

A renaissance in trace amines inspired by a novel GPCR family

Lothar Lindemann and Marius C. Hoener

F. Hoffmann-La Roche, Pharmaceuticals Division, Discovery Neuroscience, CH-4070-Basel, Switzerland

Trace amines (TAs) are endogenous compounds that are related to biogenic amine neurotransmitters and are present in the mammalian nervous system in trace amounts. Although their pronounced pharmacological effects and tight link to major human disorders such as depression and schizophrenia have been studied for decades, the understanding of their molecular mode of action remained incomplete because of the apparent absence of specialized receptors. However, the recent discovery of a novel family of G-protein-coupled receptors (GPCRs) that includes individual members that are highly specific for TAs indicates a potential role for TAs as vertebrate neurotransmitters or neuromodulators, although the majority of these GPCRs so far have not been demonstrated to be activated by TAs. The unique pharmacology and expression pattern of these receptors make them prime candidates for targets in drug development in the context of several neurological diseases. Current research focuses on dissecting their molecular pharmacology and on the identification of endogenous ligands for the apparently TA-insensitive members of this receptor family.

Trace amines find their receptors

The classical biogenic amines [serotonin (5-HT), nor-adrenaline, adrenaline, dopamine and histamine] have important roles as neurotransmitters in the central and peripheral nervous systems [1]. Their synthesis and storage, in addition to their degradation and reuptake after release, are tightly regulated, and an imbalance in the levels of biogenic amines is known to be responsible for altered brain function in many pathological conditions [2–5]. A second class of endogenous amine compounds, the so-called trace amines (TAs), overlaps significantly with the classical biogenic amines regarding structure, metabolism and subcellular localization. The TAs include *p*-tyramine, β -phenylethylamine (β -PEA), tryptamine and octopamine, and are present in the mammalian nervous system at generally lower levels than classical biogenic amines [6]. Their dysregulation has been linked to various psychiatric diseases such as schizophrenia and depression, and potential roles for TAs in other conditions such as attention deficit hyperactivity disorder, migraine

headache, Parkinson's disease, substance abuse and eating disorders have been suggested [7,8].

For several decades, TA-specific receptors had only been hypothesized based on anatomically discrete high-affinity TA binding sites in the CNS of humans and other mammals [9,10]. Accordingly, the pharmacological effects of TAs were believed to be mediated through the well-known machinery of classical biogenic amines, by either triggering their release, inhibiting their reuptake or by 'cross-reacting' with their receptor systems [8,11,12]. This view changed significantly following the recent identification of several members of a novel family of G-protein-coupled receptors (GPCRs) initially termed TA receptors [13,14]; subsequently, the complete receptor family has been identified in human, chimpanzee, rat and mouse (Table 1) [15]. So far, only two members of this receptor family, TA1 and TA2, have been reported to be sensitive to TAs [13,14] whereas all other family members that have been analyzed were found to be unresponsive to TAs [13,15]. This apparent insensitivity to TAs could be due, in part, to insufficient receptor trafficking or missing components of the signal transduction machinery in the employed expression systems [13,16], or these results might indicate that these receptors indeed do not correspond to TAs but rather to other, as yet unidentified, endogenous ligands [13,15,17]. On the basis of this information, a novel receptor nomenclature was proposed, designating the receptor family as trace amine-associated receptors (TAARs) (Table 1) [15], which reflects the fact that at least some members of the receptor family potentially do not respond to TAs. This proposed new nomenclature is based strictly on the sequential order of receptor genes on the chromosomes, includes all vertebrate TA receptors and several new GPCRs previously not recognized as members of the receptor family, and clarifies the inter-species relationship of receptor orthologs. Therefore, in the remainder of this review we will refer to this receptor family using the provisional new abbreviation TAAR and additionally provide the official receptor or gene name in brackets whenever specific receptors are being addressed.

The ongoing efforts in the characterization of this novel GPCR family contribute to a detailed understanding of TA physiology on a molecular level, suggest a role for TAs as neurotransmitters or neuromodulators [18] and might soon pave the way for rational strategies in the development of potential TA-related drugs.

