma EM, Dhonukshe-Rutten RA, van Wijngaarden JP, van der Zwaluw NL, Sohl E, In't Veld PH, van Dijk SC, Swart KM, Enneman AW, Ham AC, et al. (2016) Low vitamin D status is associated with more depressive symptoms in Dutch older adults. *Eur J Nutr* 55:1525–1534.
- Brown NC, Andreazza AC, and Young LT (2014) An updated meta-analysis of oxidative stress markers in bipolar disorder. *Psychiatry Res* 218:61–68.
- Cai X, Kallarackal AJ, Kvarita MD, Goluskin S, Gaylor K, Bailey AM, Lee HK, Hagan RL, and Thompson SM (2013) Local potentiation of excitatory synapses by serotonin and its alteration in rodent models of depression. *Nat Neurosci* 16:464–472.
- Calabrese F, Riva MA, and Molteni R (2016) Synaptic alterations associated with depression and schizophrenia: potential as a therapeutic target. *Expert Opin Ther Targets* 20:1195–1207.
- Callaly E, Walder K, Morris G, Maes M, Debnath M, and Berk M (2015) Mitochondrial dysfunction in the pathophysiology of bipolar disorder: effects of pharmacotherapy. *Mini Rev Med Chem* 15:355–365.
- Calton EK, Keane KN, and Soares MJ (2015) The potential regulatory role of vitamin D in the bioenergetics of inflammation. *Curr Opin Clin Nutr Metab Care* 18:367–373.
- Catena-Dell'Osso M, Bellantuono C, Consoli G, Baroni S, Rotella F, and Marazziti D (2011) Inflammatory and neurodegenerative pathways in depression: a new avenue for antidepressant development? *Curr Med Chem* 18:245–255.
- Chaki S, Ago Y, Palucha-Paniewiera A, Matriciano F, and Pilc A (2013) mGlu2/3 and mGlu5 receptors: potential targets for novel antidepressants. *Neuropharmacology* 66:40–52.
- Chan R, Chan D, Woo J, Ohlsson C, Mellström D, Kwok T, and Leung P (2011) Association between serum 25-hydroxyvitamin D and psychological health in older Chinese men in a cohort study. *J Affect Disord* 130:251–259.
- Chen G, Zeng WZ, Yuan PX, Huang LD, Jiang YM, Zhao ZH, and Manji HK (1999) The mood-stabilizing agents lithium and valproate robustly increase the levels of the neuroprotective protein bcl-2 in the CNS. *J Neurochem* 72:879–882.
- Cipriani A, Saunders K, Attenburrow MJ, Stefanik J, Panchal P, Stockton S, Lane TA, Tunbridge EM, Geddes JR, and Harrison PJ (2016) A systematic review of calcium channel antagonists in bipolar disorder and some considerations for their future development. *Mol Psychiatry* 21:1324–1332.
- Clay HB, Sullivan S, and Konradi C (2011) Mitochondrial dysfunction and pathology in bipolar disorder and schizophrenia. *Int J Dev Neurosci* 29:311–324.
- Consiglio M, Viano M, Casarin S, Castagnoli C, Pescarmona G, and Silvagno F (2015) Mitochondrial and lipogenic effects of vitamin D on differentiating and proliferating human keratinocytes. *Exp Dermatol* 24:748–753.
- Corson TW, Woo KK, Li PP, and Warsh JJ (2004) Cell-type specific regulation of calcitriol and Bcl-2 expression by mood stabilizer drugs. *Eur Neuropharmacol* 14:143–150.
- Croarkin PE, Levinson AJ, and Daskalakis ZJ (2011) Evidence for GABAergic inhibitory deficits in major depressive disorder. *Neurosci Biobehav Rev* 35:818–825.
- Cui J, Shao L, Young LT, and Wang JF (2007) Role of glutathione in neuroprotective effects of mood stabilizing drugs lithium and valproate. *Neuroscience* 144:1447–1453.
- Cui X, Gooch H, Groves NJ, Sah P, Burne TH, Eyles DW, and McGrath JJ (2015) Vitamin D and the brain: key questions for future research. *J Steroid Biochem Mol Biol* 148:305–309.
- Dantzer R, O'Connor JC, Freund GG, Johnson RW, and Kelley KW (2008) From inflammation to sickness and depression: when the immune system subjugates the brain. *Nat Rev Neurosci* 9:46–56.

- Darwish H, Zeinoun P, Ghous H, Khoury B, Tamim H, and Khoury SJ (2015) Serum 25-hydroxyvitamin D predicts cognitive performance in adults. *Neuropsychiatr Dis Treat* **11**:2217–2223.
- Dean B, Gibbons AS, Tawadros N, Brooks L, Everall IP, and Scarr E (2013) Different changes in cortical tumor necrosis factor- $\alpha$ -related pathways in schizophrenia and mood disorders. *Mol Psychiatry* **18**:767–773.
- Dean O, Giorlando F, and Berk M (2011) N-acetylcysteine in psychiatry: current therapeutic evidence and potential mechanisms of action. *J Psychiatry Neurosci* **36**:78–86.
- Dean OM, van den Buuse M, Bush AI, Copolov DL, Ng F, Dodd S, and Berk M (2009) A role for glutathione in the pathophysiology of bipolar disorder and schizophrenia? Animal models and relevance to clinical practice. *Curr Med Chem* **16**:2965–2976.
- Deranigh RM and Greenberg ML (2009) Cellular consequences of inositol depletion. *Biochem Soc Trans* **37**:1099–1103.
