International Union of Pharmacology. LXXII. Recommendations for Trace Amine Receptor Nomenclature

JANET J. MAGUIRE, WILLIAM A. E. PARKER, STEVEN M. FOORD, TOM I. BONNER, RICHARD R. NEUBIG, AND ANTHONY P. DAVENPORT

Abstract

Trace amines such as p-tyramine and β-phenylethylamine are found endogenously as well as in the diet. Concomitant ingestion of these foodstuffs with monoamine oxidase inhibitors may result in the hypertensive crisis known as the “beer, wine, and cheese effect” attributed to their sympathomimetic action. Trace amines have been shown to act on one of a novel group of mammalian seven transmembrane spanning G protein-coupled receptors belonging to the rhodopsin superfamily, cloned in 2001. This receptor encoded by the human TAAR1 gene is also present in rat and mouse genomes (Taar1) and has been shown to be activated by endogenous trace amine ligands, including p-tyramine and β-phenylethylamine. A number of drugs, most notably amphetamine and its derivatives, act as agonists at this receptor. This review proposes an official nomenclature designating TAAR1 as the trace amine 1 receptor following the convention of naming receptors after the endogenous agonist, abbreviated to TA1 where necessary. It goes on to discuss briefly the significance of the receptor, agents acting upon it, its distribution, and currently hypothesized physiological and pathophysiological roles. In humans, a further five genes are thought to encode functional receptors (TAAR2, TAAR5, TAAR6, TAAR8, and TAAR9). TAAR3 seems to be a pseudogene in some individuals but not others. TAAR4 is a pseudogene in humans, but occurs with TAAR3 as a functional gene in rodents. Nine further genes are present in rats and mice. The endogenous ligands are not firmly established but some may respond to odorants consistent with their expression in olfactory epithelium.

I. Introduction

Trace amines, such as p-tyramine and β-phenylethylamine (β-PEA1) were discovered more than a century ago [e.g., β-PEA by Nencki in 1876 (reviewed in Grandy, 2007)] and are well known sympathomimetics (Dale and Dixon, 1909; Barger and Dale, 1910) described as “false
transmitters.” In mammals, trace amines are synthesized from aromatic amino acids at rates comparable with classic monoamines (for example, tyramine from tyrosine, catalyzed by aromatic L-amino acid decarboxylase) (David et al., 1974; Boulton, 1976; Bowsher and Henry, 1983; Brier et al., 1991). However, they are detectable only at trace levels because they are substrates for monoamine oxidase and have a half-life of approximately 30 s (Durden and Philips, 1980; Paterson et al., 1990). Trace amines are also present in significant amounts in fermented foods (Chaytor et al., 1975; Hannah et al., 1988), and concomitant ingestion of these with monoamine oxidase inhibition may result in the hypertensive crisis known as the “beer, wine, and cheese effect” (Blackwell, 1963; Cooper, 1989; Caston et al., 2002).

In invertebrates, tyramine and octopamine are well characterized neurotransmitters, modulating metabolism and muscle tone (Axelrod and Saavedra, 1977; Roeder, 2005) via their own G protein coupled receptors, which have been cloned (Arakawa et al., 1990; Saudou et al., 1990).

II. Trace Amine Receptors

A. Designation of the Trace Amine 1 Receptor

In 2001, a novel mammalian G-protein-coupled receptor (GPCR) was cloned in a search for further subtypes of the 5HT receptor. It was shown to have high (nanomolar) affinity for trace amines and was therefore named the trace amine 1 (TA1) receptor (Borowsky et al., 2001). Subsequently, a family of genes encoding trace amine receptors was cloned (Borowsky et al., 2001; Lindemann et al., 2005) that showed closest homology to the aminegic receptors. The gene name was at first abbreviated to TA then TAR after the initial pairing. However, it was subsequently shown that not all family members may have high affinity for trace amines, which has led to the adoption of the nomenclature of “trace amine-associated receptors” (TAARs) for the genes encoding the receptors (Lindemann et al., 2005). The Human Genome Organization (HUGO) Gene Nomenclature Committee has approved the gene symbol for the trace amine receptor 1 as TAAR1 (http://www.genenames.org/cgi-bin/hgnc_search.pl) because it also avoids confusion with existing genes and ensures that this family has a unique name that can be searched on databases. This nomenclature links together the other members of the “Associated Receptors” that are homologous but for which the precise pharmacology remains to be determined.