Corresponding authors: Lindemann, L. (lothar.lindemann@roche.com), Hoener, M.C. (marius.hoener@roche.com).
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Table 1. The new nomenclature for trace amine-associated receptors (TAARs)^a

New name Generic	Old name			
	Human	Chimpanzee	Rat	Mouse
Group 1				
TAAR1	TRAR1, TA1, TAR1 ^b	NA	TRAR1, TA1, TAR1 ^{b-d}	TA1, TAR1 ^{b,d}
TAAR2	GPR58	Pseudogene (NA)	NA	NA
TAAR3	Pseudogene (GPR57P)	Pseudogene (NA)	NA	NA
TAAR4	Pseudogene (TA2P, 5-HT4P)	Pseudogene (NA)	TA2 ^b	NA
Group 2				
TAAR5	PNR	NA	NA	NA
Group 3				
TAAR6	TRAR4, TA4	TRAR4	TRAR4, TA4	NA
TAAR7	Pseudogene (NA)	Pseudogene (NA)		
TAAR7a			NA	NA
TAAR7b			TA12	NA
TAAR7c			NA	Pseudogene (NA)
TAAR7d			TA15	NA
TAAR7e			TA14	NA
TAAR7f			Pseudogene (TA13P)	NA
TAAR7g			TA9	
TAAR7h			TA6	
TAAR7i			Pseudogene (NA)	
TAAR8	TRAR5, TA5, TAR5, GPR102	Pseudogene (NA)		
TAAR8a			TA11	NA
TAAR8b			TA7	NA
TAAR8c			TA10	NA
TAAR9	TRAR3, TA3, TAR3	Pseudogene (NA)	TA3	NA

^aOld gene names are given as far as they had been reported previously in original publications (NA, no published old gene name available). Only the receptors TAAR1 (TA1) and TAAR4 (TA2) have been characterized experimentally as TA receptors. The proposed distinction of three subgroups is based on the phylogenetic relationships (Figure 1a), the pharmacophore similarity analysis of the TAAR family [15] and the available pharmacological data [13–15]. For a comprehensive summary of the available sequence information for human, chimpanzee (*Pan troglodytes*), rat and mouse TAAR genes, details of the nomenclature system and a discussion of the proposed subgroup distinction see [15].

^bSensitivity to TAs was tested by either measuring cAMP elevation in stably transfected cell lines [13–15] or by electrophysiological recordings on *Xenopus* oocytes [13].

^cBunzow *et al.* [14] reported activation of rat TAAR1 (TA1) by several psychoactive compounds such as amphetamines and ergot alkaloids.

^dScanlan *et al.* [17] reported an activation of rat and mouse TAAR1 (TA1) by several thyronamine derivatives. [P (suffix), pseudogene.]

Molecular properties of trace amine-associated receptors

All mammalian TAARs analyzed to date share several molecular properties [15]. All except one TAAR gene [TAAR2 (*GPR58*)] are single-exon encoded, locate to a narrow region of ~100–200 kb of a single chromosome and have coding sequences of ~1 kb in length. The total number of genes and the proportion of intact genes compared with the proportion of pseudogenes differ substantially between species: there are 19 (including 2 pseudogenes) and 16 (including 1 pseudogene) TAAR genes in rat and mouse genomes, respectively, but only 9 TAAR genes in human (including 3 pseudogenes) and chimpanzee (including 6 pseudogenes) genomes. These remarkable inter-species differences indicate the potential importance of TAAR genes in the context of adaptation processes during evolution, and underscore their link to several diseases, which might be related to the fundamentally different lifestyles and body functions of human and other species [19]. In spite of high overall sequence identities to, for example, amine receptors, TAARs comprise a well-defined, coherent gene family that is clearly distinct from other GPCR gene families, as revealed by phylogenetic studies (Figure 1a) [15] and the presence of a TAAR-specific peptide fingerprint motif (Figure 1b) that is missing in all other known GPCRs.