- Deutschenbaur L, Beck J, Kiyhankhadiv A, Mühlhauser M, Borgwardt S, Walter M, Hasler G, Söllberger D, and Lang UE (2016) Role of calcium, glutamate and NMDA in major depression and therapeutic application. *Prog Neuropsychopharmacol Biol Psychiatry* **64**:325–333.
- de Viragh PA, Haglid KGMR, and Celio MR (1989) Parvalbumin increases in the caudate putamen of rats with vitamin D hypervitaminosis. *Proc Natl Acad Sci USA* **86**:3887–3890.
- Distelhorst CW and Bootman MD (2011) Bcl-2 interaction with the inositol 1,4,5-trisphosphate receptor: role in Ca<sup>2+</sup> signaling and disease. *Cell Calcium* **50**:234–241.
- Dogra S, Sonu C, Kumar A, and Yadav PN (2016) Epigenetic regulation of G protein coupled receptor signaling and its implications in psychiatric disorders. *Int J Biochem Cell Biol* **77** (Pt B):226–239.
- Dong HS, Han C, Jeon SW, Yoon S, Jeong HG, Huh YJ, Pae CU, Patkar AA, and Steffens DC (2016) Characteristics of neurocognitive functions in mild cognitive impairment with depression. *Int Psychogeriatr* **28**:1181–1190.
- Donoso P, Sanchez G, Bull R, and Hidalgo C (2011) Modulation of cardiac ryanodine receptor activity by ROS and RNS. *Front Biosci (Landmark Ed)* **16**:553–567.
- Drevets WC, Zarate CA Jr, and Furey ML (2013) Antidepressant effects of the muscarinic cholinergic receptor antagonist scopolamine: a review. *Biol Psychiatry* **73**:1156–1163.
- Dubovsky SL (1993) Calcium antagonists in manic-depressive illness. *Neuropsychobiology* **27**:184–192.
- Dubovsky SL, Murphy J, Thomas M, and Rademacher J (1992) Abnormal intracellular calcium ion concentration in platelets and lymphocytes of bipolar patients. *Am J Psychiatry* **149**:118–120.
- Duman RS and Aghajanian GK (2012) Synaptic dysfunction in depression: potential therapeutic targets. *Science* **338**:68–72.
- Duman CH and Duman RS (2015) Spine synapse remodeling in the pathophysiology and treatment of depression. *Neurosci Lett* **601**:20–29.
- Eickholt BJ, Towers GJ, Ryves WJ, Eikel D, Adley K, Ylinen LM, Chadborn NH, Harwood AJ, Nau H, and Williams RS (2005) Effects of valproic acid derivatives on inositol trisphosphate depletion, teratogenicity, glycogen synthase kinase-3 $\beta$  inhibition, and viral replication: a screening approach for new bipolar disorder drugs derived from the valproic acid core structure. *Mol Pharmacol* **67**:1426–1433.
- Feng W, Tu J, Yang T, Vernon PS, Allen PD, Worley PF, and Pessah IH (2002) Homer regulates gain of ryanodine receptor type 1 channel complex. *J Biol Chem* **277**:44722–44730.
- Ferreira MA, O'Donovan MC, Meng YA, Jones IR, Ruderfer DM, Jones L, Fan J, Kirov G, Perlis RH, Green EK, et al. (2008) Wellcome Trust Case Control Consortium (2008) Collaborative genome-wide association analysis supports a role for ANK3 and CACNA1C in bipolar disorder. *Nat Genet* **40**:1056–1058.
- Fitzgerald PB, Laird AR, Maller J, and Daskalakis ZJ (2008) A meta-analytic study of changes in brain activation in depression. *Hum Brain Mapp* **29**:683–695.
- Franzen PL and Buysse DJ (2008) Sleep disturbances and depression: risk relationships for subsequent depression and therapeutic implications. *Dialogues Clin Neurosci* **10**:473–481.
- Friedman AK, Juarez B, Ku SM, Zhang H, Calizo RC, Walsh JJ, Chaudhry D, Zhang S, Hawkins A, Dietz DM, et al. (2016) KCNQ channel openers reverse depressive symptoms via an active resilience mechanism. *Nat Commun* **7**:11671.
- Frye MA, Watzl J, Banakar S, O'Neill J, Mintz J, Davanzo P, Fischer J, Chirichigno JW, Ventura J, Elman S, et al. (2007) Increased anterior cingulate/medial prefrontal cortical glutamate and creatine in bipolar depression. *Neuropsychopharmacology* **32**:2490–2499.
- Furey ML and Drevets WC (2006) Antidepressant efficacy of the antimuscarinic drug scopolamine: a randomized, placebo-controlled clinical trial. *Arch Gen Psychiatry* **63**:1121–1129.
- Galeotti N, Bartolini A, and Ghelardini C (2006) Blockade of intracellular calcium release induces an antidepressant-like effect in the mouse forced swimming test. *Neuropharmacology* **50**:309–316.
- Galeotti N, Vivoli E, Bartolini A, and Ghelardini C (2008a) A gene-specific cerebral types 1, 2, and 3 R $\gamma$ R protein knockdown induces an antidepressant-like effect in mice. *J Neurochem* **106**:2385–2394.
- Galeotti N, Vivoli E, Norcini M, Bartolini A, and Ghelardini C (2008b) An antidepressant behaviour in mice carrying a gene-specific InsP<sub>3</sub>R1, InsP<sub>3</sub>R2 and InsP<sub>3</sub> protein knockdown. *Neuropharmacology* **55**:1156–1164.