To facilitate comparison between members of this family, current and previous nomenclatures for both the receptor proteins and the family of genes encoding them are given in Table 1. To date, only one receptor, TA1, has been shown to respond to a cognate ligand, and several different groups replicated the results (Borowsky et al., 2001; Bunzow et al., 2001, Liberles and Buck, 2006), leading to the International Union of Pharmacology (IUPHAR)-recommended nomenclature for the receptor protein encoded by the gene TAAR1 as trace amine receptor 1, abbreviated to TA1, first proposed by Borowsky et al. (2001). This follows the agreed convention on naming receptor proteins after the cognate endogenous ligand. According to IUPHAR convention no R is added to the abbreviated name for receptor proteins.

It has been shown that the rat TA1 receptor, expressed in HEK293 cells, was also activated by thyronamines (decarboxylated and deiodinated metabolites of the thyroid hormones) (Scanlan et al., 2004; Hart et al., 2006) with a potency similar to that of tyramine (Bunzow et al., 2001). Cardiac effects of iodothyronamines have been reported in rat, but the rank order of potencies and affinities in ligand binding assays were not consistent with activation of TA1 and led the authors to suggest that iodothyronamines might be acting at different trace amine-associated receptors (Frascarelli et al., 2008).

The main focus of this review is the recommendation of nomenclature for TA1 receptors. For excellent, comprehensive reviews on trace amines, TA1, and the related family of receptors, see Grandy (2007), Zucchi et al. (2006), Lewin (2006), Lindemann and Hoener (2005), and Davenport (2003).

B. TAAR1 Gene

TAAR1 is localized in humans, along with genes for other trace amine-associated receptors, to a 109-kilobase region of chromosome 6q23.2 (Borowsky et al., 2001; Bunzow et al., 2001; Lindemann et al., 2005). Taar genes have also been found in the rat (Table 1; Bunzow et al., 2001) and mouse (Table 1; Borowsky et al., 2001). Designation of these genes follows the International Committee on Standardized Genetic Nomenclature for Mice and Rat Genome and Nomenclature Committee recommendation to use lower case italics (e.g., Taar1). This distinguishes the human gene, written in capitals, from those of rodents. The rat and mouse genes are localized to chromosomes 1p12 (Bunzow et al., 2001) and 10A3 (Borowsky et al., 2001; Reese et al., 2007), respectively.

C. Other Family Members

The unofficial receptor names for the remaining receptors are included, for comparison, in Table 1 and await clear identification of their endogenous ligands, together with the official gene names. In humans, a further five genes are predicted to exist encoding trace amine-associated receptors [TAAR2, TAAR5, TAAR6, TAAR8, and TAAR9 (Table 1)], and these are thought to be functional genes. TAAR3 seems to be a pseudogene in some individuals but not others (Gloriam et al., 2005,
Vanti et al., 2003). **TAAR4** is a pseudogene in humans but occurs, with **TAAR3**, as a functional gene in rats and mice. Nine further genes are present in rats (Table 1; Bunzow et al., 2001) and mice (Table 1; Borowsky et al., 2001), but not in humans (Foord et al., 2005). The focus of this review is on human and rodent receptors; however, **TAAR** genes have also been reported in rhesus monkey (Miller et al., 2005) and avian (Mueller et al., 2008) genomes (Foord et al., 2005).