The phylogenetic relationships of the receptor genes suggest the distinction of three TAAR subgroups (Table 1, Figure 1a) that overlap exactly with the differences in the ligand preferences of the receptors predicted by means of pharmacophore similarity analysis [15]. This approach is

a molecular modeling-driven procedure that provides a quantitative measure for the similarities in the ligand preferences of different GPCRs and is based on the X-ray crystal structure of bovine rhodopsin and on data from mutational and pharmacological studies carried out on a wide range of different GPCRs [20]. The complete match of the three TAAR subgroups defined by either the phylogenetic relationships or the pharmacophore similarity analysis, in agreement with the available pharmacological data, suggests that receptors belonging to the different subgroups might display different pharmacological profiles. The similarity of the predicted ligand binding pockets throughout the entire receptor family suggests that potential, as yet unidentified, ligands of the apparently TA-insensitive TAARs might resemble small-molecular-weight compounds that are structurally and chemically similar to TAs. These potential new ligands could be, for example: (i) metabolites of amino acids or neurotransmitters that have so far been considered to be biologically inactive; (ii) derivatives of indolamines or phenylethylamines [18,21]; or (iii) iodothyronamines, some of which have been demonstrated recently to act directly on TAAR1 (TA1) [17].

Trace amine metabolism and pharmacology

TAs (β -PEA, *p*-tyramine, octopamine and tryptamine) are all primary amines generated directly by enzymatic decarboxylation of their respective precursor amino acids or, in the case of octopamine, via additional conversion by dopamine β -hydroxylase (DBH) (Figure 2). TAs are metabolized to biologically inactive degradation