- Gawryluk JW, Wang JF, Andrezza AC, Shao L, and Young LT (2011) Decreased levels of glutathione, the major brain antioxidant, in post-mortem prefrontal cortex from patients with psychiatric disorders. *Int J Neuropsychopharmacol* **14**:123–130.
- Gezen-Ak D, Dursun E, and Yilmazer S (2011) The effects of vitamin D receptor silencing on the expression of LVSCC-A1C and LVSCC-A1D and the release of NGF in cortical neurons. *PLoS One* **6**:e17553.
- Gigante AD, Bond DJ, Lafer B, Lam RW, Young LT, and Yatham LN (2012) Brain glutamate levels measured by magnetic resonance spectroscopy in patients with bipolar disorder: a meta-analysis. *Bipolar Disord* **14**:478–487.
- Gracious BL, Finucane TL, Friedman-Campbell M, Messing S, and Parkhurst MN (2012) Vitamin D deficiency and psychotic features in mentally ill adolescents: a cross-sectional study. *BMC Psychiatry* **12**:38.
- Green KN and LaFerla FM (2008) Linking calcium to Abeta and Alzheimer's disease. *Neuron* **59**:190–194.
- Grossmann RE, Zughaier SM, Liu S, Lyles RH, and Tangpricha V (2012) Impact of vitamin D supplementation on markers of inflammation in adults with cystic fibrosis hospitalized for a pulmonary exacerbation. *Eur J Clin Nutr* **66**:1072–1074.
- Grudet C, Malm J, Westrin A, and Brundin L (2014) Suicidal patients are deficient in vitamin D, associated with a pro-inflammatory status in the blood. *Psychoneuroendocrinology* **50**:210–219.
- Guidotti A, Auta J, Chen Y, Davis JM, Dong E, Gavin DP, Grayson DR, Matrisciano F, Pinna G, Satta R, et al. (2011) Epigenetic GABAergic targets in schizophrenia and bipolar disorder. *Neuropharmacology* **60**:1007–1016.
- Harrison PJ (2016) Molecular neurobiological clues to the pathogenesis of bipolar disorder. *Curr Opin Neurobiol* **36**:1–6.
- Harwood AJ (2005) Lithium and bipolar mood disorder: the inositol-depletion hypothesis revisited. *Mol Psychiatry* **10**:117–126.
- Hashimoto K, Sawa A, and Iyo M (2007) Increased levels of glutamate in brains from patients with mood disorders. *Biol Psychiatry* **62**:1310–1316.
- Hasler G, van der Veen JW, Tuminis T, Meyers N, Shen J, and Drevets WC (2007) Reduced prefrontal glutamate/glutamine and gamma-aminobutyric acid levels in major depression determined using proton magnetic resonance spectroscopy. *Arch Gen Psychiatry* **64**:193–200.
- Hewison M (2010) Vitamin D and the immune system: new perspectives on an old theme. *Endocrinol Metab Clin North Am* **39**:365–379.
- Heyes S, Pratt WS, Rees E, Dahimene S, Ferron L, Owen MJ, and Dolphin AC (2015) Genetic disruption of voltage-gated calcium channels in psychiatric and neurological disorders. *Prog Neurobiol* **134**:36–54.
- Hidalgo C and Donoso P (2008) Crosstalk between calcium and redox signaling: from molecular mechanisms to health implications. *Antioxid Redox Signal* **10**:1275–1312.
- Holick MF, MacLaughlin JA, Clark MB, Holick SA, Potts JT Jr, Anderson RR, Blank IH, Parrish JA, and Elias P (1980) Photosynthesis of previtamin D<sub>3</sub> in human skin and the physiologic consequences. *Science* **210**:203–205.
- Hoogendijk WJ, Lips P, Dik MG, Deeg DJ, Beekman AT, and Penninx BW (2008) Depression is associated with decreased 25-hydroxyvitamin D and increased parathyroid hormone levels in older adults. *Arch Gen Psychiatry* **65**:508–512.
- Hwang SY, Wei J, Westhoff JH, Duncan RS, Ozawa F, Volpe P, Inokuchi K, and Koulen P (2003) Differential functional interaction of two Ves/ Homer protein isoforms with ryanodine receptor type 1: a novel mechanism for control of intracellular calcium signaling. *Cell Calcium* **34**:177–184.
- Itkin A, Dupres V, Dufrene YF, Bechinger B, Ruyschaert JM, and Raussens V (2011) Calcium ions promote formation of amyloid  $\beta$ -peptide (1–40) oligomers causally implicated in neuronal toxicity of Alzheimer's disease. *PLoS One* **6**:e18250.
- Jääskeläinen T, Knekt P, Suvisaari J, Männistö S, Partonen T, Sääksjärvi K, Kaartinen NE, Kanerva N, and Lindfors O (2015) Higher serum 25-hydroxyvitamin D concentrations are related to a reduced risk of depression. *Br J Nutr* **113**:1418–1426.
- Jacobs BL, van Praag H, and Gage FH (2000) Adult brain neurogenesis and psychiatry: a novel theory of depression. *Mol Psychiatry* **5**:262–269.
- Jacobson JPR, Medvedev IO, and Caron MG (2012) The 5-HT deficiency theory of depression: perspectives from a naturalistic 5-HT deficiency model, the tryptophan hydroxylase 2Arg439His knockin mouse. *Philos Trans R Soc Lond B Biol Sci* **367**:2444–2459.
- Johansson P, Alehagen U, van der Wal MH, Svensson E, and Jaarsma T (2016) Vitamin D levels and depressive symptoms in patients with chronic heart failure. *Int J Cardiol* **207**:185–189.