Odorants are detected in the nasal olfactory epithelium by the odorant receptor family, whose ~1000 members allow the discrimination of many different odorants. In a key article, Liberles and Buck (2006) reported the presence of trace amine-associated receptors that, like odorant receptors, are expressed in unique subsets of neurons dispersed in the mouse olfactory epithelium. Interestingly **Taar1** was not detected. They expressed some of the mouse **Taar** genes in HEK293 cells linked to a fluorescent reporter and found that several resembled to various amine ligands: 1) In agreement with previous reports for human and rat **TA1**, mouse **TA1** receptor recognized β-PEA with an EC$_{50} = 0.1$ μM (Liberles and Buck, 2006). 2) The mouse **Taar3** gene product responded to several primary amines, including isoamylamine (EC$_{50} = 10$ μM) and cyclohexylamine but, interestingly, not to the corresponding alcohols, isoamylalcohol and cyclohexanol, indicating slight variations in ligand structure eliminated ligand activity in some cases. 3) Mouse **Taar5** gene product responded to the tertiary amine, N-methylpiperidine (EC$_{50} = 0.3$ μM) and N-n-propylpiperidine, but not to the related compounds methylyamine, dimethylamine, and tetramethylammonium chloride. 4) Mouse **Taar7f** gene product responded to the tertiary amine, N-methylpiperidine (EC$_{50} = 20$ μM).
It is noteworthy that three of the ligands identified that activate mouse Taar gene products are natural components of mouse urine, a major source of social cues in rodents. Mouse Taar4 gene product recognizes β-PEA, a compound whose elevation in urine is correlated with increases in stress and stress responses in both rodents and humans. The gene products of mouse Taar3 and Taar5 detected compounds (isoamylamine and trimethylamine, respectively) that are enriched in male versus female mouse urine. Isoamylamine in male urine is reported to act as a pheromone, accelerating puberty onset in female mice (Liberles and Buck, 2006). The authors suggest the Taar family has a chemosensory function that is distinct from odorant receptors, with a role associated with the detection of social cues. In mice, a clear discrepancy between the expression pattern of mRNA encoding Taar1 and the other Taar family members has been confirmed by Regard et al. (2008). They have reported the anatomical distribution of mRNA for GPCRs in mouse tissues and shown highest expression of Taar1 in pancreatic islets of Langerhans and white adipose with no evidence for expression in the olfactory epithelium, in contrast to the other family members that are relatively highly expressed in this tissue (Regard et al., 2008).

Human homologs of Taar3, Taar4, and Taar7 are thought to be pseudogenes but Taar5 does have an apparently functional human ortholog and the results suggest that functional members of the family more generally respond to trace amines. Responses were not reported for the gene products of other human orthologs TAAR2, TAAR6, TAAR8, and TAAR9 (although it was not established that they were successfully expressed in HEK293 cells) and a role in humans for these TAARs is not yet clear.

D. Phylogeny

In addition to Taar genes being present in the rat (Table 1; Bunzow et al., 2001) and mouse (Table 1; Borowsky et al., 2001, Regard et al., 2008), they have also been reported in other species including rhesus monkey (Miller et al., 2005), avian (Mueller et al., 2008), fish, and amphibian genomes (Hashiguchi and Nishida, 2007) (see Foord et al., 2005).

The evolutionary pattern of the TAAR gene family is characterized by lineage-specific phylogenetic clustering (Gloriam et al., 2005; Lindemann et al., 2005; Hashiguchi and Nishida, 2007). These characteristics are very similar to those observed in the olfactory GPCRs and vomeronasal (V1R, V2R) GPCR gene families. Hashiguchi and Nishida (2007) carried out a careful phylogenetic analysis of the trace amine receptors in fish, amphibians, birds, and mammals and concluded (from the species they considered) that there are five types of trace amine receptor genes. The first type included expanded “trace amine-like” GPCR families within fish (fish can respond to catecholamines and their metabolites when these are introduced into their water). However, type I also included the murine Taar receptors demonstrated to have an olfactory role and the human trace amine receptors, TAAR5, TAAR6, and TAAR8. Subfamily II also contained Taar genes that, in the mouse, are expressed in the olfactory epithelium and their products function as receptors for volatile amines (Liberles and Buck, 2006; Regard et al., 2008). Subfamilies III and V had no mammalian members. Subfamily IV contained human and murine TAAR1 and Taar1 genes, respectively. To date, these analyses suggest that the TAAR1 gene alone encodes a trace amine receptor that may serve a nonsensory function. “Trace amine pharmacology” probably extends beyond the putative trace amine receptors. It will require further characterization using pharmacology and physiology to determine whether the trace amine receptors are “sensory” or not (Grandy, 2007).