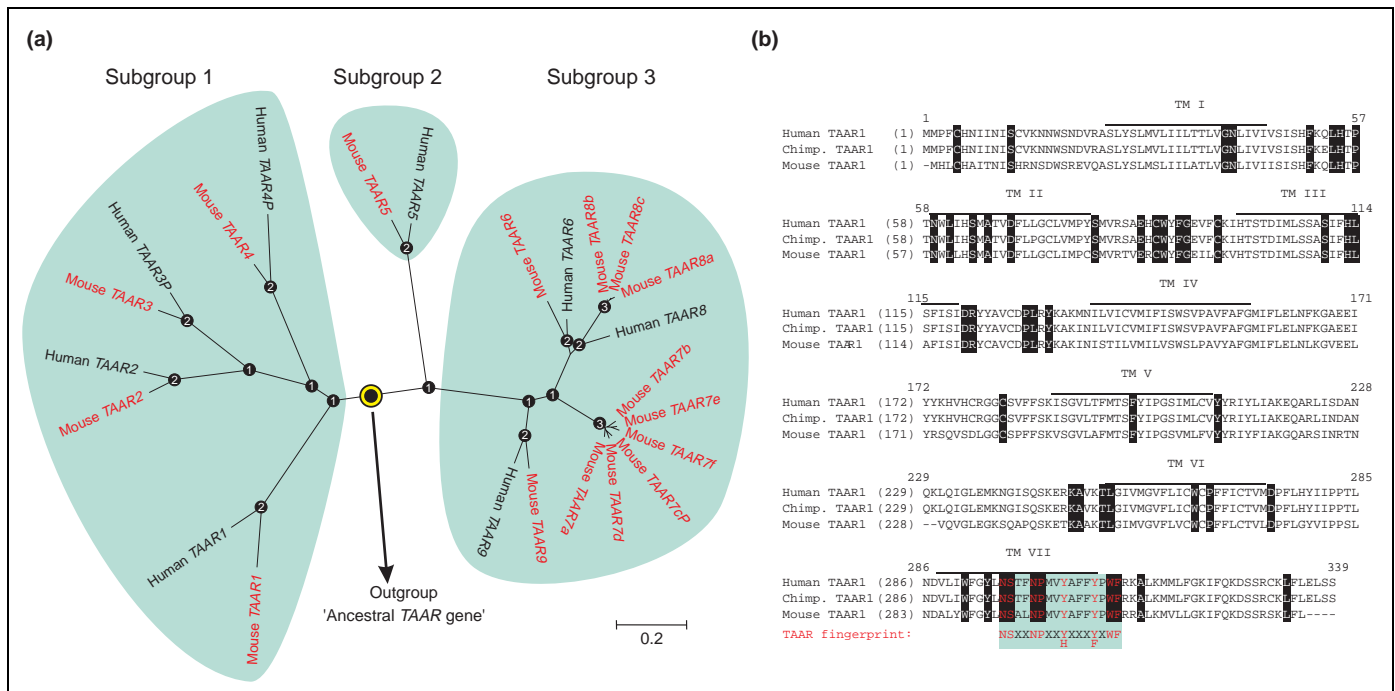


Figure 1. Phylogeny and membrane topology of TAARs. **(a)** The phylogenetic relationship of human and mouse TAAR genes. The TAAR family most probably evolved from a common ancestor gene sharing closest similarity to the human gene encoding the 5-HT₄ receptor (*HTR4*) by a series of gene duplication and speciation events: (1) gene duplication before the rodent and human lineage split; (2) speciation leading to separate primate and rodent lineages; and (3) gene duplication within the rodent lineage. The phylogenetic relationship suggests the distinction of three TAAR subgroups with potentially different pharmacological profiles. The human TAAR7P pseudogene has been omitted from the phylogenetic tree because only a gene fragment of ~210 base pairs is preserved in the human genome. **(b)** Membrane topology of TAARs, as revealed by an alignment of human, chimpanzee (chimp.) and mouse TAAR1 (TA1). All TAARs share a predictive peptide fingerprint motif (red) that largely overlaps with the seventh transmembrane domain (TM VII) and is absent from all other GPCRs, and have short N- and C-terminal domains of 23–49 and 27–33 amino acids, respectively. The TMs are indicated as predicted for human TAAR1 (TA1), and amino acid positions conserved in all vertebrate TAARs are highlighted by black shading. Abbreviation: P (suffix), pseudogene. Redrawn and modified, with permission, from [15].

products predominantly via monoamine oxidase (MAO) with different selectivities for the MAO-A or MAO-B subtype. As a result of the rapid turnover rate of TAs, the endogenous extracellular levels of TAs in brain tissue are in the low nanomolar range and therefore several hundred-fold below those of the classical biogenic amine neurotransmitters dopamine, noradrenaline and 5-HT [18]. In addition to the main metabolic pathway, TAs can also be converted by nonspecific N-methyltransferase (NMT) [22] and phenylethanolamine N-methyltransferase (PNMT) [23] to the corresponding secondary amines (e.g. synephrine [14], N-methylphenylethylamine and N-methyltyramine [15]), which display similar activities on TAAR1 (TA1) as their primary amine precursors

For a discussion of the *in vivo* effects of TAs it is important to distinguish the biological activities observed at physiological concentrations from the so-called 'amphetamine-like' effects triggered by the high nanomolar to low micromolar TA concentrations employed in most *in vivo* studies (generally in combination with MAO inhibitors). On the molecular level, these 'amphetamine-like' effects are reflected mainly by TAs increasing the release of noradrenaline, dopamine and 5-HT and inhibiting the reuptake of these biogenic amines [18]. By contrast, lower, more physiological concentrations of TAs appear to have neuromodulatory effects mainly on dopamine-mediated (β -PEA, *p*-tyramine and tryptamine), noradrenaline-mediated (octopamine) and 5-HT-mediated (tryptamine) neurotransmission [18,24–26]. As summarized in Table 2, TAAR1 (TA1) orthologs from human,

mouse and rat are activated by low to submicromolar concentrations of β -PEA and tyramine, whereas tryptamine activates rodent, but not human, TAAR1 (TA1) with similar potency. The potency of octopamine at human and rodent TAAR1 (TA1) is much lower than that of the other TAs. In contrast to TAs, classical biogenic amines either are unable to activate TAAR1 (TA1) or act as partial agonists on TAAR1 (TA1) from rat (5-HT) or all species tested (dopamine) (Table 2) [13–15].

In an excellent review, Berry [18] recently discussed the possible function of TAs as neuromodulators or neurotransmitters, with a neuromodulator only able to modify the activity of a coexisting neurotransmitter and a neurotransmitter able to alter the electrical excitability of a postsynaptic neuron on its own. Berry [18] considers TAs as potential neuromodulators rather than neurotransmitters, mainly because most of them are not released in an activity-dependent manner under physiological conditions (particularly β -PEA and tryptamine, which are membrane permeable), and because they do not seem to alter the electrical excitability of a neuron at physiological concentrations in the absence of other neurotransmitters (the neurotransmitter-like properties that are apparent from some 'amphetamine-like' activities of TAs were not considered physiological). This view is further supported by a recent study reporting that β -PEA and tyramine specifically depress the GABA_B receptor response in rat dopamine-containing midbrain neurons without affecting postsynaptic potentials on their own [27].

