Cellular and Molecular Neurobiology (2020) 40:257–272
https://doi.org/10.1007/s10571-019-00774-5

ORIGINAL RESEARCH

TAAR Agonists

Zhengrong Xu[1,3,4] **· Qian Li**[1,2]

Received: 28 July 2019 / Accepted: 7 December 2019 / Published online: 17 December 2019
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Abstract

Trace amine-associated receptors (TAARs) are a family of G protein-coupled receptors (GPCRs) that are evolutionarily conserved in vertebrates. The first discovered TAAR1 is mainly expressed in the brain, and is able to detect low abundant trace amines. TAAR1 is also activated by several synthetic compounds and psychostimulant drugs like amphetamine. Activation of TAAR1 by specific agonists can regulate the classical monoaminergic systems in the brain. Further studies have revealed that other TAAR family members are highly expressed in the olfactory system which are termed olfactory TAARs. In vertebrates, olfactory TAARs can specifically recognize volatile or water-soluble amines. Some of these TAAR agonists are produced by decarboxylation of amino acids. In addition, some TAAR agonists are ethological odors that mediate animal innate behaviors. In this study, we provide a comprehensive review of TAAR agonists, including their structures, biosynthesis pathways, and functions.

Keywords Trace amine-associated receptor (TAAR) · G protein-coupled receptor (GPCR) · Olfactory receptor · Agonist · Trace amines · Volatile amines

Introduction

Trace amine-associated receptors (TAARs) constitute a distinct subfamily of class A G protein-coupled receptors (GPCRs) (Lindemann and Hoener 2005). There are six functional TAARs in human, 15 in mouse, 17 in rat, and 112 in zebrafish (Hussain et al. 2009; Lindemann et al. 2005). The number of *Taar* genes varies in other vertebrate species revealed by genome-wide search, showing a relatively large expansion in teleosts (Azzouzi et al. 2015; Eyun et al. 2016; Gao et al. 2017; Hashiguchi and Nishida 2007; Hussain et al. 2009; Tessarolo et al. 2014). Among all the TAARs, TAAR1 is mainly expressed in different regions of the brain, while low expression of TAAR1 is also observed in other tissues (stomach, intestines, testes, leukocytes, et al.) (Rutigliano et al. 2017). In contrast, all other TAARs are highly expressed in the olfactory system and function as olfactory receptors. Thus, all the TAARs except TAAR1 are also referred to as olfactory TAARs.

Since the discovery of TAARs, researchers have made great progress in identifying the agonists for both non-olfactory and olfactory TAARs. Trace amines are the first compounds characterized as ligands for non-olfactory TAAR1. Common trace amines include β-phenylethylamine, para-tyramine, meta-tyramine, tryptamine, para-octopamine, and meta-octopamine (Berry 2004). TAAR1 can also recognize other endogenous ligands such as dopamine, serotonin, thyroid hormone-derivative 3-iodothyronamine (T_1AM, or 3IT), and catechol-O-methyl transferase products 3-methoxytyramine (3-MT) (Panas et al. 2010; Scanlan et al. 2004; Sotnikova et al. 2010). In addition, plenty of amine derivatives, synthetic compounds, and psychostimulant drugs act as TAAR1 agonists. On the other hand, olfactory TAARs specifically recognize amines in vertebrates, including monoamines, diamines, and polyamines (Hussain et al. 2013; Li et al. 2015; Liberles and Buck 2006; Saraiva et al. 2016). Those olfactory TAAR agonists identified by

✉ Qian Li
liqian@shsmu.edu.cn

1 Collaborative Innovation Center for Brain Science, Department of Anatomy and Physiology, Shanghai Jiao Tong University School of Medicine, Shanghai 200025, China

2 Shanghai Research Center for Brain Science and Brain-Inspired Intelligence, Shanghai 201210, China

3 Department of Otolaryngology Head and Neck Surgery, Jiangsu Provincial Key Medical Discipline (Laboratory), Affiliated Drum Tower Hospital of Nanjing University Medical School, Nanjing 210008, China

4 Research Institute of Otolaryngology, Nanjing 210008, China

in vitro and in vivo assays are mostly consistent. Olfactory TAARs detect their specific agonists with distinct recognition motifs. In addition, some olfactory TAAR agonists are enriched in natural animal specimens, and can elicit distinct animal behaviors.

In this review, we aim to comprehensively summarize the known agonists for TAARs. We start with a brief summary of TAAR evolution and TAAR signaling pathways. Next, the agonists for non-olfactory TAAR1 and olfactory TAARs are discussed in details. We further provide the current knowledge on the physiological effects of those agonists. We also discuss about the biosynthesis pathways of TAAR agonists, and the structural basis of TAARs for agonist recognition.

History and Evolution of TAARs

TAARs were initially discovered by two groups in 2001 (Borowsky et al. 2001; Bunzow et al. 2001). Using a degenerate PCR approach, Borowsky et al. identified TAARs in mouse, rat, and human with broad tissue expression patterns (Borowsky et al. 2001). The authors originally named TAARs as trace amine receptors (short for TA_X) based on the fact that two TAAR members (TA_1/TAAR1 and TA_2/TAAR4) detect a number of trace amines. It is the first time to identify a vertebrate GPCR family as receptors detecting trace amines. And this receptor family is distinct from trace amine receptor families found in invertebrates (Zucchi et al. 2006). In another independent study, Bunzow and colleagues performed RT-PCR in multiple cell lines to search for catecholamine receptors, leading to the discovery of the rat trace amine receptor 1 (rTAR1/TAAR1) (Bunzow et al. 2001). Similar trace amine agonists as reported by Borowsky et al. were identified for rTAR1. In addition, Bunzow et al. extended the findings of rTAR1 agonists to psychostimulant and hallucinogenic amphetamine, numerous ergoline derivatives, adrenergic ligands, and 3-methylated metabolites of the catecholamine neurotransmitters. The following studies have shown that all the mammalian *Taar* genes form a single cluster in the genome. Therefore, the nomenclature of mammalian TAARs was proposed in 2005 based on their chromosomal positions, and has been well accepted (Lindemann and Hoener 2005). However, *Taar* genes may be located in two or more chromosomes in other vertebrates, especially in teleosts. Those *Taar* genes were named according to the evolutionary relationships with mammalian *Taar* genes (Hussain et al. 2009).