- Jou SH, Chiu NY, and Liu CS (2009) Mitochondrial dysfunction and psychiatric disorders. *Chang Gung Med J* **32**:370–379.
- Kabir ZD, Lee AS, and Rajadhyaksha AM (2016) L-type Ca<sup>2+</sup> channels in mood, cognition and addiction: integrating human and rodent studies with a focus on behavioural endophenotypes. *J Physiol* **594**:5823–5837.
- Kaluff AV, Eremim KO, and Tuohimaa P (2004) Mechanisms of neuroprotective action of vitamin D(3). *Biochemistry (Mosc)* **69**:738–741.
- Kato T (2007) Mitochondrial dysfunction as the molecular basis of bipolar disorder: therapeutic implications. *CNS Drugs* **21**:1–11.
- Kaup AR, Byers AL, Falvey C, Simonsick EM, Satterfield S, Ayonayon HN, Smagula SF, Rubin SM, and Yaffe K (2016) Trajectories of depressive symptoms in older adults and risk of dementia. *JAMA Psychiatry* **73**:525–531.
- Kempermann G, Song H, and Gage FH (2015) Neurogenesis in the adult hippocampus. *Cold Spring Harb Perspect Biol* **7**:a018812.
- Kerr DC, Zava DT, Piper WT, Saturn SR, Frei B, and Gombart AF (2015) Associations between vitamin D levels and depressive symptoms in healthy young adult women. *Psychiatry Res* **227**:46–51.
- Kida J, Nemoto K, Ikejima C, Bun S, Kakuma T, Mizukami K, and Asada T (2016) Impact of depressive symptoms on conversion from mild cognitive impairment subtypes to Alzheimer's Disease: A community-based longitudinal study. *J Alzheimers Dis* **51**:405–415.
- Kim HK, Andrezza AC, Yeung PY, Isaacs-Trepanier C, and Young LT (2014) Oxidation and nitration in dopaminergic areas of the prefrontal cortex from patients with bipolar disorder and schizophrenia. *J Psychiatry Neurosci* **39**:276–285.
- Kim HJ and Thayer SA (2009) Lithium increases synapse formation between hippocampal neurons by depleting phosphoinositides. *Mol Pharmacol* **75**:1021–1030.
- Klausberger T, Magill PJ, Márton LF, Roberts JD, Cobden PM, Buzsáki G, and Somogyi P (2003) Brain-state- and cell-type-specific firing of hippocampal interneurons in vivo. *Nature* **421**:844–848.
- Kobayashi K, Ikeda Y, Haneda E, and Suzuki H (2008) Chronic fluoxetine bidirectionally modulates potentiating effects of serotonin on the hippocampal mossy fiber synaptic transmission. *J Neurosci* **28**:6272–6280.

- Koh PO, Undie AS, Kabbani N, Levenson R, Goldman-Rakic PS, and Lidow MS (2003) Up-regulation of neuronal calcium sensor-1 (NCS-1) in the prefrontal cortex of schizophrenic and bipolar patients. *Proc Natl Acad Sci USA* **100**:313–317.
- Krystal JH, Mathew SJ, D'Souza DC, Garakani A, Gunduz-Bruce H, and Charney DS (2010) Potential psychiatric applications of metabotropic glutamate receptor agonists and antagonists. *CNS Drugs* **24**:669–693.
- Kulak A, Steullet P, Cabungcal JH, Werge T, Ingason A, Cuenod M, and Do KQ (2013) Redox dysregulation in the pathophysiology of schizophrenia and bipolar disorder: insights from animal models. *Antioxid Redox Signal* **18**:1428–1443.
- Kunz M, Gama CS, Andreazza AC, Salvador M, Ceresér KM, Gomes FA, Belmonte-de-Abreu PS, Berk M, and Kapczinski F (2008) Elevated serum superoxide dismutase and thiobarbituric acid reactive substances in different phases of bipolar disorder and in schizophrenia. *Prog Neuropsychopharmacol Biol Psychiatry* **32**:1677–1681.
- Lee KW, Westin L, Kim J, Chang JC, Oh YS, Amreen B, Gresack J, Flajole M, Kim D, Aperia A, et al. (2015) Alteration by p11 of mGluR5 localization regulates depression-like behaviors. *Mol Psychiatry* **20**:1546–1556.
- Leonard B and Maes M (2012) Mechanistic explanations how cell-mediated immune activation, inflammation and oxidative and nitrosative stress pathways and their sequels and concomitants play a role in the pathophysiology of unipolar depression. *Neurosci Biobehav Rev* **36**:764–785.
- Levinson AJ, Fitzgerald PB, Favalli G, Blumberger DM, Daigle M, and Daskalakis ZJ (2010) Evidence of cortical inhibitory deficits in major depressive disorder. *Biol Psychiatry* **67**:458–464.
- Lock JT, Sinkins WG, and Schilling WP (2011) Effect of protein S-glutathionylation on Ca<sup>2+</sup> homeostasis in cultured aortic endothelial cells. *Am J Physiol Heart Circ Physiol* **300**:H493–H506.
- Lubrich B and van Calker D (1999) Inhibition of the high affinity myo-inositol transport system: a common mechanism of action of antibipolar drugs? *Neuropsychopharmacology* **21**:519–529.
- Luo P, Li X, Fei Z, and Poon W (2012) Scaffold protein Homer 1: implications for neurological diseases. *Neurochem Int* **61**:731–738.
- Luscher B, Shen Q, and Sahir N (2011) The GABAergic deficit hypothesis of major depressive disorder. *Mol Psychiatry* **16**:383–406.
