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Receptors of Mammalian Trace Amines

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ABSTRACT

The discovery of a family of G-protein coupled receptors, some of which bind and are activated by biogenic trace amines, has prompted speculation as to the physiological role of these receptors. Observations associated with the distribution of these trace amine associated receptors (TAARs) suggest that they may be involved in depression, attention-deficit hyperactivity disorder, eating disorders, migraine headaches, and Parkinson's disease. Preliminary in vitro data, obtained using cloned receptors, also suggest a role for TAARs in the function of hallucinogens.

KEYWORDS: Trace amine associated receptor, TAAR, mammalian, G-protein coupled receptor, ADHD, hypothyroidism-associated depression, prepulse inhibition

INTRODUCTION

Endogenous amines such as tyramine, tryptamine, phenethylamine, and octopamine have long been known to be present in mammalian brain at potentially relevant physiological concentrations. In fact, some of these so-called trace amines have for over 25 years been thought to be associated with affective behavior,[1] paranoid chronic schizophrenia,[2] and depression.[3,4] Moreover, specific binding sites with unique pharmacology and localization for some tritium-labeled trace amines have been reported.[5-9] This mini-review provides a summary of the mammalian trace amine receptor literature up to the end of calendar year 2004.

LITERATURE REVIEW

Although trace amines have important functions in invertebrates, and particularly in insects, no role has been associated with these materials in mammals. The invertebrate receptors for trace amines, also referred to as octopamine receptors, are known to belong to the family of G-protein coupled receptors (GPCRs).[10] Four of them have been distinguished using pharmacological tools, and they have been found to show different coupling to second messenger systems, including activation and inhibition of adenylyl cyclase, activation of phospholipase C, and coupling to a chloride channel. Recently, octopamine receptors from mollusks and insects have been cloned. In humans and other mammals the existence of functional receptors for trace amines had, until recently, only been hypothesized.

A mammalian receptor for trace amines was identified with the discovery of a G-protein coupled receptor capable of binding both tyramine and phenethylamine and coupling to the stimulation of adenylate cyclase through Gαs G-protein, leading to accumulation of cAMP. In 2001, scientists[11] at Synaptic Corp (Paramus, NJ) reported the identification of a phylogenetic tree for the human, rat, and mouse trace amine receptors; human 5-HT receptors; human α1a receptor (AR-$_{\alpha 1a}$); GPR57; GPR58; putative neurotransmitter receptor (PNR); 5-HT$_{4\Psi}$; Drosophila receptors for octopamine; 5-HT; and tyramine receptors from *Caenorhabditis elegans*, bee and locust, and a snail octopamine receptor. For rat, 14 trace amine receptors had been identified while 4 human trace amine receptors were found.[11] The abbreviation TA was used by these authors for these new receptors. Human and rat trace amine receptors were also described by Bunzow et al[12] who used the abbreviation TAR for the same receptors.

These newly discovered receptors have prompted multiple speculations regarding their physiological and pathological relevance. Trace amines have been hypothesized to act as neurotransmitters or neuromodulators,[13] as endogenous enhancer substances,[14] as monoamine releasers,[15] and even as vasoconstrictors.[16] A recent review has suggested that they may heterodimerize, for example, with dopamine (DA) receptors, which may increase the intrinsic activity of DA receptors by increasing their affinity to agonist ligands.[17] Indirect activation of dopamine autoreceptors by trace amines has also been proposed to be caused by an efflux of newly synthesized dopamine.[18]

Recently, a new nomenclature has been proposed for trace amine receptors.[19] Part of the rationale justifying the need for new nomenclature is because the terms TA and TAR are both used in other contexts. For example, *TA*$_5$ has been used to refer to the human *GPR 102,* and *TAR* refers to *Escherichia coli* aspartate receptors. The new term trace amine

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associated receptor (TAAR) is proposed to avoid such ambiguity, as well as to include members of the trace amine receptor family that do not respond to trace amines (vide infra). Based on the sequential order of the receptor genes on the chromosomes as well as their phylogenetic relationships across species, a series of rules for the naming of TAARs has also been proposed. These rules stipulate that

- the term TAAR would be followed by a number identifying the specific ortholog;
- a letter suffix distinguishing genes that are paralogues would follow the number identifying the specific ortholog; and
- pseudogenes would be identified by the suffix P.