Evolutionary studies suggest that *Taar* genes are distantly related to biogenic amine receptors and are most likely evolved from 5-hydroxytryptamine receptor 4 (*Htr4*) (Hashiguchi and Nishida 2007; Li and Liberles 2016). However, there are still debates about the birth of *Taa*r genes. Some researchers believed that the *Taar* gene family emerged early in jawless vertebrates such as sea lamprey (Hashiguchi and Nishida 2007; Libants et al. 2009). While others suggested that *Taar* genes originated after the emergence of jawed fish, as all the homologous genes in sea lamprey formed a monophyletic clade in the *Taar* phylogenetic tree. Furthermore, those homologous genes lack the canonical TAAR motif in the transmembrane α-helix VII, and were named *Taar-like* genes (Eyun et al. 2016; Hussain et al. 2009; Li and Liberles 2016; Scott et al. 2019). The most ancestral *Taar* genes containing the TAAR motif are uncovered in cartilaginous fishes, including elephant shark, catshark, white shark, whale shark, which are basal to all jawed vertebrates (Hussain et al. 2009; Marra et al. 2019; Sharma et al. 2019). Nevertheless, the evolutionary relationship of *Taar-like*, *Taar*, and *Htr4* genes still requires further investigation.

The number of functional *Taar* genes varies among species, with 6 in human, 15 in mouse, and 17 in rat. *Taar* genes are largely expanded in teleosts including zebrafish (112 *Taar* genes), suggesting an important role of TAARs in aquatic chemosensation. In primates, *Taar* genes undergo accelerated pseudogenization likely associated with their arboreal inhabitants (Eyun 2019). Phylogenetic tree construction classified *Taar* genes into three clades (Ferrero et al. 2012; Hussain et al. 2009; Li et al. 2015). Mammalian *Taar* genes are only found in clade I and II, while clade III is teleost-specific. In mammals, TAAR1-4 belong to clade I receptors and TAAR5-9 belong to clade II receptors. Interestingly, their phylogenetic separation is correlated with the distinct agonist preferences for primary or tertiary amines (Ferrero et al. 2012). In teleosts, the large expansion of clade III TAARs could be resulted from the fish-specific third round whole-genome duplication (3R-WGD) and subsequent gene duplications and mutations.

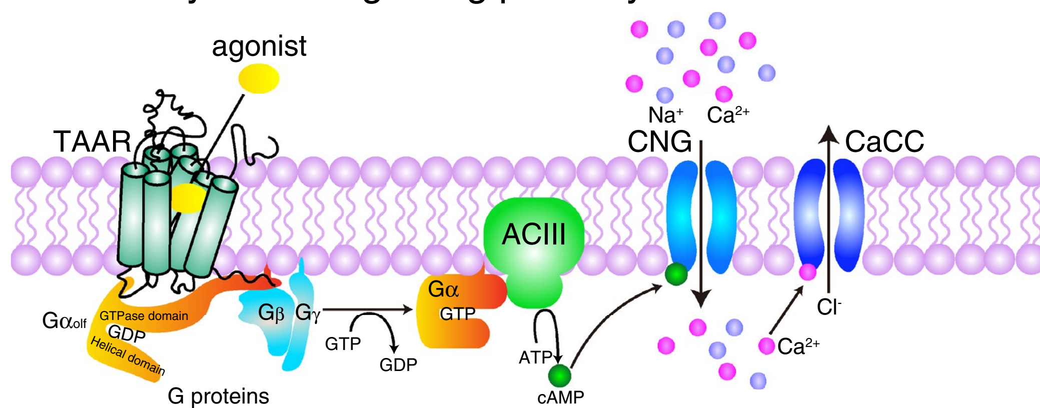
TAAR Signaling Pathways

The mRNA of TAAR1 can be detected in a variety of tissues, including brain, kidney, lung and small intestines. In the brain, TAAR1 is expressed in several different regions such as amygdala, cerebellum, hippocampus, hypothalamus, dorsal raphe nucleus, and the nucleus of the solitary tract (Borowsky et al. 2001; Lindemann et al. 2008). In contrast, all the other TAARs except TAAR1 are highly expressed in the main olfactory epithelium (Liberles and Buck 2006). Further studies strongly suggest that those TAARs function as a distinct subfamily of olfactory receptors, which is evolutionarily distinct from the classical odorant receptor (OR) family (Grus and Zhang 2008). Thus, TAAR1 and all the other TAARs are referred to as non-olfactory TAAR and olfactory TAARs, respectively. It is worth noting that the olfactory TAARs are also found in other tissues, albeit with much lower expression levels (Babusyte et al. 2013;

Chiellini et al. 2012; Ito et al. 2009; Kubo et al. 2015; Nelson et al. 2007).

