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

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***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 TA_1 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-PEA[1]) 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

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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 (TA_1) 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 aminergic 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" (*TAAR*s) 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, TA_1, 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 TA_1, 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 TA_1 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 TA_1 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 TA_1 receptors. For excellent, comprehensive reviews on trace amines, TA_1, 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,

[1] Abbreviations: β-PEA, β-phenylethylamine; GPCR, G-protein coupled receptor; TA_1, trace amine 1; IUPHAR, International Union of Pharmacology; HEK, human embryonic kidney.

TABLE 1
Summary of human, mouse, and rat genes encoding trace amine and trace amine-associated receptors

Receptor	Human Gene			Mouse Gene		Rat Gene	
	Old Name	New Name	Swiss Prot RefSeq	Name	Swiss Prot RefSeq	Name	Swiss Prot RefSeq
IUPHAR Receptor Nomenclature							
TA_1	*TAR1*	*TAAR1*	Q96RJ0 NP_612200	*Taar1*	Q923Y8 NP_444435	*Taar1*	Q923Y9 NP_599155
Unofficial Receptor Terminology[a]							
TA_2				*Taar4*	Q5QD15 NP_001008499	*Taar4*	Q923Y7 NP_783173
TA_3	*TAR3*	*TAAR9*	Q96R19[b] NP_778227	*Taar9*	Q5QD04 NP_001010831	*Taar9*	Q923Y6 NP_783192
TA_4	*TAR4*	*TAAR6*	Q96R18[c] NP_778237	*Taar6*	Q5QD13 NP_001010828	*Taar6*	Q923Y5 NP_783174
TA_5	*GPR102*	*TAAR8*	Q969N4 NP_444508				
TA_6						*Taar7h*	Q923Y4 NP_783177
TA_7				*Taar8b*	Q5QD06 NP_001010837	*Taar8b*	Q923Y3 NP_783191
TA_8				*Taar7a*	Q5QD12 NP_001010829	*Taar7a*	Q923Y2 NP_783175
TA_9						*Taar7g*	Q923Y1 NP_783178
TA_{10}				*Taar8c*	Q5QD05 NP_001010840	*Taar8c*	Q923Y0 NP_783190
TA_{11}				*Taar8a*	Q5QD07 NP_001010830	*Taar8a*	Q923X9 NP_783189
TA_{12}				*Taar7b*	Q5QD11 NP_001010827	*Taar7b*	Q923X8 NP_783176
TA_{13}				*Taar7f*	Q5QD08 NP_001010839	*Taar7f*	Pseudogene
TA_{14}				*Taar7e*	Q5QD09 NP_001010835	*Taar7e*	Q923X6 NP_783180
TA_{15}				*Taar7d*	Q5QD10 NP_001010838	*Taar7d*	Q923X5 NP_783181
GPR57				*Taar3*	Q5QD16 NP_001008429		
GPR58	*GPR58*	*TAAR2*	Q9P1P5 NP_001028252 or NP_055441	*Taar2*	Q5QD17 NP_001007267	*Taar2*	Q5QD25 NP_001008512
PNR	*PNR*	*TAAR5*	O14804 NP_003958	*Taar5*	Q5QD14 NP_001009574	*Taar5*	Q5QD23 NP_001009650

[a] Nomenclature as designated by Borowsky et al. (2001). See Lindemann and Hoener (2005) for further information on TAARs and Foord et al. (2005) and Schöneberg et al. (2007) for further information on pseudogenes.
[b] Stop codon present in 10% of humans.
[c] Polymorphisms in the human gene have been reported to be associated with schizophrenia and bipolar disorder (Duan et al., 2004; Pae et al., 2008a,b).

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 responded to various amine ligands: 1) In agreement with previous reports for human and rat TA_1, mouse TA_1 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 (an ortholog also exists in humans; Table 1) responded to tertiary amines trimethylamine (EC_{50} = 0.3 μM) and *N*-methylpiperidine, but not to the related compounds methylamine, 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 TA_1 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 TA_1 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 TA_1 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 TA_1 protein expres-