This mini-review will use this new nomenclature. Table 1 shows the new nomenclature and its relationship to terms used in previous publications. In addition, Table 1 demonstrates the identification of 19 individual TAARs for rat, 9 each for human and chimpanzee, and 16 for mouse.

Considerable homology had been reported between the human and rat TAARs: *hTAAR* 1 and *rTAAR* 1 share 79% identity; *hTAAR* 9 and *rTAA*R 9 share 87% identity; and *hTAAR* 6 and *rTAA*R 6 share 88% identity.[11] In fact, *hTAAR* 1 has been called the human ortholog of *rTAAR* 1.[12] For rhesus monkey, *TAAR* 1 and *TAAR* 9 were reported to be >96% homologous to the human orthologs, with only a single amino acid residue in the extracellular N terminus of monkey *TAAR* 1 differing from *hTAAR* 1.[20] Subsequent work revealed that although the chimpanzee *TAAR* 1 and *TAAR* 9P genes had 99.1% and 97.3% overall sequence identity, respectively, only 3 of the chimpanzee genes (*TAAR* 1, *TAAR* 5, and *TAAR* 6) had intact open reading frames, while the other 5 *TAAR* genes were pseudogenes.[19] Surprisingly, there are twice as many functional *TAAR* genes in human as in chimpanzee. An additional obvious interspecies difference is the absence of any functional counterpart of the rodent *TAAR* 7 orthologs in human.[19]

The reported phylogeny of the *TAAR* genes across species reveals the existence of 3 distinct subfamilies into which the orthologs can be grouped (Table 1).[19] All 4 species examined to date (human, chimpanzee, rat, and mouse) have at least one functional *TAAR* gene for each of the 3 subgroups, suggesting that each subgroup may have physiological relevance. At present putative, potential endogenous ligands for *TAAR* 1 and *TAAR* 4 have been identified. Specifically, in humans, *TAAR* 1 responds to tyramine,[11,21] β-phenethylamine,[11,21] octopamie,[11] and dopamine,[11] and the *TAAR* 4 is activated by tyramine[11] and β-phenethylamine.[11] No ligands are currently known to activate other TAARs. Overall, it has been concluded that TAARs represent a well-defined, coherent gene family, and not an extension of an established, closely related family, such as the 5-HT receptors.[19]

The discovery of the TAARs has prompted speculations as to their physiological role(s). Specifically, it has been pointed out[22] that although there do not appear to be any mammalian neurons using any of the trace amines, these molecules may function as traditional neuromodulators working through their own receptors. The fact that the mRNA for *rTAAR* 1 and *rTAAR* 4 receptor proteins is expressed in certain cells of the substantia nigra/ventral tegmental area, locus coeruleus, and dorsal raphe, which are all areas where cell bodies of the classic biogenic amines are found, further supports such a role for trace amines. Low levels of *hTAAR* 1, as well as *mTAAR* 1 mRNA, were found to be expressed in the amygdala. Only trace levels of *hTAAR* 1 were found in cerebellum, dorsal root ganglia, hippocampus, hypothalamus, medulla, and pituitary. *hTAAR* 6 mRNA at low level was also found to be expressed in amygdala, and *hTAAR* 8 mRNA was expressed in both amygdala and hippocampus.

It had been noted that *hTAAR* genes map to chromosome 6q23.2, close to SCDZ5, a susceptibility locus for schizophrenia, and it has been proposed that *hTAAR* 6 may be a susceptibility gene for schizophrenia.[23] Since the 6q chromosomal area has been linked to bipolar disorder, *hTAAR* 6 may be involved in both disorders. In addition, it has been suggested that[13] TAARs may be involved in depression, attention-deficit hyperactivity disorder (ADHD), eating disorders, migraine headaches, and Parkinson's disease.