Due to the different expression patterns, the non-olfactory TAAR1 and olfactory TAARs utilize different signaling pathways (Fig. 1). TAAR1 is commonly coupled to $G\alpha_s$, which increases the intracellular concentration of cyclic adenosine monophosphate (cAMP) and further activates downstream signaling molecules (Bunzow et al. 2001). Besides, TAAR1 can also recruit $G\alpha_q$ and $G\alpha_{13}$ (Lewin et al. 2009; Underhill et al. 2019). On the other side, TAAR1 activates Gβγ proteins and eventually leads to outward K^+ current through G protein-coupled inwardly rectifying potassium (GIRK) channels, reducing the basal firing frequency of dopaminergic and serotonergic neurons (Bradaia et al. 2009; Revel et al. 2011). G protein-independent β-arrestin 2 cascade is also involved in TAAR1 signaling pathway (Fig. 1b) (Harmeier et al. 2015). In the olfactory system, TAARs are coupled to the olfactory type Gα proteins ($G\alpha_{olf}$) that activate adenylyl cyclase type III (ACIII) and increase the cAMP production (Liberles and Buck 2006). cAMP directly activates the cyclic nucleotide-gated channels (CNG channels) to permit Na^+ and Ca^{2+} entry, which depolarizes olfactory sensory neurons (OSNs). This depolarization is further amplified by Cl^- efflux through opening of calcium-gated chloride channels (CaCCs) (Fig. 1a) (Kaupp 2010). Extraolfactory signaling pathways of the olfactory

a Olfactory TAAR signaling pathway



b Other TAAR signaling pathways

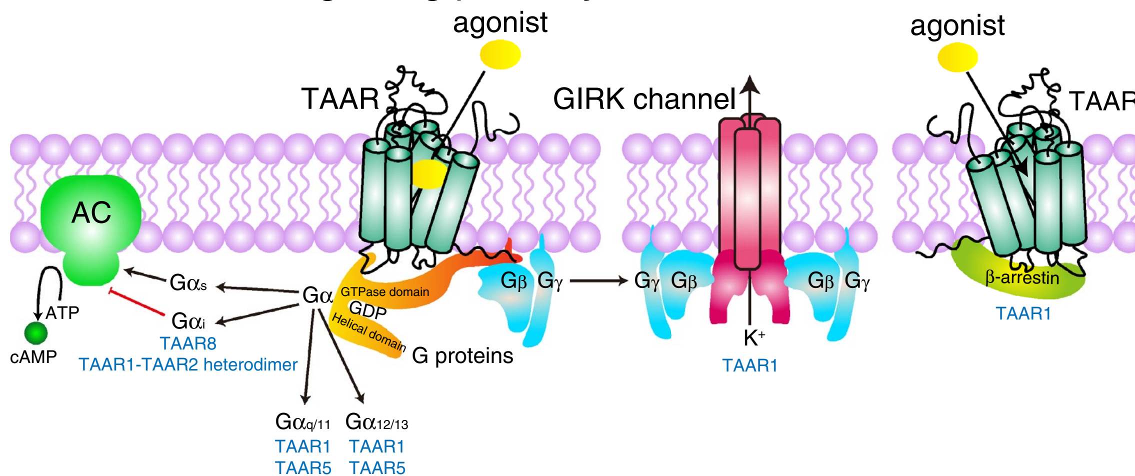
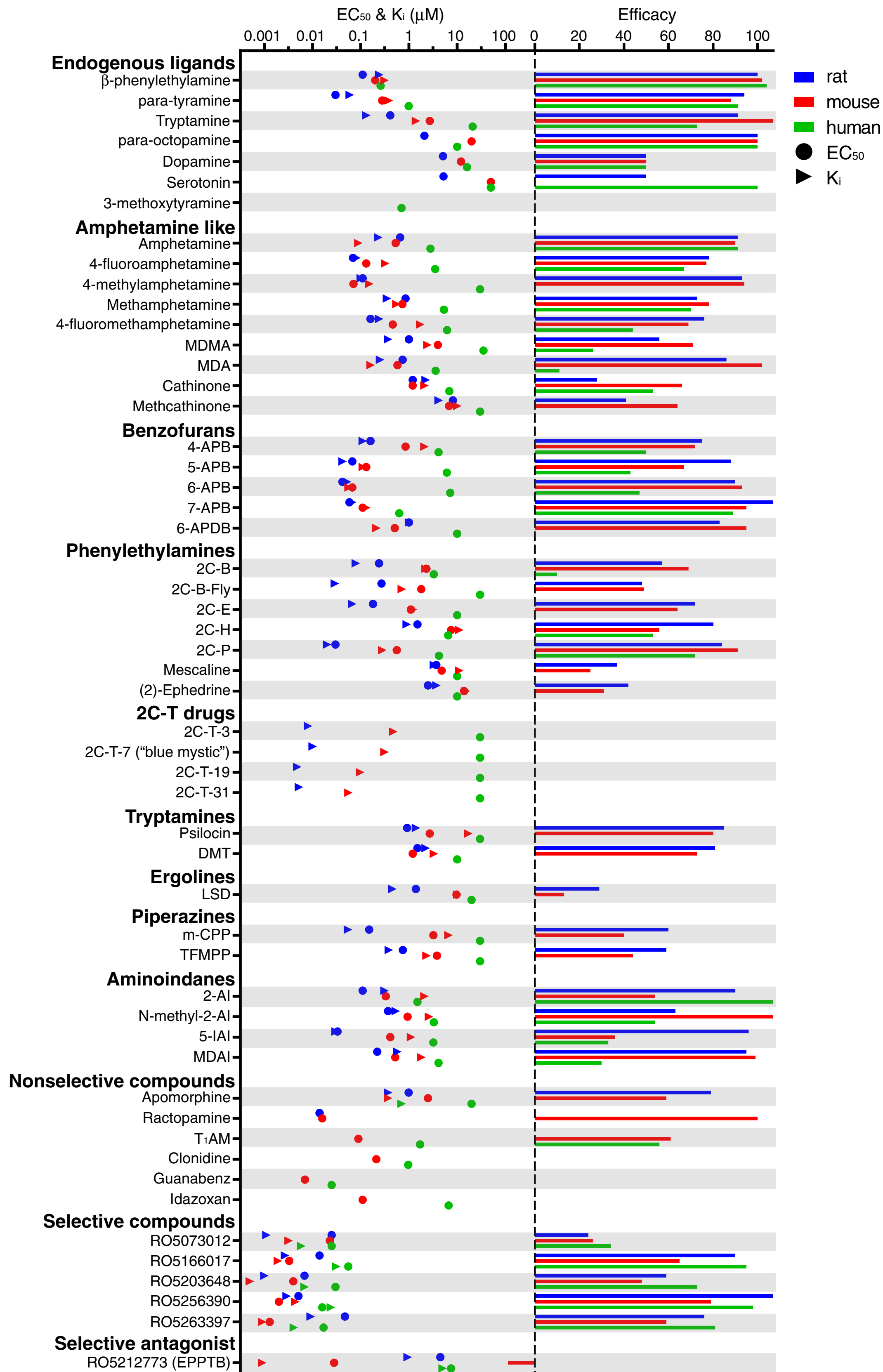


