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Trace amine-associated receptors: ligands, neural circuits, and behaviors

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Abstract

Trace amine-associated receptors (TAARs) are G Protein-Coupled Receptors that function as vertebrate olfactory receptors. Like odorant receptors, TAARs constitute an ever-evolving sensory subsystem, with individual TAARs recognizing particular chemicals and some evoking stereotyped behaviors. Several TAARs mediate aversion or attraction towards volatile amines that include the mouse odor trimethylamine, the predator odor 2-phenylethylamine, and the death-associated odor cadaverine. TAAR-expressing sensory neurons achieve monoallelic receptor expression, use canonical olfactory signaling molecules, and target a dedicated olfactory bulb region. In mouse, TAAR4 and TAAR5 are encoded by adjacent genes and localize to adjacent glomeruli, yet mediate opposing behaviors. Future studies are needed to understand how TAAR-expressing sensory neurons engage higher-order neural circuits to encode odor valence.

Introduction

Trace amine-associated receptors (TAARs) were discovered in 2001 [1,2], and initially proposed to recognize low abundance neurotransmitters termed trace amines [3]. This early model of TAAR function, for which these receptors were named, was largely based on studies involving TAAR1. Subsequent work revealed a functional dichotomy in the TAAR family, with all other TAARs instead serving predominantly or exclusively as chemosensory receptors in the main olfactory system [4]. Much progress has since been made to understand TAAR signaling- from detection of odors to production of behaviors.

The TAAR family

TAARs are distantly related to biogenic amine receptors and not phylogenetically related to canonical odorant receptors (ORs) or other chemosensory receptors. The TAAR repertoire varies between species, with 15 full-length TAARs in mouse (mTAARs), 17 in rat (rTAARs), 6 in macaque (macTAARs), and 6 in human (hTAARs) [5–8]. In these mammals, *Taar* genes are found in a single genomic cluster and, except for *Taar2*, contain one translated exon. Mammalian TAAR orthologs generally display sequence conservation across species, unlike vomeronasal receptors that are rapidly diverging [5]. In teleost fish, the TAAR family is larger, more variable, and encoded by genes on multiple chromosomes [6,9,10]. There are 48 full-length TAARs in stickleback, 27 in salmon, 25 in medaka, 18 in

pufferfish, and 112 in zebrafish (zTAARs), with most fish TAARs part of a unique clade that arose in teleosts [9–11]. While the precise timing is debated, TAARs likely originated early in vertebrates, around the emergence of jawed fish [10–12].

TAAR Expression

All TAARs except TAAR1 function as olfactory receptors, based on studies in rodent, primate, and fish [4,7,10]. TAAR expression is highly enriched in the olfactory system by quantitative PCR (qPCR) analysis, with little or no expression in other tissues examined [4]. In the nose, TAARs display characteristic hallmarks of OR expression: confinement to sparse sensory neurons (~0.1%) and distribution within a spatial zone (Figure 1) [4]. TAARs are also expressed in the neonatal Grueneberg ganglion [13], a distinct olfactory substructure, but not the vomeronasal organ [4].

Each *Taar* allele defines a unique sensory neuron population that does not express other *Taars* or *Ors* [4,14,15]. The epigenetic signature observed on silenced *Or* genes is absent from *Taar* genes, suggesting a different gene choice mechanism [14]. Neurons selecting a *Taar* pseudogene express a second receptor with bias towards re-selection of a second *Taar* gene [14,15], raising the possibility that TAAR neurons undergo committed cell fate determination prior to receptor choice. Furthermore, the second *Taar* allele is usually chosen from the other chromosome [15], suggesting blockade of the originally chosen cluster as occurs during vomeronasal receptor re-selection [16]. Cell fate markers, transcription factors, locus control regions, and epigenetic modifications that contribute to TAAR neuron specification are unknown.

Within sensory neurons, TAAR proteins are localized to olfactory cilia, the site of odor detection, and to axons, where they may participate in axon guidance [14]. TAARs and ORs likely engage similar intracellular pathways, as TAAR neurons express $G_{\alpha_{olf}}$ and other canonical olfactory signaling molecules [4,17]. Furthermore, activated TAARs couple to cAMP pathways in heterologous cells [4,18], and pharmacological inhibition of adenylyl cyclase blocks odor responses in TAAR neurons [17].