TABLE 2
Classification of trace amine 1 receptor

Receptor	Trace Amine 1, TA_1
Previous names	TAR_1, $TRAR_1$, BO111, TAAR1 (approved human gene symbol)
Structural information	7TM Human: 339 aa (SwissProt Q96RJ0), chr 6q23.2 (Entrez 134864) Rat: 332 aa (SwissProt Q923Y9), chr 1p12 (Entrez 113914) Mouse: 332 aa (SwissProt Q923Y8) chr 10A3 (Entrez 111174)
Functional assays	COS-7/HEK293 cells transfected with TA_1 and $G\alpha_s$ (Borowsky et al., 2001; Lindemann et al., 2005; Wolinsky et al., 2007); *X. laevis* oocytes cotransfected with TA_1 and CFTR (Borowsky et al., 2001); CHO cells expressing TA_1 and promiscuous $G\alpha_{16}$ (Navarro et al., 2006)
Endogenous agonists	Tyramine (pEC_{50} = 6.4–6.7), β-PEA (pEC_{50} = 6.2–7.0), (Borowsky et al., 2001; Wainscott et al., 2007; Barak et al., 2008)
Antagonists	None currently commercially available
Radioligand assays	COS-7 cells transiently transfected with human TA_1 and rat $G\alpha_s$ (Borowsky et al., 2001)
Radioligands	[^{3}H]tyramine (pK_D = 7.7) (Borowsky et al., 2001); [^{125}I]-,[^{2}H]-, [^{3}H]3-iodothyronamine (Miyakawa and Scanlan, 2006)
Transduction	Couples to $G\alpha_s$ (Borowsky et al., 2001; Lindemann et al., 2005; Wolinsky et al., 2007) and $G\alpha_{16}$ (Navarro et al., 2006; Lewin et al., 2008) in vitro
Receptor distribution	Studies in humans, RT-PCR showed mRNA encoding TA_1 in stomach, amygdala, kidney, lung, small intestine, cerebellum, dorsal root ganglion, hippocampus, hypothalamus, liver, medulla, pancreas, pituitary, reticular formation, prostate, skeletal muscle, spleen (Borowsky et al., 2001), pancreatic islets (Regard et al., 2007), circulating leukocytes (D'Andrea et al., 2003), and intestinal mucosa/endothelium (Kidd et al., 2008); in rats, mRNA found in cardiac ventricles (Chiellini et al., 2007); in mice, in situ hybridization localized mRNA encoding TA_1 to discrete CNS areas, including the mitral cell layer of the olfactory bulb, trigeminal nuclei, cerebellar Purkinje cells, spinal cord, amygdala, hippocampus, monoaminergic nuclei (Borowsky et al., 2001), and dopaminergic neurons of the substantia nigra (Xie et al., 2007)
Tissue function	Inhibits uptake and induces efflux of monoamines at striatal and thalamic synapses (Xie et al., 2008; Xie and Miller, 2008)

7TM, seven transmembrane; aa, amino acid(s); chr, chromosome; CFTR, cystic fibrosis transmembrane conductance regulator; CHO, Chinese hamster ovary; RT-PCR, reverse transcriptase polymerase chain reaction; CNS, central nervous system.

sion in the dopaminergic neurons of the substantia nigra (Xie et al., 2007).

In the rat, mRNA encoding TA_1 has been found in the cardiac ventricular wall (Chiellini et al., 2007). Bunzow et al. (2001) showed the subcellular localization of the rat TA_1 protein in a HEK293 expression system to be intracellular and punctate using immunocytochemistry. For experimental purposes, stable membrane expression of TA_1 has been achieved using a human-rat chimera, with a modified coding sequence including an influenza-derived hemagglutinin leader sequence and rat TA_1-derived N and C termini and third intracellular loop (Lindemann et al., 2005) or by the generation of an *N*-glycosylated human TA_1 variant (Barak et al., 2008) that shows appropriate activation by β-PEA. The in vivo subcellular localization of TA_1 is yet to be confirmed.

V. Radiolabeled Ligands

[^{3}H]Tyramine (pK_D = 7.7) has been available for a long time, but few studies have been carried out in expression systems of TA_1 (Borowsky et al., 2001). Radioactive thyronamines (e.g., [^{125}I]3-iodothyronamine) have been synthesized (Miyakawa and Scanlan, 2006) but as yet are neither pharmacologically characterized nor commercially available.

VI. Agonists

Endogenous trace amines act as agonists of the TA_1 receptor, for example *p*-tyramine and β-PEA (pEC_{50} 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 (T_1AM); pEC_{50} at rat receptor = 7.9; Scanlan et al., 2004; Hart et al., 2006] have affinity for TA_1. 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 TA_1 response but may be mediated by a different trace amine-associated receptor, several of which are expressed in rat heart (Frascarelli et al., 2008).

Of the classic biogenic amines, only dopamine is reported to bind to expressed human TA_1 (K_i 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 TA_1 receptor, which shows higher deduced amino acid sequence homology to the human receptor (96%) than do rodent receptors (<79% homology with human TA_1) (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.