Fig. 1 TAAR signal transduction pathways. **a** The odor-induced signaling pathway in OSNs. The binding of odorant agonist to the olfactory TAARs activates $G\alpha_{olf}$, ACIII, CNG channel, and CaCC, resulting in neuron depolarization. **b** Other signaling pathways of non-olfactory TAAR1 and ectopically expressed olfactory TAARs. There are G protein-dependent (Gα- and Gβγ-dependent) and G protein-independent pathways. Left, almost all TAARs activate $G\alpha_s$ and AC to increase cAMP levels. Some TAARs are coupled to $G\alpha_i$, $G\alpha_{q/11}$, $G\alpha_{12/13}$ cascades. Middle, TAAR1 can also active GIRK channels through Gβγ proteins. Right, activation of TAAR1 is able to recruit G protein-independent pathways that signal through β-arrestin. *$G\alpha_{olf}$* olfactory-specific guanosine triphosphate (GTP)-binding protein α subunit, *ACIII* adenylyl cyclase type III, *CNG channels* cyclic nucleotide-gated ion channels, *CaCC* calcium-activated chloride channels, *GIRK channels* G protein-coupled inwardly rectifying potassium channels



EC₅₀ & Kᵢ (µM)
0.001 0.01 0.1 1 10 100
Efficacy
0 20 40 60 80 100
rat
mouse
human
EC₅₀
Kᵢ
Endogenous ligands
β-phenylethylamine
para-tyramine
Tryptamine
para-octopamine
Dopamine
Serotonin
3-methoxytyramine
Amphetamine like
Amphetamine
4-fluoroamphetamine
4-methylamphetamine
Methamphetamine
4-fluoromethamphetamine
MDMA
MDA
Cathinone
Methcathinone
Benzofurans
4-APB
5-APB
6-APB
7-APB
6-APDB
Phenylethylamines
2C-B
2C-B-Fly
2C-E
2C-H
2C-P
Mescaline
(2)-Ephedrine
2C-T drugs
2C-T-3
2C-T-7 ("blue mystic")
2C-T-19
2C-T-31
Tryptamines
Psilocin
DMT
Ergolines
LSD
Piperazines
m-CPP
TFMPP
Aminoindanes
2-AI
N-methyl-2-AI
5-IAI
MDAI
Nonselective compounds
Apomorphine
Ractopamine
T₁AM
Clonidine
Guanabenz
Idazoxan
Selective compounds
RO5073012
RO5166017
RO5203648
RO5256390
RO5263397
Selective antagonist
RO5212773 (EPPTB)

◂**Fig. 2** Summary of agonists for TAAR1 in rat, mouse, and human. TAAR1 agonists are categorized into endogenous ligands, selected psychoactive ligands, and selective synthetic compounds. A selective inverse agonist EPPTB for TAAR1 is also included. Data are modified from Gainetdinov et al. (2018). EC_{50} and K_i are shown in micromolar, and the values for efficacy are calculated using the maximal cAMP levels of rat TAAR1 response to β-phenylethylamine as 100. IC_{50} values of EPPTB are presented in lieu of EC_{50} values. Blue, red, and green colors represent rat, mouse, and human, respectively. Circle and triangle denote EC_{50} and K_i values. *MDMA* 3,4-methyl enedioxy methamphetamine, *MDA* 3,4-methylenedioxyamphetamine, *4-APB* 4-(2-aminopropyl)benzofuran, *5-APB* 5-(2-aminopropyl)benzofuran, *6-APB* 6-(2-aminopropyl)benzofuran, *7-APB* 7-(2-aminopropyl)benzofuran, *6-APDB* 6-aminopropyl-2,3-dihydrobenzofuran, *2C-B* 2,5-dimethoxy-4-bromo-phenethylamine, *2C-B-Fly* 8-bromo-2,3,6,7-benzo-dihydro-difuranethylamine, *2C-E* 4-ethyl-2,5-dimethoxyphenethylamine, *2C-H* 2,5-dimethoxyphenethylamine, *2C-P* 2,5-dimethoxy-4-propyl-phenethylamine, *DMT N*,*N*-dimethyltryptamine, *LSD* lysergic acid diethylamide, *2C-T-3* 2,5-dimethoxy-4-(beta-methallyl)thiophenethylamine, *2C-T-7* 2,5-dimethoxy-4-(*n*)-propylthiophenethylamin, *2C-T-19* 2,5-dimethoxy-4-*n*-butylthiophenethylamine, *2C-T-31* 2,5-dimethoxy-4-(4-trifluoromethylbenzylthio)phenethylamine, *m-CPP* m-chlorophenylpiperazine, *TFMPP* trifluoromethylphenylpiperazine, *2-AI* 2-aminoindane, *N-methyl-2-AI N*-methyl-2-aminoindane, *5-IAI* 5-iodo-2-aminoindane, *MDAI* 5,6-methylenedioxy-2-aminoindane