Recently some specific data supporting the involvement of TAARs in attention-deficit hyperactivity disorder and in depression have been presented.[24] Specifically, it has been observed that phenethylamine levels may be deficient in ADHD brains, leading to the suggestion that ADHD may be associated with insufficient *TAAR* 1 activation. If this is the case, it would account for the effectiveness of inhibitors of the dopamine transporter as ADHD medications. Thus, these agents, which have been found to inhibit phenethylamine transport as well, will lead to increased phenethylamine levels, thereby ameliorating the symptoms of ADHD.

In support of the role of TAARs in depression, the observation that 3-iodothyronamine, an analog of tyramine and a metabolite of thyroid hormone, activates rat and mouse *TAAR* 1 heterologously expressed in HEK 293 cells in vitro has been interpreted to mean that *TAAR* 1 may play a role in depression associated with hypothyroidism.[25] Moreover, since synthetic 3-iodothyronamine injected intaperitoneally (mice) produces several physiological manifestations that are reminiscent of hypothyroidism-associated depression-like symptoms in humans (such as blocking the ability to thermoregulate and maintain normal cardiovascular tone at room temperature, depressing locomotor activity and metabolic rates, and elevating blood sugar levels),[25] *TAAR* 1 may be involved in these regulatory processes.

Table 1. New Nomenclature and Classification for Trace Amine Associated Receptors*†

		Old			Accession		
Sub-family	**New Name**	**Name**	**Ref**	**Bp**	**Number**	**Reference**	**Comments**
				Human			
1	TAAR 1	TA1	11, 12	1020	AF200627 AF380185	15, 16	Discrepancy: G864A
	TAAR 2	**GPR58**	11	921; 1056	AY702304 AF112460; AY703480‡	20	Discrepancies: C398T, C552T
	TAAR 3	**GPR57 P**	11	1030	AY702305 AF112461	20	Discrepancies: G57-, C134-
	TAAR 4	TA2 P, 5HT-4 P	11, 12	1049	U88828	19	
2	TAAR 5	**PNR**	11	1014	AY702306 AF021818	21	Discrepancies: A118G, T770C
3	TAAR 6	TA4, TRAR4	11, 22	1038	AF380192	15	
	TAAR 7	**Novel P**			AY803193§		
	TAAR 8	TA5, GPR102	11, 20	1029	AF380193	15	
	TAAR 9	TA3	11, 12	1047	AF380189 AL513524	15	Discrepancies: C9T, T181A
				Chimpanzee			
1	TAAR 1	**Novel**		1020	AY702307		
	TAAR 2	**Novel P**		920; 1055	AY702308; ‖		
	TAAR 3	**Novel P**		1030	AY702309		
	TAAR 4	**Novel P**		1049	AY702310		
2	TAAR 5	**Novel**		1014	AY702311		
3	TAAR 6	**Novel**		1038	AY702312		
	TAAR 7	**Novel P**			AY803194§		
	TAAR 8	**Novel P**		1027	AY702313		
	TAAR 9	**Novel P**		1048	AY702314		
				Rat			
1	TAAR 1	**TA1**	11, 12	999	AY702315 AF380186	15, 16	Discrepancies: G72A, T509A, A660G, T867C; AF421352 discrepancy: A741G
	TAAR 2	**Novel**		1020	AY702316¶		
	TAAR 3	**Novel**		1029	AY702317		
	TAAR 4	TA2	11	1044	AF380188	15	
2	TAAR 5	**Novel**		1014	AY702318		
3	TAAR 6	TA4	11	1038	AF380191	15	
	TAAR 7a	TA8	11	1077	AF380196	15	
	TAAR 7b	**TA12**	11	1077	AY702319 AF380200		Discrepancy: ATG is 75 bp downstream
	TAAR 7c	**Novel**		1077	AY702320		
	TAAR 7d	**TA15**	11	1077	AY702321 AF380203	15	Discrepancies: T198C, C199A, G282C, T292C, A373T, C459G