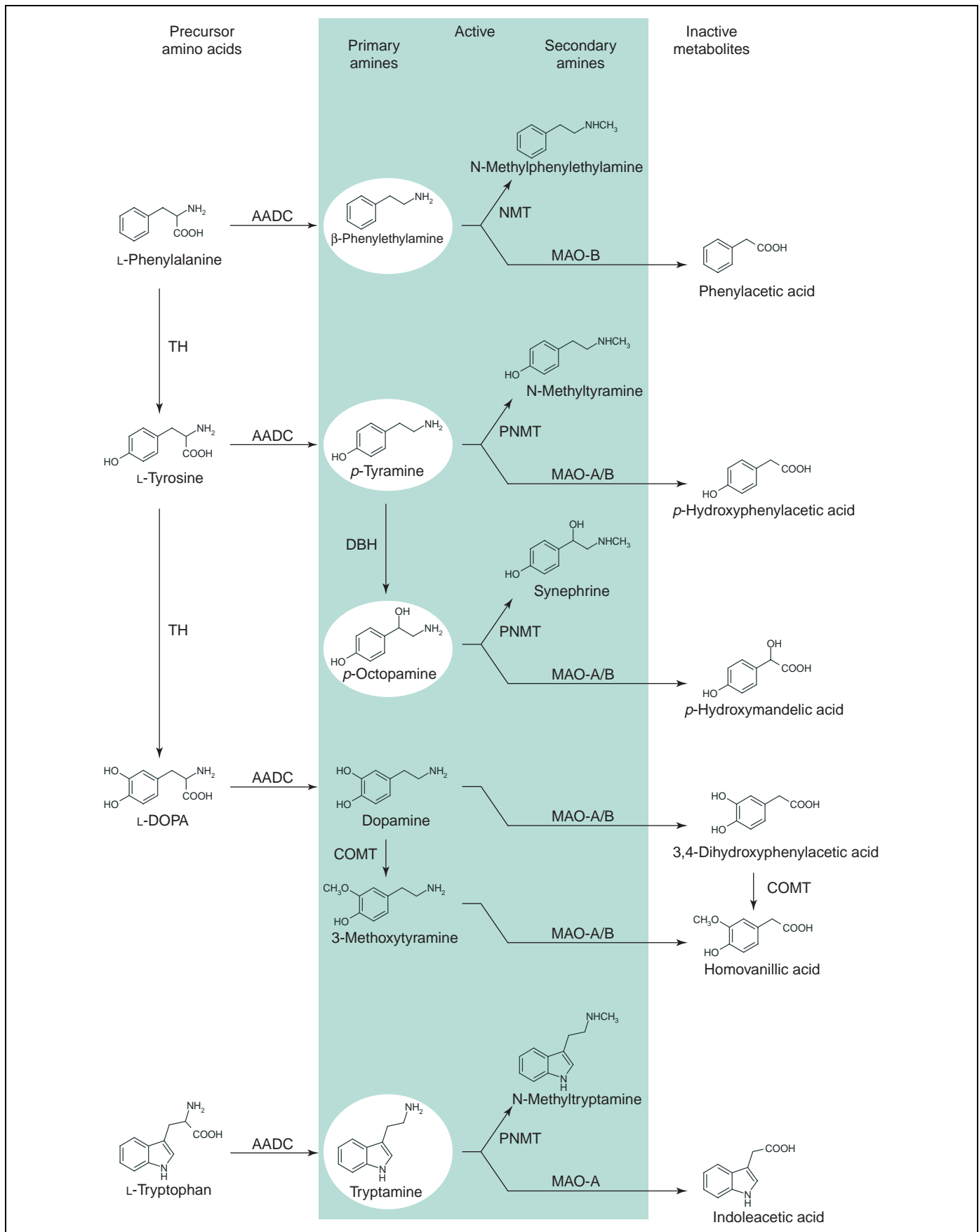


Figure 2. The main routes of TA metabolism in vertebrates. The TAs β -phenylethylamine (β -PEA), *p*-tyramine, octopamine and tryptamine (highlighted by white shading) are generated by decarboxylation from the respective precursor amino acids. They are rapidly inactivated predominantly by monoamine oxidase (MAO). To a lesser extent TAs are also N-methylated to the corresponding biologically active secondary amines (N-methylphenylethylamine, N-methyltyramine, synephrine and N-methyltryptamine). Both dopamine and 3-methoxytyramine, which do not undergo further N-methylation, are partial agonists of TAAR1 (TA1). The naturally occurring TA isoform *m*-tyramine