III. Receptor Structure

The human TA1 receptor is a member of the rhodopsin-type superfamily (i.e., it is a class A GPCR), with 339 amino acids. It has a predicted seven transmembrane spanning domain structure with short N- and C-terminal domains of 23 to 49 and 27 to 33 amino acids, respectively (Lindemann et al., 2005). Rat and mouse TA1 both have 332 amino acids, with sequence identities of 78 and 75% in relation to humans, respectively (see Table 2 and Figure 1).

IV. Distribution of Receptor and mRNA Encoding the Receptor

In humans, reverse transcriptase polymerase chain reaction has shown moderate levels (~100 copies/ng of cDNA) of mRNA encoding TA1 in the stomach; low levels (15–100 copies/ng of cDNA) in the amygdala, kidney, lung, and small intestine; and trace amounts (<15 copies/ng of cDNA) in the cerebellum, hippocampus, hypothalamus, liver, medulla oblongata, pituitary gland, pontine reticular formation, prostate gland, skeletal muscle, and spleen (Borowsky et al., 2001). Further amounts have been detected in pancreatic islets (Regard et al., 2007), circulating leukocytes of healthy subjects (D’Andrea et al., 2003; Nelson et al., 2007), and in normal small intestinal mucosal and endothelial cells (Kidd et al., 2008).

In mouse brain, mRNA encoding the receptor was detected by in situ hybridization in cerebellar Purkinje cells, trigeminal nuclei, olfactory bulb, hypothalamic nuclei, monoaminergic nuclei (such as the dorsal raphé and ventral tegmental area), amygdala, basal ganglia, cortex, and spinal cord (Borowsky et al., 2001). In peripheral tissues, mRNA encoding Taar1 is reported in pancreatic islet and white adipose cells (Regard et al., 2008). Immunohistochemistry has shown TA1 protein expres-
sion in the dopaminergic neurons of the substantia nigra (Xie et al., 2007). In the rat, mRNA encoding TA1 has been found in the cardiac ventricular wall (Chiellini et al., 2007). Bunzow et al. (2001) showed the subcellular localization of the rat TA1 protein in a HEK293 expression system to be intracellular and punctate using immunocytochemistry. For experimental purposes, stable membrane expression of TA1 has been achieved using a human-rat chimera, with a modified coding sequence including an influenza-derived hemagglutinin leader sequence and cardiac ventricular wall (Chiellini et al., 2007). Of the classic biogenic amines, only dopamine is reported to bind to expressed human TA1 (Kᵢ 422 nM compared with 8 nM for β-PEA and 34 nM for tyramine; Borowsky et al., 2001) and produced functional responses in cAMP assays in expressed human and rodent receptors in the micromolar range (Borowsky et al., 2001; Bunzow et al., 2001). In these studies, noradrenaline, adrenaline, and serotonin had a negligible effect in both binding and functional assays. It is noteworthy that the rhesus monkey TA1 receptor, which shows higher deduced amino acid sequence homology to the human receptor (96%) than do rodent receptors (<79% homology with human TA1) (Miller et al., 2005), responded to tyramine, β-PEA, octopamine, and tryptamine as expected (Miller et al., 2005; Xie and Miller, 2007) but also to comparable concentrations of dopamine, noradrenaline, and serotonin (Xie et al., 2007). The explanation and, indeed, the importance of this discrepancy is as yet unclear.