TAARs are slightly different from those in the olfactory system (Fig. 1b). In the other tissues, majority of the olfactory TAARs are coupled to $G\alpha_s$. However, there are reports showing that some olfactory TAARs are coupled to different Gα proteins. For instance, basal activity of TAAR8 might be mediated by $G\alpha_i$ to reduce the cAMP levels in heterologous cells (Muhlhaus et al. 2014). Activation of TAAR5 could also lead to $G\alpha_{q/11}$- and $G\alpha_{12/13}$-dependent MAP kinase cascades (Dinter et al. 2015c). Interestingly, TAAR2 can form heterodimer with TAAR1 in polymorphonuclear neutrophils (PMN) that is required for the chemotactic response (Babusyte et al. 2013). The signaling of TAAR1–TAAR2 heterodimer may be switched to $G\alpha_i$ cascade (Malki et al. 2015). In a word, the signaling pathways of TAARs are more complicated than previously thought and acquire careful investigation in different systems.

Agonists of Non-olfactory TAAR1

The agonists of TAARs were mainly identified in the heterologous cell lines based on the $G\alpha_s$-coupled signaling pathways (Li 2018). Among all the TAARs, TAAR1 is the first subtype whose agonists have been thoroughly investigated. TAAR1 has a broadly tuned agonist profile that includes trace amines, classical biogenic amines, thyronamines, psychostimulant drugs, and synthetic amine derivatives. So far, more than 50 agonists have been identified or synthesized for TAAR1 (Fig. 2). The affinities and efficacies of different agonists for TAAR1 from different species vary tremendously, with EC_{50} ranging from 5 nM to 50 μM. For a more detailed discussion of TAAR1 agonists, we recommend several recently published excellent reviews (Berry et al. 2017; Cichero and Tonelli 2017b; Gainetdinov et al. 2018; Rutigliano et al. 2017; Schwartz et al. 2018). In this study, we only select some high-affinity TAAR1 agonists for brief discussion.

Trace Amines

Trace amines are the first endogenous products characterized as TAAR1 agonists (Borowsky et al. 2001). Trace amines were named because of their much lower concentration (< 10 ng/g tissue) that are at least 100-fold lower than canonical biogenic amines like dopamine, epinephrine, norepinephrine, and serotonin in the brain (Berry 2004; Boulton 1974). Trace amines and classical biogenic amines have similar structures and pharmacologic properties. Their biosynthesis and metabolism pathways are also very alike, utilizing the same aromatic L-amino acid decarboxylase (AADC) and Monoamine oxidase (MAO) enzymes (Cichero and Tonelli 2017b). Since the two groups independently discovered TAAR1 in 2001, people have realized that trace amines are high-affinity TAAR1 agonists (Borowsky et al. 2001; Bunzow et al. 2001). Those trace amines consist of β-phenylethylamine, para-tyramine, tryptamine, and para-octopamine. In the heterologous cell lines, β-phenylethylamine and para-tyramine activate TAAR1 from different species (mouse, rat, and human) with the lowest EC_{50} in the range of 0.1–1 μM (Fig. 2). However, EC_{50} values for tryptamine and para-octopamine are 0.4–21 μM and 2–20 μM, respectively (Fig. 2). Trace amines can regulate the dopaminergic, serotoninergic, and adrenergic systems in the brain (Berry 2004). In addition, trace amines can function in the peripheral organs to regulate vasoconstrictor and vasodilator responses (Anwar et al. 2012; Broadley et al. 2013), induce gastrin release (Dial et al. 1991), and enhance the ability of microbiota to adhere to epithelial cells (Fernandez de Palencia et al. 2011; Luqman et al. 2018). However, it is still unclear if those effects of trace amines are mediated by TAAR1.

Other Endogenous Ligands

Apart from trace amines, TAAR1 can also be activated by a range of endogenous molecules including thyroid hormone-derivative T_1AM and 3-MT (Panas et al. 2010; Scanlan et al. 2004; Sotnikova et al. 2010). Besides, classical biogenic amines such as dopamine and serotonin are able to activate TAAR1, although in a much less potent manner (Fig. 2) (Borowsky et al. 2001).

Like trace amines, T_1AM is present in many rodent tissues (heart, liver, kidney, white adipose, skeletal muscle,

stomach, lung, and brain) as well as human blood at nanomolar levels (Assadi-Porter et al. 2018; Hoefig et al. 2011; Saba et al. 2010; Zucchi et al. 2014). It can affect learning, memory, pain perception, sleep, thermoregulation, energy metabolism, neuroprotection, and neuromodulation (Kohrle and Biebermann 2019). T_1AM is high-affinity agonist of TAAR1 with EC_{50} range from 0.01 to 1.7 μM (Fig. 2) (Scanlan et al. 2004). However, TAAR1 is not the sole target of T_1AM. It has been reported that T_1AM acts as an inverse agonist for human TAAR5 (Dinter et al. 2015c). It also activates TAAR2 (Babusyte et al. 2013; Cichero and Tonelli 2017a), and other transmembrane receptors, such as α_{2A} adrenergic receptors (Dinter et al. 2015a, b), β-adrenergic receptors (Dinter et al. 2015a; Kleinau et al. 2011), and muscarinic acetylcholine receptors (Laurino et al. 2016). Thus, the promiscuous nature of T_1AM calls for further careful investigation into the involvement of its targets including TAAR1.