Uniquely, TAAR1 does not function as an olfactory receptor in mice, macaque, human, or zebrafish [4,7,10]. TAAR1 expression is reported in many cell types [1–3], although levels are generally quite low as qPCR analysis across various tissues only detects expression in pancreas [19]. Knock-in mice containing a β -galactosidase reporter at the endogenous *Taar1* locus revealed reporter expression in rare neurons, including midbrain dopamine neurons and brainstem serotonin neurons [20]. The TAAR family displays a functional dichotomy reminiscent of the mouse formyl peptide receptor family, which includes different receptors for innate immunity and vomeronasal chemoreception [21,22].

TAAR ligands and molecular recognition properties

TAARs share homology with biogenic amine receptors, for which the biochemical and structural basis of ligand recognition is well understood [23,24]. Biogenic amine receptors recognize amines through a key salt bridge involving a conserved transmembrane three aspartic acid (Asp^{3.32}; Ballesteros-Weinstein indexing) [24]. Asp^{3.32} is retained in all

hTAARs (6/6), most mTAARs (13/15), and some zTAARs (27/112), suggesting that many TAARs would retain amine recognition capacity. High throughput chemical screens and medicinal chemistry approaches revealed ligands for TAAR1, TAAR3, TAAR4, TAAR5, TAAR7s, TAAR8s, TAAR9, and TAAR13c [1,2,4,18,25,26]. Each of these TAARs detects amines, with TAAR1 detecting various biogenic amines and olfactory TAARs detecting volatile odors, some also natural products (Figure 2).

TAAR1

TAAR1 functions in the brain to regulate neuron excitability and neurotransmitter usage [3,20,27]. TAAR1 agonists include putative trace amines (tyramine, octopamine, tryptamine, 2-phenylethylamine), psychoactive chemicals (amphetamines), thyronamines, and other amines [1,2,4,26,28]. These chemicals exert various physiological effects, presumably through TAAR1-dependent and TAAR1-independent mechanisms; for example, thyronamine-induced hypothermia persists in TAAR1 knockout mice [29]. Synthetic agonists and antagonists with improved specificity for TAAR1 acutely modulate aminergic neuron firing with effects eliminated in TAAR1 knockout mice [30,31]. Furthermore, aminergic neurons fire at elevated rates in TAAR1 knockout mice [20], with TAAR1 inhibitory effects mediated through $G\alpha_s$ and inwardly rectifying potassium channels [30].

Olfactory TAARs

Ligands for olfactory TAARs are small, volatile chemicals. Agonists for 6 mTAARs, 7 rTAARs, 1 zTAAR, 1 macTAAR, and 1 hTAAR were discovered using a heterologous expression system based on cAMP-dependent reporter induction [4,7,18,32]. These 16 olfactory TAARs detect different volatile amines, with affinities (0.1–10 μ M) like OR affinities in similar assays. Amines that activate TAAR3 (isopentylamine), TAAR4 (2-phenylethylamine), and TAAR13c (cadaverine) include primary amines derived from natural amino acids by decarboxylation [4,25]. Other TAARs prefer tertiary amines, including TAAR5 (trimethylamine), TAAR7s (*N,N*-dimethylalkylamines), TAAR8s (*N*-methylpiperidine), and TAAR9 (*N*-methylpiperidine) [4,18]. TAARs that detect primary or tertiary amines form different clades on the TAAR phylogenetic tree (Figure 3) [18]. A third TAAR clade arose in teleosts with widespread mutation of amine-contacting Asp^{3,32} and it is unclear what they detect [10]. TAAR-expressing olfactory sensory neurons recognize the same amines identified in cell culture experiments [17,33], but with enhanced sensitivity [17]. Coupling to downstream signaling components is presumably optimized in olfactory sensory neurons so activation of a small number of receptors is sufficient to cause neuron depolarization.

When functional expression is achieved, TAAR orthologs from different species recognize similar ligands, although sensitivities vary [7,18,32,33]. An exception is the rapidly evolving TAAR7 subfamily, where recent mutations changed ligand recognition properties [18]. The mouse TAAR7 lineage provides direct evidence for functional expansion of the olfactory receptor repertoire through a pattern of gene duplication and subsequent mutation.