VI. Agonists

Endogenous trace amines act as agonists of the TA1 receptor, for example p-tyramine and β-PEA (pEC₅₀ values at human receptor = 6.4–6.7, 6.2–7.0, respectively; Borowsky et al., 2001; Wainscott et al., 2007; Barak et al., 2008). In addition, the thyroid hormone derived thyronamines [e.g., 3-iodothyronamine (T₁AM); pEC₅₀ at rat receptor = 7.9; Scanlan et al., 2004; Hart et al., 2006] have affinity for TA1. In rat isolated perfused heart, trace amines and iodothyronamines are negative inotropic agents (Chiellini et al., 2007; Frascarelli et al., 2008), although the authors state that the rank order of agonist potency suggests that this is not a TA1 response but may be mediated by a different trace amine-associated receptor, several of which are expressed in rat heart (Frascarelli et al., 2008).

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Exogenous agonists include amphetamine and its derivatives [e.g., S(+)-methamphetamine (pEC₅₀ at rat receptor = 6.1; Reese et al., 2007) and 3,4-methylenedioxyamphetamine (pEC₅₀ at rat receptor =
5.8; Bunzow et al., 2001]. Both amphetamine and methamphetamine seem to show a species-dependent stereo-selectivity, at least in expression systems (Bunzow et al., 2001; Reese et al., 2007) (see Table 3 and Fig. 2).

VII. Antagonists

There are no reports yet of fully characterized antagonists of the TA1 receptor, and none are commercially available. Nonselective classical amine receptor antagonists have little TA1 blocking ability (Wainscott et al., 2007). Tan et al. (2008) were able to rationally design and synthesize lead compounds, taking into account the recently described rotamer toggle switch model of GPCR activation (Kobilka and Deupi, 2007; Rasmussen et al., 2007), concluding that a hexyloxy group and the outer or \( \beta \)-phenyl rings are essential for antagonism. It remains to be seen whether such compounds are specific and will become widely available in the near future.

VIII. Receptor Signaling

TA1 stably expressed in HEK293 or COS-7 cells has been shown to couple to Gs, leading to intracellular cAMP accumulation (Borowsky et al., 2001; Lindemann et al., 2005; Wolinsky et al., 2007) and stimulation of the cystic fibrosis transmembrane conductance regulator in Xenopus laevis oocytes (Borowsky et al., 2001). In addition, TA1 has been coupled to the promiscuous G \( \alpha \)\(_{16} \) in Chinese hamster ovary cells, producing an increase in the intracellular Ca\(^{2+} \) concentration as measured by fluorometry (Navarro et al., 2006; Lewin et al., 2008). Inhibitors of both protein kinases A and C have been shown to block TA1-mediated effects in synaptosomes (see section IX; Xie and Miller, 2007). In vivo signal transduction mechanisms are yet to be investigated.

TABLE 3

<table>
<thead>
<tr>
<th>Agonist</th>
<th>( pEC_{50} ) values</th>
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<tr>
<td></td>
<td>Human</td>
</tr>
<tr>
<td>( p )-Tyramine</td>
<td>6.4(^a)</td>
</tr>
<tr>
<td>( \beta )-PEA</td>
<td>6.2(^c)</td>
</tr>
<tr>
<td>Octopamine</td>
<td>7.0(^e)</td>
</tr>
<tr>
<td>3-Iodothyronamine</td>
<td>5.1(^g)</td>
</tr>
<tr>
<td>( S(+) )-Amphetamine</td>
<td>6.0(^i)</td>
</tr>
<tr>
<td>( R(−) )-Amphetamine</td>
<td>6.9(^j)</td>
</tr>
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\( ^a \) Wainscott et al. (2007).
\( ^b \) Reese et al. (2007).
\( ^c \) Barak et al. (2008).
\( ^d \) Bunzow et al. (2001).
\( ^e \) Wolinsky et al. (2007).
\( ^f \) Borowsky et al. (2001).
\( ^g \) Scanlan et al. (2004).
\( ^h \) Hart et al. (2006).
IX. Physiological Role