- Machado-Vieira R, Pivovarova NB, Stanika RI, Yuan P, Wang Y, Zhou R, Zarate Jr CA, Drevets WC, Brantner CA, Baum A, et al. (2011) The Bcl-2 gene polymorphism rs956572AA increases inositol 1,4,5-trisphosphate receptor-mediated endoplasmic reticulum calcium release in subjects with bipolar disorder. *Biol Psychiatry* **69**:344–352.
- Maciag D, Hughes J, O'Dwyer G, Pride Y, Stockmeier CA, Sanacora G, and Rajkowska G (2010) Reduced density of calbindin immunoreactive GABAergic neurons in the occipital cortex in major depression: relevance to neuroimaging studies. *Biol Psychiatry* **67**:465–470.
- Maes M (1995) Evidence for an immune response in major depression: a review and hypothesis. *Prog Neuropsychopharmacol Biol Psychiatry* **19**:11–38.
- Maes M (2011) Depression is an inflammatory disease, but cell-mediated immune activation is the key component of depression. *Prog Neuropsychopharmacol Biol Psychiatry* **35**:664–675.
- Malberg JE, Eisch AJ, Nestler EJ, and Duman RS (2000) Chronic antidepressant treatment increases neurogenesis in adult rat hippocampus. *J Neurosci* **20**:9104–9110.
- Manji HK, Moore GJ, and Chen G (2000) Lithium up-regulates the cytoprotective protein Bcl-2 in the CNS in vivo: a role for neurotrophic and neuroprotective effects in manic depressive illness. *J Clin Psychiatry* **61** (Suppl 9):82–96.
- Manji HK, Quiroz JA, Payne JL, Singh J, Lopes BP, Viegas JS, and Zarate CA (2003) The underlying neurobiology of bipolar disorder. *World Psychiatry* **2**:136–146.
- Mathews R, Li PP, Young LT, Kish SJ, and Warsh JJ (1997) Increased G alpha q/11 immunoreactivity in postmortem occipital cortex from patients with bipolar affective disorder. *Biol Psychiatry* **41**:649–656.
- McClung CA and Nestler EJ (2008) Neuroplasticity mediated by altered gene expression. *Neuropsychopharmacology* **33**:3–17.
- Miller AH, Maletic V, and Raison CL (2009) Inflammation and its discontents: the role of cytokines in the pathophysiology of major depression. *Biol Psychiatry* **65**:732–741.
- Miller BR and Hen R (2015) The current state of the neurogenic theory of depression and anxiety. *Curr Opin Neurobiol* **30**:51–58.
- Miller OH, Yang L, Wang CC, Hargroder EA, Zhang Y, Delpire E, and Hall BJ (2014) GluN2B-containing NMDA receptors regulate depression-like behavior and are critical for the rapid antidepressant actions of ketamine. *eLife* **3**:e03581.
- Ming GL and Song H (2011) Adult neurogenesis in the mammalian brain: significant answers and significant questions. *Neuron* **70**:687–702.
- Mirza SS, Wolters FJ, Swanson SA, Koudstaal PJ, Hofman A, Tiemeier H, and Ikram MA (2016) 10-year trajectories of depressive symptoms and risk of dementia: a population-based study. *Lancet Psychiatry* **3**:628–635.
- Missiaen L, Taylor CW, and Berridge MJ (1991) Spontaneous calcium release from inositol trisphosphate-sensitive calcium stores. *Nature* **352**:241–244.
- Money KM, Olah Z, Korade Z, Garbett KA, Shelton RC, and Mirnic K (2016) An altered peripheral IL6 response in major depressive disorder. *Neurobiol Dis* **89**:46–54.
- Morris G and Berk M (2015) The many roads to mitochondrial dysfunction in neuro-immune and neuropsychiatric disorders. *BMC Med* **13**:68.
- Mourao RJ, Mansur G, Malloy-Diniz LF, Castro Costa E, and Diniz BS (2016) Depressive symptoms increase the risk of progression to dementia in subjects with mild cognitive impairment: systematic review and meta-analysis. *Int J Geriatr Psychiatry* **31**:905–911.
- Moy FM, Hoe VC, Hair NN, Vethakkan SR, and Bulgiba A (2016) Vitamin D deficiency and depression among women from an urban community in a tropical country. *Public Health Nutr* **18**:1–7.
- Najjar S, Pearlman DM, Alper K, Najjar A, and Devinsky O (2013) Neuroinflammation and psychiatric illness. *J Neuroinflammation* **10**:43.
- Nassar A and Azab AN (2014) Effects of lithium on inflammation. *ACS Chem Neurosci* **5**:451–458.
- Navarria A, Wohleb ES, Voleti B, Ota KT, Duthiel S, Lepack AE, Dwyer JM, Fuchikami M, Becker A, Drago F, et al. (2015) Rapid antidepressant actions of scopolamine: Role of medial prefrontal cortex and M1-subtype muscarinic acetylcholine receptors. *Neurobiol Dis* **82**:254–261.
- Newell KA and Matosin N (2014) Rethinking metabotropic glutamate receptor 5 pathological findings in psychiatric disorders: implications for the future of novel therapeutics. *BMC Psychiatry* **14**:23.
- Niciu MJ, Ionescu DF, Richards EM, and Zarate CA Jr (2014) Glutamate and its receptors in the pathophysiology and treatment of major depressive disorder. *J Neural Transm (Vienna)* **121**:907–924.