Modeling TAAR-ligand interactions

Structural models were generated for agonist-bound TAAR1, TAAR7e, and TAAR7f based on crystallographic data for the β -adrenergic receptor [18,28,34]. These modeled receptors contain the canonical seven transmembrane α -helical fold and other conserved features of rhodopsin-like GPCRs. Modeling and mutational analysis predict ligand binding to occur in the membrane plane through an Asp^{3.32} salt bridge and other ligand contacts largely distributed across transmembrane α -helices. Ligand selectivity differences between TAAR7e and TAAR7f, highly related receptors with distinct response profiles, are determined by two adjacent transmembrane 3 residues (3.37, 3.38) [18]. In TAAR7e, Van der Waals interactions between the ligand and Ser^{3.37} are a key selectivity determinant, with the bulkier side chain of Tyr^{3.37} in TAAR7f sterically limiting ligand size [18].

TAARs that recognize ethological odors

Several TAARs detect natural odors derived from urine, microbial metabolism, and other ecological sources. Urine directly activates mTAAR4, mTAAR5, mTAAR7f, rTAAR8c, and rTAAR9 [4,33,35], with mTAAR4 and mTAAR5 detecting species-specific metabolites (see below). Agonists for mTAAR3 (isopentylamine) and mTAAR7e (5-methoxy-*N,N*-dimethyltryptamine) are also reported in urine [36,37]. Isopentylamine is a biogenic amine produced by leucine decarboxylation and its ecological salience is unclear, as it is innately aversive to rodents [38]. zTAAR13c and TAAR5 detect microbially derived amines emitted in decomposing flesh (see below) [7,25].

TAAR4

TAAR4 detects a carnivore odor that repels rodents [35]. Chemical fractionation of bobcat urine revealed 2-phenylethylamine to be the natural TAAR4 agonist, and quantitative analysis across 38 mammalian species indicated enriched production by carnivores, with some (lion, tiger, serval, jaguar) releasing >1,000-fold more than other animals [35]. Mice and rats innately avoid 2-phenylethylamine upon first exposure, and enzymatic depletion of 2-phenylethylamine from lion urine impairs its repellent properties [35]. Genetically defined TAAR4 olfactory sensory neurons display unusually low threshold 2-phenylethylamine responses [17], and knockout of TAAR4 eliminates avoidance of 2-phenylethylamine and bobcat urine [39]. Together, these findings provide evidence that mTAAR4 is a kairomone receptor. Interestingly, the *Taar4* gene is conserved in many carnivores [40], and 2-phenylethylamine is proposed to be a tiger pheromone [41]. Perhaps 2-phenylethylamine and TAAR4 evoke different behaviors in predators and prey.

TAAR5

TAAR5 detects trimethylamine, an abundant and sexually dimorphic mouse odor that evokes species-specific behaviors [4,33]. TAAR5 detects male mouse urine with exquisite sensitivity due to high abundance of trimethylamine (5 mM) [4], and enzymatic depletion of trimethylamine from mouse urine abrogates responses [33]. Mice release >1,000-fold more trimethylamine than rats and some other rodents [33]. Recent evolutionary forces sculpted the *Mus* trimethylamine biosynthesis pathway, which involves both gut bacteria and host enzymes [33,42].

Trimethylamine is a byproduct of commensal microflora-mediated nutrient metabolism, and, in most species, catabolized by a host enzyme (FMO3) [42]. In mice, FMO3 expression is tightly repressed in kidney and male liver, leading to abundant and sexually dimorphic trimethylamine production [33]. Trimethylamine is also found in other microbial odor sources [7], so evoked perceptions may be context-dependent.

Presented alone, trimethylamine evokes species-specific behaviors. Rats and humans avoid trimethylamine [33,43], but mice display concentration-dependent responses with attraction to lower (urinary) levels and aversion to higher levels [33]. Perhaps predator aversion to trimethylamine provided the selective pressure for enriched production in mouse scent. TAAR5 knockout mice lose behavioral attraction to trimethylamine, and have decreased attraction to mouse scent [33]. However, avoidance of high trimethylamine persists in TAAR5 knockout mice [33], suggesting detection by another low-affinity receptor that mediates dominant aversion responses. Roles for another receptor are supported by TAAR5-independent trimethylamine anosmias in humans [32].