Table 2. Pharmacology of human, rat and mouse TAAR1 (TA1)^a

Amine	Human TAAR1 EC ₅₀ (μM)	Rat TAAR1 EC ₅₀ (μM)	Mouse TAAR1 EC ₅₀ (μM)
Trace amine			
β-Phenylethylamine	0.3 ^b , 0.3 ^c	0.9 ^b , 0.2 ^d	0.7 ^b
p-Tyramine	1.1 ^b , 0.2 ^c	0.2 ^b , 0.07 ^d	1.4 ^b
Octopamine	10.3 ^b , 4.0 ^c	2.1 ^b , 1.3 ^d	19.7 ^b
Tryptamine	46.9 ^b , >6.0 ^c	1.2 ^b , 0.3 ^d	2.0 ^b
Biogenic amine			
Dopamine	15.8 ^{b,e} , 6.7 ^{c,e}	5.1 ^{b,e} , 5.9 ^{d,e}	11.8 ^{b,e}
5-HT	>50.0 ^b , >10.0 ^c	5.2 ^{b,e} , >10.0 ^d	>50.0 ^b
Noradrenaline	>50.0 ^b , >5.0 ^c	>50.0 ^b	>50.0 ^b
Histamine	>50.0 ^b , >5.0 ^c	>50.0 ^b	>50.0 ^b

^aEC₅₀ values were calculated based on the amount of cAMP produced by cell lines expressing the indicated receptors in response to stimulation with the listed compounds.

^bStably transfected HEK293 cell lines were used [15]. The human TAAR 1 employed in this study was a chimeric protein, constructed by addition of an N-terminal leader sequence and by replacing selected regions involved in G-protein coupling with the corresponding rat sequence.

^cTransiently transfected COS-7 cells were used [13].

^dStably transfected HEK293 cells were used [14].

^eThe maximal elevation of cAMP levels induced by these compounds was 50% compared with p-tyramine, indicating a partial agonist activity of dopamine and 5-HT.

Although the available data suggest that TAs act mainly as neuromodulators, there are several unresolved issues regarding their mode of action at the molecular level. Most importantly, to date, the effects of TAs on neurotransmission have not been shown to be mediated exclusively by members of the TAAR family. Even if the binding of TAs to MAO-B might mimic the presence of high-affinity TA binding sites in brain tissue [28], it cannot be excluded that TA-sensitive receptors other than TAARs might mediate the pharmacological effects of TAs, as supported by the findings that: (i) compounds that are potent activators of TAAR1 (TA1) are unable to displace radiolabeled TAs (i.e. amphetamine activates TAAR1 (TA1) but does not displace [³H]PEA) [29]; (ii) [³H]PEA, [³H]tyramine, [³H]octopamine and [³H]tryptamine are potently displaced by several compounds that do not or only weakly activate TAAR1 (TA1) [30]; and (iii) [³H]PEA, [³H]tyramine, [³H]octopamine and [³H]tryptamine are all displaced by their respective ligands at low nanomolar concentrations (Table 3) [29–32] that are insufficient to activate TAAR1 (TA1) (Table 2). In addition, the mechanisms by which TAs activate TAARs are not fully defined. As suggested by the membrane permeability of some TAs in addition to the predominantly intracellular localization of TAAR1 [13,14], which is reminiscent of the subcellular distribution reported for other GPCRs such as the 5-HT_{2A} receptor [33], TAs could trigger TAAR signaling also from intracellular receptor pools. This possibility is supported indirectly by the observation that the locomotor-stimulating activity of β-PEA is absent in transgenic mice that lack the dopamine transporter, which is known to also carry β-PEA [34]. The TAAR signaling from intracellular receptor pools could, for example, be realized in the presynaptic structure of dopamine-containing neurons where no MAO-B activity has been detected, in presynaptic terminals of noradrenaline-containing neurons, or within so-called D cells. These cells stain positively for aromatic amino acid decarboxylase (an enzyme involved in the production of TAs) but lack both tyrosine hydroxylase (the rate-limiting enzyme involved in the production of

dopamine) and 5-HT [35], and therefore might represent TAergic neurons. Future studies that address these and other issues of TAAR signal transduction and pharmacology will need to consider several technical peculiarities innate to this receptor family (Box 1).