- Okereke OI and Singh A (2016) The role of vitamin D in the prevention of late-life depression. *J Affect Disord* **198**:1–14.
- Ostacher MJ, Iosifescu DV, Hay A, Blumenthal SR, Sklar P, and Perlis RH (2014) Pilot investigation of isradipine in the treatment of bipolar depression motivated by genome-wide association. *Bipolar Disord* **16**:199–203.
- Ou X, Crane DE, MacIntosh BJ, Young LT, Arnold P, Ameis S, and Goldstein BI (2015) CACNA1C rs1006737 genotype and bipolar disorder: Focus on intermediate phenotypes and cardiovascular comorbidity. *Neurosci Biobehav Rev* **55**:198–210.
- Pałucha-Poniewiera A, Wierońska JM, Brański P, Burnat G, Chruścicka B, and Pile A (2013) Is the mGlu5 receptor a possible target for new antidepressant drugs? *Pharmacol Rep* **65**:1506–1511.
- Park KM, Yule DI, and Bowers WJ (2009) Tumor necrosis factor- $\alpha$ -mediated regulation of the inositol 1,4,5-trisphosphate receptor promoter. *J Biol Chem* **284**:27557–27566.
- Patrick RP and Ames BN (2015) Vitamin D and the omega-3 fatty acids control serotonin synthesis and action, part 2: relevance for ADHD, bipolar disorder, schizophrenia, and impulsive behavior. *FASEB J* **29**:2207–2222.
- Paul IA and Skolnick P (2003) Glutamate and depression: clinical and preclinical studies. *Ann N Y Acad Sci* **1003**:250–272.
- Paula-Lima AC, Adasme T, and Hidalgo C (2014) Contribution of Ca<sup>2+</sup> release channels to hippocampal synaptic plasticity and spatial memory: potential redox modulation. *Antioxid Redox Signal* **21**:892–914.
- Pereira F, Barbáchano A, Singh PK, Campbell MJ, Muñoz A, and Larriba MJ (2012) Vitamin D has wide regulatory effects on histone demethylase genes. *Cell Cycle* **11**:1081–1089.
- Pérez AV, Picotto G, Carpentieri AR, Rivoira MA, Peralta López ME, and Tolosa de Talamoni NG (2008) Minireview on regulation of intestinal calcium absorption. Emphasis on molecular mechanisms of transcellular pathway. *Digestion* **77**:22–34.
- Perrier E, Pompei F, Ruberto G, Vassos E, Collier D, and Frangou S (2011) Initial evidence for the role of CACNA1C on subcortical brain morphology in patients with bipolar disorder. *Eur Psychiatry* **26**:135–137.
- Perroy J, Raynaud F, Homburger V, Rousset MC, Telley L, Bockaert J, and Fagni L (2008) Direct interaction enables cross-talk between ionotropic and group I metabotropic glutamate receptors. *J Biol Chem* **283**:6799–6805.
- Polak MA, Houghton LA, Reeder AI, Harper MJ, and Conner TS. (2014) Serum 25-hydroxyvitamin D concentrations and depressive symptoms among young adult men and women. *Nutrients* **6**:4720–4730.
- Pouliquin P and Dulhunty AF (2009) Homer and the ryanodine receptor. *Eur Biophys J* **39**:91–102.
- Querfurth HW and Selkoe DJ (1994) Calcium ionophore increases amyloid beta peptide production by cultured cells. *Biochemistry* **33**:4550–4561.
- Raab-Graham KF, Workman ER, Namjoshi S, and Niere F (2016) Pushing the threshold: How NMDAR antagonists induce homeostasis through protein synthesis to remedy depression. *Brain Res* **1647**:94–104.
- Rajkowska G, O'Dwyer G, Teleki Z, Stockmeier CA, and Miguel-Hidalgo JJ (2007) GABAergic neurons immunoreactive for calcium binding proteins are reduced in the prefrontal cortex in major depression. *Neuropsychopharmacology* **32**:471–482.
- Ren Z, Pribragh H, Jefferson SJ, Shorey M, Fuchs T, Stellwagen D, and Luscher B (2016) Bidirectional homeostatic regulation of a depression-related brain state by Gamma-Aminobutyric Acidergic deficits and ketamine treatment. *Biol Psychiatry* **80**:457–468.
- Réus GZ, Titus SE, Abelaira HM, Freitas SM, Tuon T, Quevedo J, and Budni J (2016) Neurochemical correlation between major depressive disorder and neurodegenerative diseases. *Life Sci* **158**:121–129.
- Rietschel M, Mattheisen M, Frank J, Treutlein J, Degenhardt F, Breuer R, Steffens M, Mier D, Esslinger C, Walter H, et al. (2010) Genome-wide association-, replication-, and neuroimaging study implicates HOMER1 in the etiology of major depression. *Biol Psychiatry* **68**:578–585.
- Ryan ZC, Craig TA, Folmes CD, Wang X, Lanza IR, Schaible NS, Salisbury JL, Nair KS, Terzic A, Sieck GC, et al. (2016) 1 $\alpha$ ,25-Dihydroxyvitamin D<sub>3</sub> Regulates Mitochondrial Oxygen Consumption and Dynamics in Human Skeletal Muscle Cells. *J Biol Chem* **291**:1514–1528.
- Saavedra K, Molina-Márquez AM, Saavedra N, Zambrano T, and Salazar LA (2016) Epigenetic modifications of major depressive disorder. *Int J Mol Sci* **17**:1279.
- Salvadore G, Quiroz JA, Machado-Vieira R, Henter ID, Manji HK, and Zarate CA Jr (2010) The neurobiology of the switch process in bipolar disorder: a review. *J Clin Psychiatry* **71**:1488–1501.