How does trimethylamine evoke species-specific behaviors? One possibility is that aversion- and attraction-mediating olfactory receptors display variable affinities across species. Mouse and rat TAAR5 have ~200-fold improved trimethylamine sensitivity compared with human and macaque orthologs [4,7,32,33], and perhaps an aversion-mediating olfactory receptor also has species-specific affinity. A second possibility, which does not invoke a second receptor, is that mouse and rat TAAR5 differentially couple to neural circuits associated with attraction and aversion. A third possibility is that mouse attraction to trimethylamine in scent marks involves learned override of a developmentally established aversion circuit. Neural systems that control behavioral responses to species-specific odors, such as TAAR4 and TAAR5 ligands, must be sufficiently dynamic across evolution to ensure species-appropriate behaviors.

TAAR13c

zTAAR13c detects rotting flesh odors through the lysine decomposition product cadaverine [25]. Structure-activity analysis reveals a preference for medium-sized, odd-chained diamines, and indicates a binding pocket with two distinct cation recognition sites [25]. Cadaverine activates zTAAR13c in olfactory sensory neurons, and evokes innate avoidance responses in zebrafish [25]. Cadaverine also repels mice, a behavior lost in TAAR cluster knockouts [39]. Identifying an mTAAR that recognizes cadaverine (mice lack a TAAR13 ortholog) would provide a valuable tool for mechanistic analysis of odor aversion behavior.

TAAR-activated neural circuits

Olfactory sensory neurons provide highly organized inputs to the olfactory bulb at specialized structures termed glomeruli [44,45]. TAAR-expressing sensory neurons converge on glomeruli of stereotyped position within a dorsomedial domain (Figure 4A) [14,15]. Interestingly, TAAR4 and TAAR5 neurons, which mediate different behaviors, target adjacent glomeruli (Figure 4B) [14]. Furthermore, neurons that initially express a *Taar5* pseudogene can secondarily express *Taar4* [14], suggesting that coupling to aversion or attraction circuitry may occur after receptor choice. *In vivo* calcium imaging revealed that

TAAR glomeruli detect amines and natural odors previously identified in cell culture studies [39]. Amine-detecting glomeruli are also found in olfactory bulb regions that lack TAAR input [46], which makes sense since TAARs recognize some but not all amine odors. Interestingly, 2-phenylethylamine responses are sparser in the olfactory bulb [39] than olfactory epithelium [35], and of imaging-accessible glomeruli, are apparently confined to the TAAR4 glomerulus [39], perhaps due to lateral inhibition through intrinsic olfactory bulb circuits.

TAAR-activated neural circuits are uncharacterized beyond the olfactory bulb. Perhaps TAAR4 and TAAR5 provide stereotyped inputs to higher-order olfactory nuclei that mediate innate odor aversion and attraction behaviors, such as the cortical amygdala [47]. Future studies are generally needed to understand the structure and function of neural circuits that process odor valence, and how connections from particular classes of sensory neurons are specified [48].

Conclusion

TAARs, like ORs, provide an ever-changing landscape for sensory biology, with the TAAR repertoire expanding, contracting, and mutating across the phylogeny. Differently sized families of gustatory GPCRs mediate fundamentally distinct functions: bitter versus savory/sweet [49]. Several TAARs detect volatile and aversive amines, but the olfactory system is capable of discarding ligand-based or function-based constraints on TAAR evolution. Particular TAARs have mutated to recognize new ligands, with almost an entire teleost clade losing the canonical amine-recognition motif. Furthermore, while some TAARs detect aversive odors, TAAR-mediated behaviors can vary across species. Perhaps the tremendous flexibility inherent to olfactory system development allows for lineage-specific functional changes in the TAAR family. The ability of particular TAARs to mediate aversion and attraction behavior provides an exciting opportunity for mechanistic unraveling of odor valence encoding.