Psychostimulant Drugs

Psychostimulant drugs like amphetamines, methamphetamine (METH), and numerous ergoline derivatives are also potent agonists for TAAR1 (Bunzow et al. 2001; Simmler et al. 2016). Amphetamine, i.e., alpha-methylphenethylamine, has an extra methyl group compared to β-phenylethylamine. It has been used for treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy (Heal et al. 2013). The primary actions of amphetamine are to promote monoamine release, inhibit monoamine reuptake, and probably inhibit MAO, which in turn increase the synaptic concentrations of catecholamines including norepinephrine and dopamine (Heal et al. 2013). The effects of amphetamine on reward, cognition, and physical performance result in amphetamine abuse and addiction (Clemow and Walker 2014; Rickli et al. 2019). Amphetamine might act on TAAR1 to activate $G\alpha_s$ pathway and phosphorylate monoamine transporter such as dopamine transporter (DAT), leading to its internalization and ceased transport (Bunzow et al. 2001; Miller 2011). Behaviorally, knockout of TAAR1 in mice leads to locomotor supersensitivity induced by amphetamine, although the connection to regulation of monoamine system is undetermined and needs further investigation (Achat-Mendes et al. 2012; Lindemann et al. 2008).

Synthetic TAAR1 Agonists

In addition to the endogenous amines, there are plenty of synthetic compounds targeting TAAR1 for therapeutic application. Considering that many of the endogenous TAAR1 ligands have other targets, it is necessary to search and design specific TAAR1 agonists to decipher and specifically modulate the function of TAAR1. Different synthetic substances have been screened by F. Hoffmann-La Roche Ltd., leading to the identification of five selective agonists for TAAR1. Those agonists include RO5166017 [(*S*)-4-[(ethyl-phenyl-amino)-methyl]-4,5-dihydro-oxazol-2-ylamine], RO5073012 [(4-chloro-phenyl)-(3H-imidazol-4-ylmethyl)], RO5203648 [(*S*)-4-(3,4-Dichloro-phenyl)-4,5-dihydro-oxazol-2ylamine], RO5256390 [(*S*)-4-((*S*)-2-phenyl-butyl)-4,5-dihydro-oxazol-2-ylamine], and RO5263397 [(*S*)-4-(3-fluoro-2-methyl-phenyl)-4,5-dihydro-oxazol-2-ylamine] (Galley et al. 2012; Revel et al. 2011, 2012, 2013). On the other hand, a selective TAAR1 antagonist, *N*-(3-Ethoxyphenyl)-4-pyrrolidin-1-yl-3-trifluoromethyl-benzamide (EPPTB), was described in 2009 (Bradaia et al. 2009).

All the selective TAAR1 agonists and antagonist have been used in several studies to unravel the physiological function of TAAR1 in the brain. TAAR1 agonists including RO5166017, RO5256390, and RO5263397 have proven to prevent psychostimulant-induced hyperlocomotion and stress-induced hyperthermia (Revel et al. 2011, 2013). Another TAAR1 partial agonist, RO5203648, showed clear antipsychotic- and antidepressant-like activities (Revel et al. 2012). RO5256390 has been shown to block the compulsive, binge-like eating behavior in rats (Ferragud et al. 2017). In addition, these selective agonists have been reported to suppress self-stimulation and compulsive behaviors induced by drugs including cocaine, METH, and nicotine (Cotter et al. 2015; Jing et al. 2014; Liu et al. 2018; Pei et al. 2014, 2015, 2017; Revel et al. 2012; Xue et al. 2018). Collectively, the synthetic TAAR1 agonists and antagonists have provided valuable tools to investigate the function of TAAR1, and have shed light on targeting TAAR1 for the treatment of mental disorders and drug addictions.

In addition, the selective TAAR1 agonists have been used to investigate the role of TAAR1 in other systems. Activation of TAAR1 by RO5166017 and RO5256390 promotes glucose-dependent insulin secretion in β-cells lines and human islets. Furthermore, treatment of the selective TAAR1 agonist in obese mice results in reduced food intake and body weight, suggesting the potential application of TAAR1 agonists for treatment of diabetes and obesity (Michael et al. 2019; Raab et al. 2016). Another TAAR1 agonist RO5203548 has been shown to increase TAAR1 expression and may be associated with miscarriages (Stavrou et al. 2018). Future application of the synthetic TAAR1 agonists will help to reveal the function of TAAR1 in a variety of systems.

Olfactory TAAR Agonists

All TAARs except TAAR1 are highly expressed in OSNs located in the main olfactory epithelium and function as a distinct family of olfactory receptors (Johnson et al. 2012; Liberles and Buck 2006; Pacifico et al. 2012). Like the

classical ORs, TAARs also follow the "one-neuron-one-receptor" rule, meaning that one and only one TAAR is expressed in each OSN (Liberles and Buck 2006; Serizawa et al. 2004). TAARs utilize the same signaling pathways as ORs (Fig. 1a) (Liberles and Buck 2006; Zhang et al. 2013). Furthermore, TAARs respond to a specialized set of chemicals, instruct OSNs to dedicated olfactory bulb regions, and mediate distinct animal behaviors, strongly suggesting that they constitute a specific olfactory subsystem (Johnson et al. 2012; Liberles and Buck 2006; Pacifico et al. 2012). As a note, the olfactory TAARs are also ectopically expressed in other tissues but with much lower expression levels, and will not be discussed in this review.