Continued

Table 1. *Continued*

		Old			Accession		
Sub-family	**New Name**	**Name**	**Ref**	**Bp**	**Number**	**Reference**	**Comments**
	TAAR 7e	**TA14**	[11]	1077	AY702322 AF380202	[15]	Discrepancies: C71T, G398C, C403A,C405A, C467T
	TAAR 7f	**TA13P**	[11]	1089	AY702323 AF380201	[15]	Discrepancies: C135A, T151C, G186A, T294G, T475G, A515G, G759A
	TAAR 7i	**Novel P**		1067	AY702324		
	TAAR 8a	TA11	[11]	1035; 1125	AF380199; AF380199	[15]	Using 2nd ATG
	TAAR 7g	TA9	[11]	1077	AF380197	[15]	
	TAAR 7h	TA6	[11]	1077	AF380194	[15]	
	TAAR 8b	TA7	[11]	1035; 1125	AF380195; AL513524	[15]	
	TAAR 8c	**TA10**	[11]	1035; 1125	AY702325 AF380198; AL513524	[15]	Discrepancy: G214A
	TAAR 9	TA3	[11]	1017	AF380190	[15]	
				Mouse			
1	TAAR 1	**TA1**	[11]	999	AF380187	[15]	
	TAAR 2	**Novel**		1020	AY702326[#]		
	TAAR 3	**Novel**		1032	AY702327		
	TAAR 4	**Novel**		1044	AY702328		
2	TAAR 5	**Novel**		1014	AY702329		
3	TAAR 6	**Novel**		1038	AY702330		
	TAAR 7a	**Novel**		1077	AY702331		
	TAAR 7b	**Novel**		1077	AY702332		
	TAAR 7c	**Novel P**		1055	AY702333		
	TAAR 7d	**Novel**		1077	AY702334		
	TAAR 7e	**Novel**		1077	AY702335		
	TAAR 7f	**Novel**		1077	AY702336		
	TAAR 8a	**Novel**		1035	AY702337		
	TAAR 8b	**Novel**		1035	AY702338		
	TAAR 8c	**Novel**		1035	AY702339		
	TAAR 9	**Novel**		1047	AY702340		

*TAARs indicates trace amine associated receptors; ref, reference; bp, base pair; and PNR, putative neurotransmitter receptor. Genes that were resequenced are in bold. Data are adapted from Lindemann et al.[19]

†Genbank accession numbers or accession numbers referring to data from Roeder.[10]

‡Encoded by 2 exons. The presence of one transcript encompassing the coding sequence of both exons was proven on the level of cDNA.

§highly degenerated gene fragment (210 bp), sharing 62.6% nucleotide sequence identity to the corresponding rat *TAAR 7h* sequence.

‖The intron/exon structure as well as coding sequences of human and chimpanzee are well conserved, suggesting that also chimpanzee *TAAR 2* is encoded by 2 exons, which were amplified and sequenced separately from chimpanzee genomic DNA. However, the presence of transcripts encoding both exons has not been experimentally verified owing to unavailability of chimpanzee brain RNA.

¶Rat *TAAR 2* is encoded by 2 exons. The presence of one transcript encompassing the coding sequence of both exons was proven on the level of cDNA.

#Mouse *TAAR 2* is encoded by 2 exons. The presence of one transcript encompassing the coding sequence of both exons was proven on the level of cDNA.

Only a very limited amount of information regarding activation of TAARs is available. Obtaining this information is difficult since the level of TAAR expression in both the central nervous system (CNS) and peripheral tissue is low. For *hTAAR* 1, only 15 to 100 copies/ng cDNA are expressed in amygdala, and <15 copies/ng cDNA are found in cerebellum, dorsal root ganglia, hippocampus, hypothalamus, medulla, and pituitary. The highest levels (100 copies/ng cDNA) are present in stomach.[11] Message from *hTAAR* 9, *hTAAR* 5, and *hTAAR* 6 was found in kidney; the first was also detected in the hippocampus and the latter 2 were also expressed in amygdala. All are expressed at low (<15 copies/ng cDNA) levels.[11] Countermanding these low receptor densities required the development of expression systems for screening purposes. This was accomplished by the cloning of rat, mouse, and human *TAAR* 1[11,12,19]; *rTAAR* 1 was stably expressed in HEK 293 cells,[12,19,26] as was *mTAAR* 1.[19] Transient transfection has been reported for *hTAAR* 1.[11] Stable expression of *hTAAR* 1 in HEK 293 cells was achieved by modification of the coding sequence by the addition of an influenza hemaglutinin viral leader sequence and by replacement of selected regions with the corresponding *rTAAR* 1 sequences.[19] A stable cell line expressing *hTAAR* 1 (no details given) has been reported.[21]