- Sanacora G, Gueorguieva R, Epperson CN, Wu YT, Appel M, Rothman DL, Krystal JH, and Mason GF (2004) Subtype-specific alterations of gamma-aminobutyric acid and glutamate in patients with major depression. *Arch Gen Psychiatry* **61**:705–713.
- Scaini G, Rezin GT, Carvalho AF, Streck EL, Berk M, and Quevedo J (2016) Mitochondrial dysfunction in bipolar disorder: Evidence, pathophysiology and translational implications. *Neurosci Biobehav Rev* **68**:694–713.
- Schildkraut JJ (1965) The catecholamine hypothesis of affective disorders: a review of supporting evidence. *Am J Psychiatry* **122**:509–522.
- Schlecker C, Boehmerle W, Jeromin A, DeGray B, Varshney A, Sharma Y, Szigeti-Buck K, and Ehrlich BE (2006) Neuronal calcium sensor-1 enhancement of InsP<sub>3</sub> receptor activity is inhibited by therapeutic levels of lithium. *J Clin Invest* **116**:1668–1674.

- Serchov T, Clement HW, Schwarz MK, Iasevoli F, Tosh DK, Idzko M, Jacobson KA, de Bartolomeis A, Normann C, Biber K, et al. (2015) Increased signaling via adenosine A1 receptors, sleep deprivation, Imipramine, and Ketamine inhibit depressive-like behavior via induction of Homer1a. *Neuron* **87**:549–562.
- Serchov T, Heumann R, van Calker D, and Biber K (2016) Signaling pathways regulating Homer1a expression: implications for antidepressant therapy. *Biol Chem* **397**:207–214.
- Shao L, Cui J, Young LT, and Wang JF (2008) The effect of mood stabilizer lithium on expression and activity of glutathione s-transferase isoenzymes. *Neuroscience* **151**: 518–524.
- Sikoglu EM, Navarro AA, Starr D, Dvir Y, Nwosu BU, Czerniak SM, Rogan RC, Castro MC, Edden RA, Frazier JA, et al. (2015) Vitamin D3 supplemental treatment for mania in youth with Bipolar Spectrum Disorders. *J Child Adolesc Psychopharmacol* **25**:415–424.
- Silvagno F, Consiglio M, Foglizzo V, Destefanis M, and Pescarmona G (2013) Mitochondrial translocation of vitamin D receptor is mediated by the permeability transition pore in human keratinocyte cell line. *PLoS One* **8**:e54716.
- Silvagno F, De Vivo E, Attanasio A, Gallo V, Mazzucco G, and Pescarmona G (2010) Mitochondrial localization of vitamin D receptor in human platelets and differentiated megakaryocytes. *PLoS One* **5**:e8670.
- Sinha A, Hollingsworth KG, Ball S, and Cheetham T (2013) Improving the vitamin D status of vitamin D deficient adults is associated with improved mitochondrial oxidative function in skeletal muscle. *J Clin Endocrinol Metab* **98**:E509–E513.
- Soeiro-de-Souza MG, Salvadore G, Moreno RA, Otaduy MC, Chaim KT, Gattaz WF, Zarate CA Jr, and Machado-Vieira R (2013) Bcl-2 rs956572 polymorphism is associated with increased anterior cingulate cortical glutamate in euthymic bipolar I disorder. *Neuropsychopharmacology* **38**:468–475.
- Steckert AV, Valvassori SS, Moretti M, Dal-Pizzol F, and Quevedo J (2010) Role of oxidative stress in the pathophysiology of bipolar disorder. *Neurochem Res* **35**: 1295–1301.
- Stewart R and Hirani V (2010) Relationship between vitamin D levels and depressive symptoms in older residents from a national survey population. *Psychosom Med* **72**:608–612.
- Stokes CS, Grünhage F, Baus C, Volmer DA, Wagenpfeil S, Riemenschneider M, and Lammert F (2016) Vitamin D supplementation reduces depressive symptoms in patients with chronic liver disease. *Clin Nutr* **35**:950–957.
- Sukoff Rizzo SJ, Neal SJ, Hughes ZA, Beyna M, Rosenzweig-Lipson S, Moss SJ, and Brandon NJ (2012) Evidence for sustained elevation of IL-6 in the CNS as a key contributor of depressive-like phenotypes. *Transl Psychiatry* **2**:e199.
- Sutton MA, Taylor AM, Ito HT, Pham A, and Schuman EM (2007) Postsynaptic decoding of neural activity: eEF2 as a biochemical sensor coupling miniature synaptic transmission to local protein synthesis. *Neuron* **55**:648–661.
- Swardfager W, Rosenblat JD, Benlamri M, and McIntyre RS (2016) Mapping inflammation onto mood: Inflammatory mediators of anhedonia. *Neurosci Biobehav Rev* **64**:148–166.
- Szumliński KK, Kalivas PW, and Worley PF (2006) Homer proteins: implications for neuropsychiatric disorders. *Curr Opin Neurobiol* **16**:251–257.
- Tao HW, Li YT, and Zhang LI (2014) Formation of excitation-inhibition balance: inhibition listens and changes its tune. *Trends Neurosci* **37**:528–530.
- Terentyev D, Györke I, Belevych AE, Terentyeva R, Sridhar A, Nishijima Y, de Blanco EC, Khanna S, Sen CK, Cardounel AJ, et al. (2008) Redox modification of ryanodine receptors contributes to sarcoplasmic reticulum Ca<sup>2+</sup> leak in chronic heart failure. *Circ Res* **103**:1466–1472.