Olfactory TAAR Agonists Identified In Vitro

Using an in vitro heterologous system, Liberles and Buck performed a high-throughput screening of structurally diverse chemicals on mammalian olfactory TAARs and identified ligands for 4 mouse TAARs, all of which are volatile amines (Liberles and Buck 2006). In the following studies, several groups have identified ligands for many additional TAARs (Ferrero et al. 2012; Saraiva et al. 2016). So far, agonists for 16 mammalian olfactory TAARs, including 8 mouse TAARs, 6 rat TAARs, 1 macaque TAAR, and 1 human TAAR, have been identified using cAMP-based screening assays. Those TAARs recognize different volatile amines with EC_{50} values ranging from 0.032 to 650 μM (Fig. 3a, b). The most sensitive TAAR agonists include isoamylamine/isobutylamine (mouse TAAR3), β-phenylethylamine (mouse and rat TAAR4), trimethylamine (mouse, rat, macaque, and human TAAR5), *N,N*-dimethyloctylamine (mouse TAAR7b), *N,N*-dimethylcyclohexylamine (mouse TAAR7f), and *N*-methylpiperidine (rat TAAR8c) (Fig. 3a, b). In zebrafish, agonists for 12 out of 112 TAAR members have been discovered. As previously stated, zebrafish TAARs are phylogenetically clustered into clade I and clade III. Deorphaned clade I olfactory TAARs include TAAR10a, TAAR10b, TAAR12h, and TAAR12i that detect serotonin, tryptamine, β-phenylethylamine, and 3-MT. TAAR16c, TAAR16e, and TAAR16f belong to clade III TAARs and are able to detect *N*-methylpiperidine, *N,N*-dimethylcyclohexylamine, and isoamylamine, respectively. Other clade III TAARs, such as TAAR13a, TAAR13c, TAAR13d, TAAR13e, and TAAR14d recognize diamines including putrescine, cadaverine, histamine, and agmatine (Figs. 3, 4c) (Hussain et al. 2013; Li et al. 2015). Interestingly, a recent paper showed that a TAAR-like receptor, TAAR348 in sea lamprey, can be activated by spermine and its structural analog 1-naphthylacetyl spermine (nap-spermine). The authors also reported that another sea lamprey TAAR-like receptor, TAAR346a, responds to cadaverine (Scott et al. 2019).

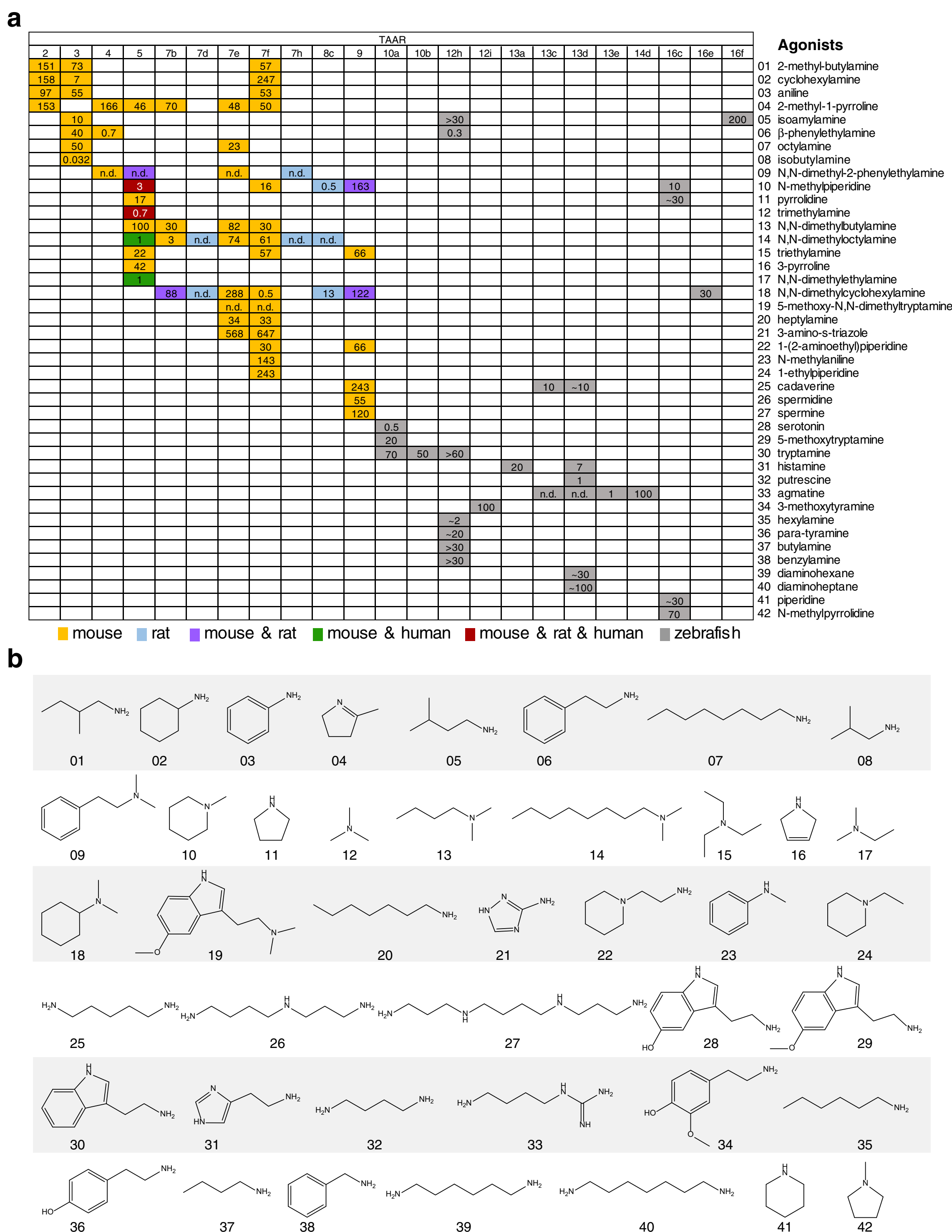
In Vivo Responses of Olfactory TAAR Agonists