The rat clone was used to qualitatively screen several CNS-active compounds for activation of *rTAAR* 1. The results showed amphetamines and lysergic acid diethylamide (LSD)-related compounds to be agonists,[12] leading to the hope that TAARs may provide insight into the molecular mode of action of these drugs of abuse. Evidence for the involvement of TAARs in psychostimulant activity has resulted from observations made in a line of mice lacking the *mTAAR* 1. These animals demonstrated reproducible deficits in prepulse inhibition, a condition that has been significantly correlated with abnormal functional interactions between the muscarinic, cholinergic, and dopaminergic systems,[27] with no difference in baseline startle response.[28] In addition, the mice lacking the *mTAAR* 1 displayed enhanced, dose-dependent sensitivity to the psychomotor stimulating effects of amphetamine, compared with the wild-type littermates, as well as a larger increase in the release of both dopamine and norepinephrine in the dorsal striatum. These observations have been interpreted to suggest that activation of *TAAR* 1 may serve to dampen the stimulatory effects of amphetamine.[28]

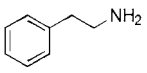
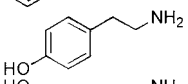
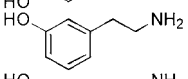
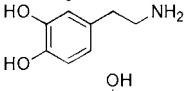
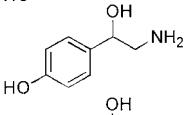
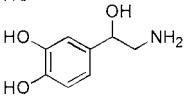
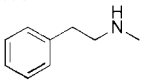
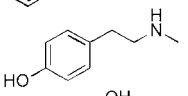
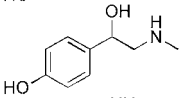
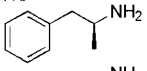
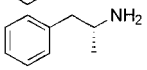
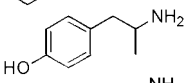
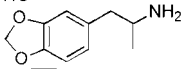
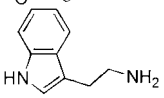
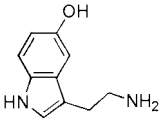
Use of the clones expressing *mTAAR* 1 and *rTAAR* 1 to screen thyronamine derivatives has demonstrated that both are activated by 3-iodothyronamine, a thyroid hormone derivative found in rodent brain.[26] Based on this observation, it has been suggested that a signaling pathway, stimulation of which leads to consequences opposite those associated with excess thyroid hormone, may exist. However, considering the significant differences in pharmacology observed[19] for rat and human *TAAR* 1 (see below and Table 2) such interpretations must be viewed with caution.

The potency of "trace amines" and their congeners to activate *TAAR* 1 are shown in Tables 2 and 3. The data in Table 2 emphasize the interspecies differences as well as the effects associated with expression systems. As pointed out in the literature[19] there appears to be greater correspondence between the assay data for mouse and human *TAAR* 1, than between mouse and rat *TAAR* 1. However, it needs to be understood that the number of data points is very small. Perhaps more meaningful is the difference observed between data obtained using stably and transiently expressed receptors, particularly for tryptamine (entry 14). It should also be noted that it is not known what effect the use of "modified" *hTAAR* 1 to prepare a stable expression system[19] has on potency to activate *hTAAR* 1. Despite these caveats, some trends are detectable. Thus, introduction of a p-hydroxy group provides for slightly increased potency (compare entries 1 and 2, 7 and 8, 10/11 and 12) whereas introduction of an m-hydroxy group decreases potency by about an order of magnitude (compare entries 1 and 3, 2 and 4, 5 and 6). Similarly, the replacement of one of the amine protons by a methyl group slightly enhances potency (compare entries 1 and 7, 2 and 8, 5 and 9). The effect of aromatic iodo substituents (Table 3) is intriguing. Again, interspecies differences are apparent. While a single m-iodo group increases potency by an order of magnitude in both mouse and rat receptors (compare entries 1 and 2), a second m-iodo group in the second aromatic ring (compare entries 2 and 4) has a modest effect in *rTAAR* 1, but a significantly larger effect in *mTAAR* 1.