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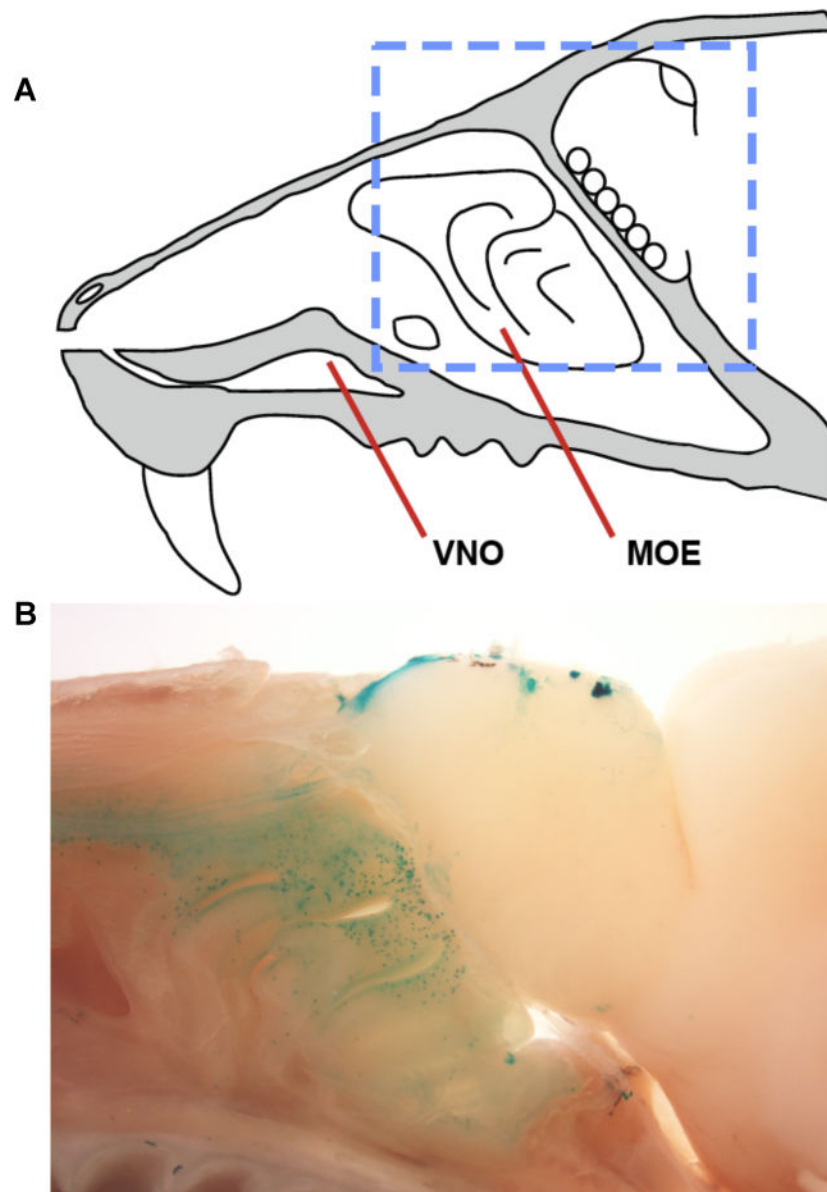


Figure 1. TAAR expression in the olfactory system

(A) Anatomy of the mouse nose in sagittal view, with major chemosensory structures displayed (VNO- vomeronasal organ; MOE-main olfactory epithelium). (B) A sagittal section of olfactory tissue with TAAR-expressing neurons genetically labeled. Images are derived from TAAR5 knockout mice, in which β -galactosidase is expressed from the endogenous *Taar5* locus. Labeled neurons include a subset of all TAAR neuron types (see discussion of receptor re-selection following *Taar* pseudogene expression), and are visualized by wholemount X-gal staining. The imaged region is indicated in panel A by the blue dashed box. Multiple TAAR-innervating glomeruli are observed in the olfactory bulb, as shown in Figure 4A. Image in panel A is adapted from [50].

TAAR	Species	Expression	Ligand (EC₅₀)	Odor source	Behavior
1	h, m, r, z	non-olfactory	trace amines, other		
2	h, m, r	OE (m: dorsal)			
3	m, r	OE (m: dorsal)	isopentylamine A (10 μM)		Aversion (m)
4	m, r	OE (m: dorsal)	2-phenylethylamine B (3 μM)	carnivore urine	Aversion (m*, r)
5	h, m, r	OE (m: dorsal)	trimethylamine C (300 nM)	male mouse urine	Attraction (m*) Aversion (r, h)
6	h, m, r	OE (m: ventral)			
7s	m (5), r (7)	OE (m: both)	<i>N,N</i> -dimethylalkylamines D (1-30 μM)		
8s	h, m (3), r (3)	OE (m: dorsal)	<i>N</i> -methylpiperidine E (100 nM)		
9	h, m, r	OE (m: dorsal)	<i>N</i> -methylpiperidine E (20 μM)		Aversion (m)
13c	z	OE	cadaverine F (20 μM)	decomposing tissue	Aversion (z, m)