TAARs as potential drug targets for the treatment of psychiatric disorders

The dysregulation of TA levels has been linked to several diseases, which highlights the corresponding members of the TAAR family as potential targets for drug development. In this article, we focus on the relevance of TAs and their receptors to nervous system-related disorders, namely schizophrenia and depression; however, TAs have also been linked to other diseases such as migraine, attention deficit hyperactivity disorder, substance abuse and eating disorders [7,8,36].

Clinical studies report increased β-PEA plasma levels in patients suffering from acute schizophrenia [37] and elevated urinary excretion of β-PEA in paranoid schizophrenics [38], which supports a role of TAs in schizophrenia. As a result of these studies, β-PEA has been referred to as the body's 'endogenous amphetamine' [39], which is consistent with the observation that prolonged administration of amphetamine can induce psychiatric symptoms that largely resemble paranoid schizophrenia [40]. In addition, a genetic deficiency of MAO-B might trigger psychotic symptoms by resulting in elevated β-PEA levels [41]. Furthermore, linkage studies identified the chromosomal region harboring the TAAR genes as a schizophrenia susceptibility locus [42], which subsequently was narrowed down specifically to the TAAR6 (TRAR4, TA4) gene [43].

Taken together, the current evidence that connects elevated β-PEA levels or individual TAAR genes to schizophrenia is suggestive, and TA levels in addition to the recently identified single nucleotide polymorphism in the TAAR6 (TRAR4, TA4) gene might prove to be valuable diagnostic parameters. However, a causal link between schizophrenia and TAs or TAARs remains to be

(not shown) has been demonstrated to activate rat TAAR1 (TA1), albeit with ~80 times lower potency compared with p-tyramine [14], and has been reported to modulate noradrenaline-mediated neurotransmission [24]. Abbreviations: AADC, aromatic amino acid decarboxylase; COMT, catechol-O-methyltransferase; DBH, dopamine β-hydroxylase; NMT, nonspecific N-methyltransferase; PNMT, phenylethanolamine N-methyltransferase; TH, tyrosine hydroxylase.

Table 3. Affinity of TAs and biogenic amines to human TAAR1 (TA1) and brain membranes

Amine	[³ H]Tyramine on human TAAR1 ^a K _i (μM)	[³ H]Tyramine on rat brain ^b K _i (μM)	[³ H]Tryptamine on rat brain ^c K _i (μM)	[³ H]Tryptamine on human brain ^d K _i (μM)
Trace amine				
β-Phenylethylamine	0.008	0.425	0.087	0.480
p-Tyramine	0.034	0.016	0.940	0.315
Octopamine	0.493	0.292	–	182.373
Tryptamine	1.084	–	0.002	0.006
Biogenic amine				
Dopamine	0.422	0.013	0.470	7.953
5-HT	> 6.000	0.668	0.280	0.682
Noradrenaline	> 10.000	0.092	22.400	32.835
Histamine	3.107	–	–	–

^aTransiently transfected COS-7 cells were used (K_d=20 nM) [13].

^bMembrane preparations from rat striatum were used (K_d=11.5 nM, B_{max}=1659 fmol mg protein⁻¹) [30].

^cMembrane preparations from rat cortex were used (K_d=2.8 nM, B_{max}=429 fmol mg protein⁻¹) [32].

^dMembrane preparations from human cortex were used (K_d=2.1 nM, B_{max}=164 fmol mg protein⁻¹) [9].

established, which is complicated by the complexity and limited knowledge of the disease mechanism of schizophrenia [44].

The strongest argument for a role for TAs in depression is supported by the so-called 'PEA hypothesis', which suggests that a deficit in the level or turnover of β-PEA underlies the etiology of endogenous depression, whereas an excess might result in manic episodes [45,46]. The PEA hypothesis is supported directly by clinical studies that reported a relief from depression symptoms in 60% of depressed patients following administration of β-PEA or its precursor L-phenylalanine even following prolonged treatment [47], in addition to reduced β-PEA levels in the cerebrospinal fluid of depressed patients, compared with healthy control subjects [48]. It is believed that the antidepressant effect of MAO inhibitors is mediated in part by triggering a marked increase of TA brain levels [49] by inhibiting the main route of TA catabolism (MAO) (Figure 2) [18]. Moreover, MAO-B-deficient transgenic mice, in which β-PEA levels in the CNS are increased eightfold compared with wild-type mice whereas the levels of various other monoamines are largely unaffected,