Exogenous agonists include amphetamine and its derivatives [e.g., *S*(+)methamphetamine (pEC_{50} at rat receptor = 6.1; Reese et al., 2007) and 3,4-methylenedioxymethamphetamine (pEC_{50} at rat receptor =

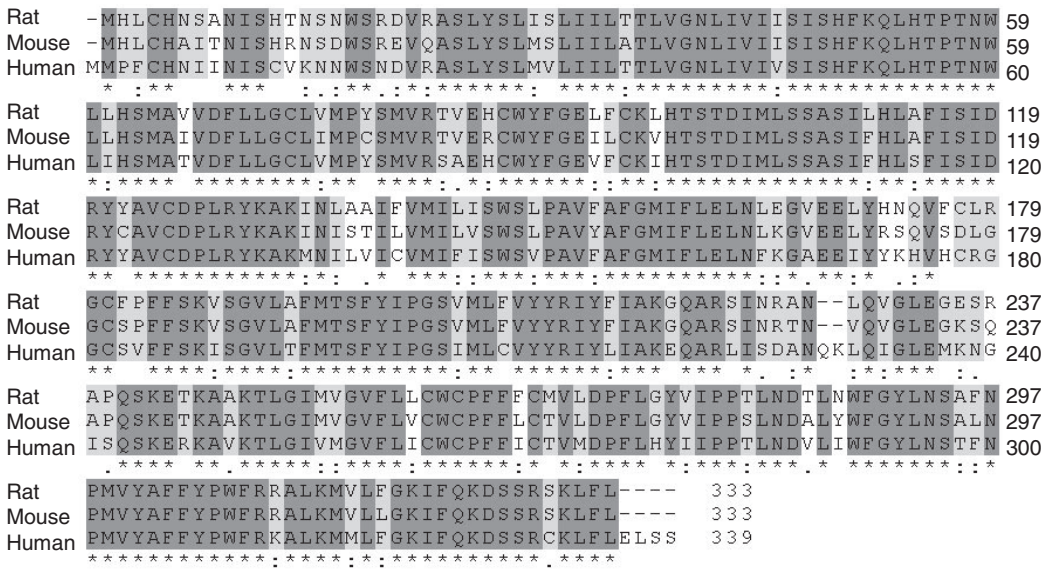

FIG. 1. Alignment of amino acid sequences of the rat, mouse, and human trace amine 1 (TA_1) receptor. Produced using ClustalW2 (http://www.uniprot.org/?tab=align).

5.8; Bunzow et al., 2001)]. Both amphetamine and methamphetamine seem to show a species-dependent stereoselectivity, 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 TA_1 receptor, and none are commercially available. Nonselective classical amine receptor antagonists have little TA_1 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 β-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.

TABLE 3
Selected agonists of the TA_1 receptor and reported species-specific pEC_{50} values

All values are for receptors in cell expression systems.

Agonist	pEC_{50} values		
	Human	Rat	Mouse
p-Tyramine	6.4[a]	7.1[b]	6.2[b]
	6.5[c]	7.2[d]	7.1[e]
	6.7[f]		
β-PEA	6.2[c]	6.4[b]	6.3[b]
	6.5[f]	6.6[d]	7.4[e]
	7.0[a,c]		
Octopamine	5.1[a]	5.9[d]	5.8[e]
	5.4[f]		
	5.8[c]		
3-Iodothyronamine	No data	7.9[g,h]	7.0[g,h]
S(+)-Amphetamine	6.0[c]	6.1[b]	6.7[b]
	6.9[c]	6.4[d]	8.7[e]
R(−)-Amphetamine	6.6[c]	6.5[b]	5.3[b]
		6.7[d]	7.2[e]

[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).

VIII. Receptor Signaling

TA_1 stably expressed in HEK293 or COS-7 cells has been shown to couple to G_s, 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, TA_1 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 TA_1-mediated effects in synaptosomes (see section IX; Xie and Miller, 2007). In vivo signal transduction mechanisms are yet to be investigated.

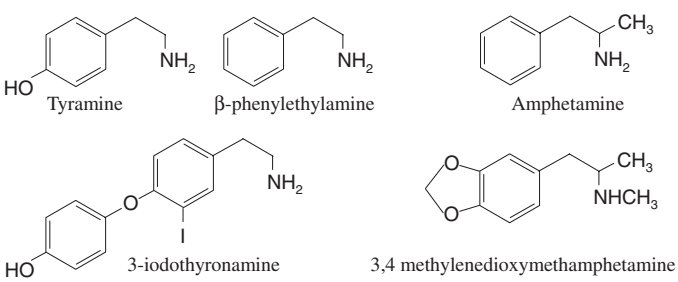

FIG. 2. Examples of chemical structures of trace amine 1 (TA_1) receptor endogenous and exogenous agonists.

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 pK_i values for human TA_1 of 8.1 and 7.5, respectively (Borowsky et al., 2001) with pEC_{50} 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 pK_i of 6.0 to 6.5 for α_1- and β_1-adrenergic receptors and pEC_{50} values again in the high nanomolar range (NC-IUPHAR GPCR database: http://www.iuphar-db.org/GPCR/ReceptorFamiliesForward). Selective TA_1 antagonists have not yet been developed but are required to confirm the precise physiology of this receptor system.

The role of the TA_1 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 its 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 TA_1 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, TA_1 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; Sabelli and Mosnaim, 1974; Boulton, 1980), although a specific role for TA_1 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 TA_1 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 (Davenport, 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 TA_1, 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 D_2 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 TA_1-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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