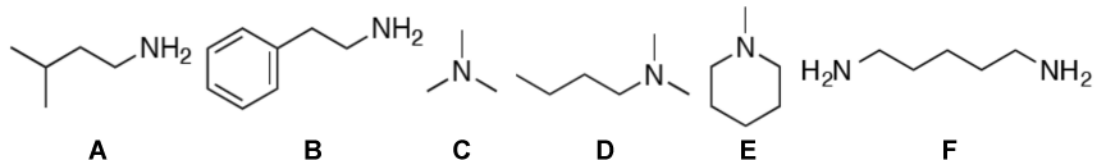


Figure 2. TAAR ligands, expression patterns, and behavioral roles

Human (h), mouse (m), rat (r), and/or zebrafish (z) genomes contain genes from indicated TAAR subfamilies. Mice and rats have multiple TAAR7s and TAAR8s, as indicated in parenthesis. All mammalian subfamilies, but not all teleost subfamilies, are depicted. All TAARs except TAAR1 are expressed in olfactory epithelium (OE), and in mouse, all TAARs are located dorsally except TAAR6, TAAR7a, and TAAR7b. The identities, ecological sources, and evoked behavioral responses of TAAR ligands are shown (*behavioral response lost in TAAR knockout mice, EC₅₀ determined in HEK-293 cells).