display a behavioral profile that resembles animals treated with traditional antidepressants [50]. The pharmacology of TAs might also contribute to a molecular understanding of the well-recognized antidepressant effect of physical exercise [51]. In addition to the various beneficial effects for brain function mainly attributed to an upregulation of peptide growth factors [52,53], exercise induces a rapidly enhanced excretion of the main β-PEA metabolite β-phenylacetic acid (β-PAA) by on average 77%, compared with resting control subjects [54], which mirrors increased β-PEA synthesis in view of its limited endogenous pool half-life of ~30 s [18,55].

The above-summarized data, mainly focusing on β-PEA, provide substantial evidence for an important role for TAs in the pathophysiology, and potentially the treatment, of depression. These studies reveal TAs as suitable biomarkers for depression, and TA-related compounds with improved metabolic properties might be promising candidates for the advanced pharmacological treatment of depression, which so far is almost exclusively limited to drugs that target the classical biogenic amine systems.

Box 1. Technical peculiarities of targeting TAARs in drug development

From the perspective of the pharmaceutical industry, TAARs are attractive targets for drug development because of the good chemical tractability inherent to GPCRs, which currently account for ~50% of all drugs on the market [58]. The tight link of TAARs to several disease areas, in addition to their high pharmacological potential, evident from the fact that various classes of psychoactive compounds such as amphetamines and ergot alkaloids directly act on TAAR1 (TA1) [14], make them exceptionally promising molecules. However, several technical issues innate to this receptor family will require close attention for the successful development of TA-related drugs:

Species differences

The remarkable species differences with regard to the total number of receptors and pseudogenes and to the sensitivity of the receptors to individual TAs [15] require caution for the extrapolation of pharmacological data between species.

Expression levels and localization

Overall, the available data on the tissue distribution of TAARs are few, and detailed expression studies will be needed for a meaningful interpretation of the receptor pharmacology on a systems level. At present, the distribution of TAARs in human and rodents is thought to

be restricted to discrete brain areas [13], and levels of transcripts, but not of protein, are reported to be low.

Receptor trafficking and signaling

When expressed in eukaryotic cell lines TAARs show a predominantly intracellular localization [13,14] that seems to closely resemble the *in vivo* situation in mammalian brain tissue. It is not known if the membrane-permeable TAs β-PEA and tryptamine might trigger signaling from an intracellular receptor pool, and, if regulated, membrane insertion in addition to receptor heterodimerization [59,60] might serve to adjust receptor sensitivity and specificity. In contrast to its rodent orthologs, human TAAR1 (TA1) displays a reduced signaling capability in standard heterologous expression systems, which can be restored by replacing either parts of the receptor sequence or the stimulatory G-protein with the corresponding rat counterparts [13,15].

Unknown ligands for most TAARs

To date, no functional ligands have been identified for most TAARs. Identification of functional TAAR ligands will support attempts to target these receptors in drug development, and will determine whether TAARs correspond predominantly to TAs or any other class of endogenous ligands.

Outlook and future perspectives

The identification of specific receptors has always been key to the understanding of the biological function and pharmacology of any transmitter-like biological compound, as the example of histamine illustrates well: when the importance of amine-mediated systems emerged in the 1960s, it was only after the identification of specific receptors that histamine was generally accepted as an established neurotransmitter [56,57]. Likewise, it is only the recent identification of TAARs, some of which have been characterized as specialized TA receptors, that will enable a detailed understanding of TAs as potential vertebrate neuromodulators at the molecular level. For a full understanding of the physiological relevance of TAs and the TAAR family, numerous vital issues need to be resolved. In addition to thorough studies of the tissue distribution and signal transduction mechanisms of the TAARs, the characterization of physiological high-affinity ligands for the apparently TA-insensitive majority of TAARs will be essential. Given the well-established disease relevance of TAs and the TAAR family, in addition to their high pharmacological potency, answering these questions promises to identify TAs and potentially other TA-related compounds as equally important as classical biogenic amines for the understanding of psychiatric conditions such as depression and schizophrenia. The ongoing research on these issues could soon pave the way for an advanced treatment of these highly prevalent diseases.

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