Levels of trace amines have been measured in human plasma and are in the low nanomolar range (for example, see Zhou et al., 2001; D’Andrea et al., 2003). Tyramine and β-PEA have pKᵢ values for human TA₁ of 8.1 and 7.5, respectively (Borowsky et al., 2001) with pEC₅₀ values in the high nanomolar range (6.2–7.0; Table 3). For comparison, the biogenic amines noradrenaline and adrenaline circulate at similar low nanomolar concentrations (Goldstein et al., 2003) but are functional at higher concentrations, with pKᵢ of 6.0 to 6.5 for α₁- and β₁-adrenergic receptors and pEC₅₀ values again in the high nanomolar range (NC-IUPHAR GPCR database: http://www.iuphar-db.org/GPCR/ReceptorFamiliesForward). Selective TA₁ antagonists have not yet been developed but are required to confirm the precise physiology of this receptor system.

The role of the TA₁ receptor is most understood in the central nervous system, where it is believed to modulate monoaminergic neurotransmission, thus affecting a number of neural networks and processes. β-PEA inhibits uptake and induces efflux of dopamine and serotonin in striatal synaptosomes and of norepinephrine in thalamic synaptosomes in vitro by interacting with transporters, for example the dopamine transporter (Xie and Miller, 2007, 2008; Xie et al., 2008). The effect is abolished in the TA₁ knockout (Lindemann et al., 2008; Xie and Miller, 2008; Xie et al., 2008) and by inhibitors of protein kinases A and C (Xie and Miller, 2007). In addition, TA₁ may be immunomodulatory, because mRNA encoding the receptor is up-regulated in circulating leukocytes after administration of the mitogen phytohemagglutinin (Nelson et al., 2007). Trace amines, β-PEA in particular, have long been associated with sustaining mood (Fischer and Heller, 1972; Sabeli and Mosnaim, 1974; Boulton, 1980), although a specific role for TA₁ in this has yet to be elucidated. The effect of genetically disrupting synthesis of the endogenous agonists tyramine and β-PEA has not been assessed.

X. Pathophysiological Role

Large increases in plasma trace amine levels can occur in patients or animals on monoamine oxidase inhibitors, and alterations in levels have been reported in some diseases. The TA₁ receptor has not been directly linked with any pathophysiological process, although trace amines are known to be associated with the hypertensive “beer, wine, and cheese effect” and are thought to play a role in psychiatric disorders such as schizophrenia (O’Reilly et al., 1991) and depression (Boulton, 1980; Premont et al., 2001) as well as primary headache (D’Andrea et al., 2004). Modulation of trace amine systems may be a potential therapeutic avenue (Branchek and Blackburn, 2003; Berry, 2007), particularly because the receptors are likely to be amenable as drug targets (Davenort, 2003). Linkage analysis has also shown a correlation between schizophrenia and polymorphisms in the chromosomal region encoding the trace amine-associated receptors (Levi et al., 2005; Pae et al., 2008a,b) but not TA₁, polymorphisms of which are yet to be reported.

XI. Genetically Modified Animals

Deletion of the Taar1 gene in mice results in viable, fertile animals. They exhibit a phenotype characterized by minor spontaneous hyperactivity, reduced prepulse inhibition, increased sensitization to the psychomotor-stimulatory effects of amphetamine, raised levels of dopamine and norepinephrine in the dorsal striatum, increased striatal D₂ receptor expression, and an elevated spontaneous firing rate of dopaminergic neurons in the ventral tegmental area compared with the wild type (Wolinsky et al., 2007; Sotnikova et al., 2008; Xie and Miller, 2008; Xie et al., 2008). This phenotype has been proposed as an animal model of schizophrenia (Wolinsky et al., 2007) and also as hemi-Parkinsonian (Sotnikova et al., 2008). In addition, in TA₁-deficient mice, β-PEA was unable to modify the uptake or efflux of classic amine transmitters in striatal or thalamic synaptosomes as had been shown for wild type (Xie and Miller, 2008; Xie et al., 2008). The effect of genetically disrupting synthesis of the endogenous agonists tyramine and β-PEA has not been assessed, although because these compounds are also metabolites, they cannot readily be disrupted-out without identifying enzymes exclusive to their production.

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