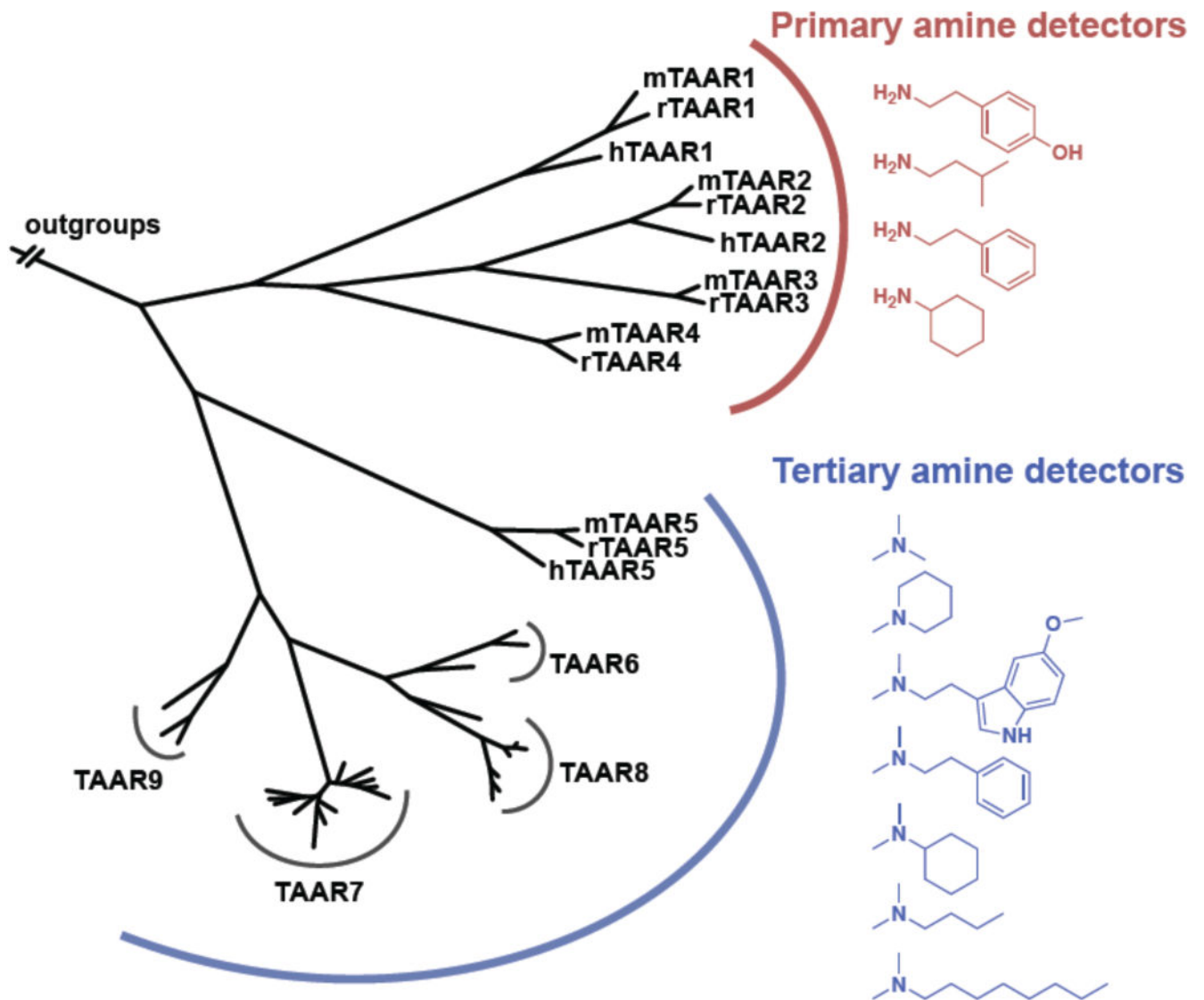


Figure 3. Mapping odor preferences on the mammalian TAAR phylogeny

Two branches of the TAAR phylogenetic tree prefer primary amines (TAARs 1–4) and tertiary amines (TAARs 5–9). zTAAR13c is not depicted but clusters with primary amine detectors. A third major TAAR clade evolved in teleosts (not shown), with almost all losing the canonical Asp^{3.32} amine recognition site. Image adapted from [18].

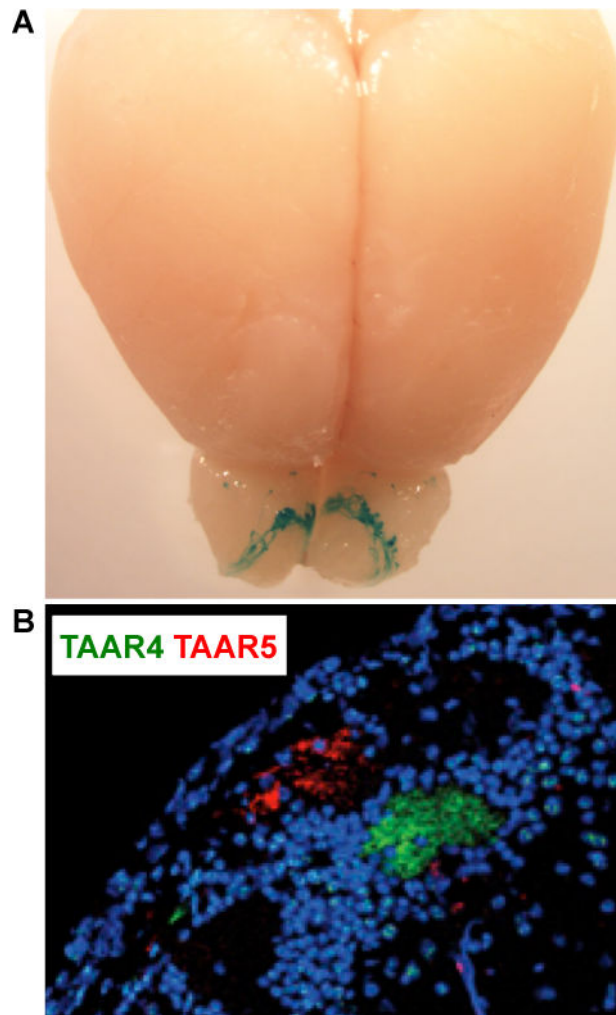


Figure 4. Projections of TAAR neurons in the brain

(A) Wholemount view of TAAR inputs in the olfactory bulb. Subsets of all TAAR-expressing neuron types were simultaneously visualized using genetic approaches, as described for Figure 1B. (B) Two-color immunohistochemistry for TAAR4 (green) and TAAR5 (red) labels adjacent glomeruli in the olfactory bulb. Image adapted from [14].