- Tesli M, Skatun KC, Ousdal OT, Brown AA, Thoresen C, Agartz I, Melle I, Djurovic S, Jensen J, and Andreassen OA (2013) CACNA1C risk variant and amygdala activity in bipolar disorder, schizophrenia and healthy controls. *PLoS One* **8**:e56970.
- Thompson SM, Kallarackal AJ, Kvarita MD, Van Dyke AM, LeGates TA, and Cai X (2015) An excitatory synapse hypothesis of depression. *Trends Neurosci* **38**: 279–294.
- Tsankova N, Renthal W, Kumar A, and Nestler EJ (2007) Epigenetic regulation in psychiatric disorders. *Nat Rev Neurosci* **8**:355–367.
- Tu JC, Xiao B, Yuan JP, Lanahan AA, Leoffert K, Li M, Linden DJ, and Worley PF (1998) Homer binds a novel proline-rich motif and links group 1 metabotropic glutamate receptors with IP<sub>3</sub> receptors. *Neuron* **21**:717–726.
- Turek FW (2005) Insomnia and depression: if it looks and walks like a duck.... *Sleep* **28**:1362–1363.
- Turrigiano GG (2008) The self-tuning neuron: synaptic scaling of excitatory synapses. *Cell* **135**:422–435.
- Uemura T, Green M, Corson TW, Perova T, Li PP, and Warsh JJ (2011) Bcl-2 SNP rs956572 associates with disrupted intracellular calcium homeostasis in bipolar I disorder. *Bipolar Disord* **13**:41–51.
- Uemura T, Green M, and Warsh JJ (2015) CACNA1C SNP rs1006737 associates with bipolar I disorder independent of the Bcl-2 SNP rs956572 variant and its associated effect on intracellular calcium homeostasis. *World J Biol Psychiatry* **17**: 525–534.
- Van der Musselle S, Franssen E, Struyfs H, Luyckx J, Mariën P, Saerens J, Somers N, Goeman J, De Deyn PP, and Engelborghs S (2014) Depression in mild cognitive impairment is associated with progression to Alzheimer's disease: a longitudinal study. *J Alzheimers Dis* **42**:1239–1250.
- von Känel R, Fardad N, Steurer N, Horak N, Hindermann E, Fischer F, and Gessler K (2015) Vitamin D deficiency and depressive symptomatology in psychiatric patients hospitalized with a current depressive episode: A factor analytic study. *PLoS One* **10**:e0138550.
- Wang JF, Shao L, Sun X, and Young LT (2009) Increased oxidative stress in the anterior cingulate cortex of subjects with bipolar disorder and schizophrenia. *Bipolar Disord* **11**:523–529.
- Warsh JJ, Andreopoulos S, and Li PP (2004) Role of intracellular calcium signaling in the pathophysiology and pharmacotherapy of bipolar disorder: current status. *Clin Neurosci Res* **4**:201–213.
- Wasserman RH (2004) Vitamin D and the dual processes of intestinal calcium absorption. *J Nutr* **134**: 3137–3139.
- Wei R and Christakos S (2015) Mechanisms underlying the regulation of innate and adaptive immunity by Vitamin D. *Nutrients* **7**:8251–8260.
- Wohleb ES, Franklin T, Iwata M, and Duman RS (2016) Integrating neuroimmune systems in the neurobiology of depression. *Nat Rev Neurosci* **17**:497–511.
- Wohleb ES, Gerhard D, Thomas A, and Duman RS (2017) Molecular and cellular mechanisms of rapid-acting antidepressants ketamine and scopolamine. *Curr Neuropharmacol* **15**:11–20.
- Wyskiel DR and Andrade R (2016) Serotonin excites hippocampal CA1 GABAergic interneurons at the stratum radiatum-stratum lacunosum moleculare border. *Hippocampus* **26**:1107–1114.
- Xia L, Zhang D, Wang C, Wei F, and Hu Y (2012) PC-PLC is involved in osteoclastogenesis induced by TNF- $\alpha$  through upregulating IP<sub>3</sub>R1 expression. *FEBS Lett* **586**:3341–3348.
- Yuan JP, Kiselyov K, Shin DM, Chen J, Shcheynikov N, Kang SH, Dehoff MH, Schwarz MK, Seeburg PH, Muallem S, et al. (2003) Homer binds TRPC family channels and is required for gating of TRPC1 by IP<sub>3</sub> receptors. *Cell* **114**:777–789.
- Zhang C, Wu Z, Zhao G, Wang F, and Fang Y (2016b) Identification of IL6 as a susceptibility gene for major depressive disorder. *Sci Rep* **6**:31264.
- Zhang X, Tang Y, Maletic-Savatic M, Sheng J, Zhang X, Zhu Y, Zhang T, Wang J, Tong S, Wang J, et al. (2016a) Altered neuronal spontaneous activity correlates with glutamate concentration in medial prefrontal cortex of major depressed females: An fMRI-MRS study. *J Affect Disord* **201**:153–161.
- Zhang X, Zhang C, Wu Z, Wang Z, Peng D, Chen J, Hong W, Yuan C, Li Z, Yu S, et al. (2013) Association of genetic variation in CACNA1C with bipolar disorder in Han Chinese. *J Affect Disord* **150**:261–265.
- Zorov DB, Juhaszova M, and Sollott SJ (2014) Mitochondrial reactive oxygen species (ROS) and ROS-induced ROS release. *Physiol Rev* **94**:909–950.