In invertebrates lipophilicity, dipole moment, and molecular shape have been correlated to the agonist and antagonist efficacy of 49 trace amines in locust thoracic nerve cord.[29] Subsequent application of a 3-dimensional molecular field analysis to the same data set and to a larger set of 70 analogs, combined with a genetic algorithm/partial least squares statistical analysis, provided useful information in the characterization and differentiation of (insect) receptor types and subtypes.[30] Recently, a 3D quantitative structure activity relationship (QSAR) for a new series of 59 agonists provided a good correlation using a pharmacophore consisting of a positive charge center, aromatic ring, and 3 hydrophobic sites.[31] Clearly a significant amount of work remains to be done before any similar correlations can be performed for mammals and particularly humans.

At present the discovery of trace amine-associated receptors holds the promise of providing potentially important novel insights into the origins and treatments of CNS disorders. Although cloned membranes expressing *hTAAR* 1 have been prepared and used to screen a few compounds, the validity of these assays remains to be determined. In particular, the

Table 2. Potency Values for Phenethylamine Analogs

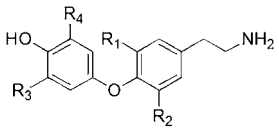
		EC_{50} (μM)				
		rTAAR **1**		*hTAAR* **1**		*mTAAR* **1**
Entry No.	**Structure**	**Bunzow[12]**	**Lindeman[19]**	**Borowsky[11]**	**Lindemann[19]**	**Lindemann[19]**
1		0.24	0.9	0.324	0.3	0.66
2		0.069	0.21	0.214	1.07	1.37
3		5.4				
4		5.9	5.14	6.7	15.78	11.76
5		1.3	2.13	4.03	10.29	19.71
6			>50 000		>50 000	>50 000
7			0.3		0.16	0.15
8			0.14		2.05	1.02
9		0.58				
10		0.21				
11		0.44				
12		0.051				
13		1.7				
14		0.3	5.24	>6	46.87	1.99
15		>10	>50 000	>10	>50 000	>50 000

different results reported for the efficacy of ligands to activate *hTAAR* 1 must be resolved. Thus, the effects of modification of the coding sequence and replacement of certain segments with *rTAAR* 1 sequences to obtain a stable expression system for *hTAAR* 1, as well as the use of a transient expression system relative to stable expression system for *hTAAR* 1 must be ascertained before meaningful QSAR studies can be undertaken and before specific drug leads can be targeted for in vitro evaluation. Even more demanding will be the development of an animal model for in vivo testing. Homozygote *TAAR* 1 knockout mice are viable[13] and have been used to study the physiological role of *TAAR* 1 in the CNS.[28] However, considering the significant differences in pharmacology observed for rodent and human *hTAAR* 1 and in responses to trace amines and their analogs, it may be necessary to develop a *hTAAR* 1 transgenic rodent in order to get meaningful results.

CONCLUSIONS

Three distinct subfamilies of TAARs, comprising as many as 21 individual receptors, have been fully identified and

Table 3. Potency Values for Thyronamine Derivatives*



Substituents				EC_{50} (μM)	
R_1	R_2	R_3	R_4	r*TAAR* 1	m*TAAR* 1
H	H	H	H	0.131	~1
I	H	H	H	0.014	0.112
H	H	I	H	~1	>1
I	H	I	H	0.041	~1
I	I	H	H	0.056	0.371
H	H	I	I	>1	>1
I	I	I	H	0.087	>1
I	H	I	I	>1	>1
I	I	I	I	>1	>1

*Data adapted from Grandy and Scanlon.[25]

characterized in human, chimpanzee, rat, and mouse. Significant interspecies differences have been found. Only 2 TAARs have had functional ligands, which are associated with them, identified. Owing to their low density in tissue, TAARs must be cloned and expressed for in vitro assays. At present very few stable expression systems have been generated. The scant data available suggest significant differences between results obtained in different expression systems and point to important species differences. The TAARs are an important new target for investigation in light of their likely involvement in neuropsychiatric and neurodegenerative disorders, as well as in drug abuse.

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