The in vivo recordings of TAAR OSNs and their corresponding glomeruli validated TAAR ligands discovered in vitro, although they are more sensitive and more broadly tuned to different amines, especially at high concentrations (Zhang et al. 2013). TAAR OSNs are preferentially responsive to amine mixtures rather than other odorant mixtures, such as acids, aldehydes, and ketones. Further analysis on the responses of TAAR OSNs to different amines showed that they are very broadly tuned to amines. For example, the most effective stimuli for TAAR3 OSNs are isoamylamine and cyclohexylamine. But TAAR3 OSNs also responded to β-phenylethylamine, the most sensitive TAAR4 agonist, as well as trimethylamine, the most sensitive TAAR5 agonist (Zhang et al. 2013). The same phenomenon was observed using the in vivo imaging and behavioral assays. Low concentrations of isoamylamine, β-phenylethylamine, and trimethylamine specifically activate the TAAR3, TAAR4, and TAAR5 glomeruli, respectively. In contrast, the same ligands elicit responses in a number of distinct TAAR glomeruli with increasing concentrations (Dewan et al. 2018). Consistent with this finding, deletion of the *Taar* cluster (*Taar2-9*) causes more severe deficits in amine detection than loss of the most sensitive TAAR. However, knockout of the most sensitive TAAR does reduce the behavioral sensitivity to its ligand. Those results strongly suggest that although olfactory TAARs are broadly tuned; the ligand detection threshold is set by the single highest affinity TAAR (Dewan et al. 2018).

The detection thresholds for TAAR agonists in vivo are much lower than those in cultured cells (Table 1). For instance, TAAR4 OSNs recognize β-phenylethylamine with EC_{50} at 1 pM, while TAAR4 is activated by β-phenylethylamine with EC_{50} at 0.7 μM in vitro (Zhang et al. 2013). Similar findings were observed in TAAR-like receptors. Spermine activates sea lamprey TAAR348, the TAAR-like receptor, at concentrations higher than 1 μM, but attracts females at concentrations as low as 0.01 pM (Scott et al. 2019). The differences in specificity and sensitivity of TAAR ligands between the in vitro and in vivo assays may be partly due to lack of endogenous OSN proteins in the cultured cells. It is also possible that immature TAAR OSNs co-expressing multiple TAARs can recognize different ligands and were included in the analyses (Tan et al. 2015). Nevertheless, the most sensitive ligands identified are consistent across different experimental paradigms, and are validated in the knockout animals that will be discussed in the sections below.

Recognition Motifs of Olfactory TAAR Agonists

As previously mentioned, TAARs can be classified into three clades. Both clade I and II TAARs contain an aspartic



Agonists	TAAR 2	3	4	5	7b	7d	7e	7f	7h	8c	9	10a	10b	12h	12i	13a	13c	13d	13e	14d	16c	16e	16f
01 2-methyl-butylamine	151	73						57															
02 cyclohexylamine	158	7						247															
03 aniline	97	55						53															
04 2-methyl-1-pyrroline	153		166	46	70		48	50															
05 isoamylamine		10												>30									200
06 β-phenylethylamine		40	0.7											0.3									
07 octylamine		50					23																
08 isobutylamine		0.032																					
09 N,N-dimethyl-2-phenylethylamine			n.d.	n.d.			n.d.		n.d.														
10 N-methylpiperidine				3				16		0.5	163										10		
11 pyrrolidine				17																	~30		
12 trimethylamine				0.7																			
13 N,N-dimethylbutylamine				100	30		82	30															
14 N,N-dimethyloctylamine				1	3	n.d.	74	61	n.d.	n.d.													
15 triethylamine				22				57			66												
16 3-pyrroline				42																			
17 N,N-dimethylethylamine				1																			
18 N,N-dimethylcyclohexylamine					88	n.d.	288	0.5		13	122											30	
19 5-methoxy-N,N-dimethyltryptamine							n.d.	n.d.															
20 heptylamine							34	33															
21 3-amino-s-triazole							568	647															
22 1-(2-aminoethyl)piperidine								30			66												
23 N-methylaniline								143															
24 1-ethylpiperidine								243															
25 cadaverine											243						10	~10					
26 spermidine											55												
27 spermine											120												
28 serotonin												0.5											
29 5-methoxytryptamine												20											
30 tryptamine												70	50	>60									
31 histamine																20		7					
32 putrescine																		1					
33 agmatine																	n.d.	n.d.	1	100			
34 3-methoxytyramine															100								
35 hexylamine														~2									
36 para-tyramine														~20									
37 butylamine														>30									
38 benzylamine														>30									
39 diaminohexane																		~30					
40 diaminoheptane																		~100					
41 piperidine																					~30		
42 N-methylpyrrolidine																					70		

Fig. 3 Summary of agonists for olfactory TAARs in rat, mouse, human, and zebrafish. The table shows the names (**a**) and structures (**b**) of agonists for TAARs from different species. The numbers in the table represent EC_{50} (μM) values of each TAAR agonist. Mouse, rat, and zebrafish TAARs are colored in orange, light blue, and gray, respectively. While violet color marks TAARs in mouse and rat, green color marks TAARs in mouse and human, and dark red marks TAARs in mouse, rat, and human. Only EC_{50} values of the mouse TAAR agonist are shown in violet, green, and dark red cells. Data are extracted from these papers (Ferrero et al. 2012; Harmeier et al. 2018; Li et al. 2015; Saraiva et al. 2016). *n.d.* not determined

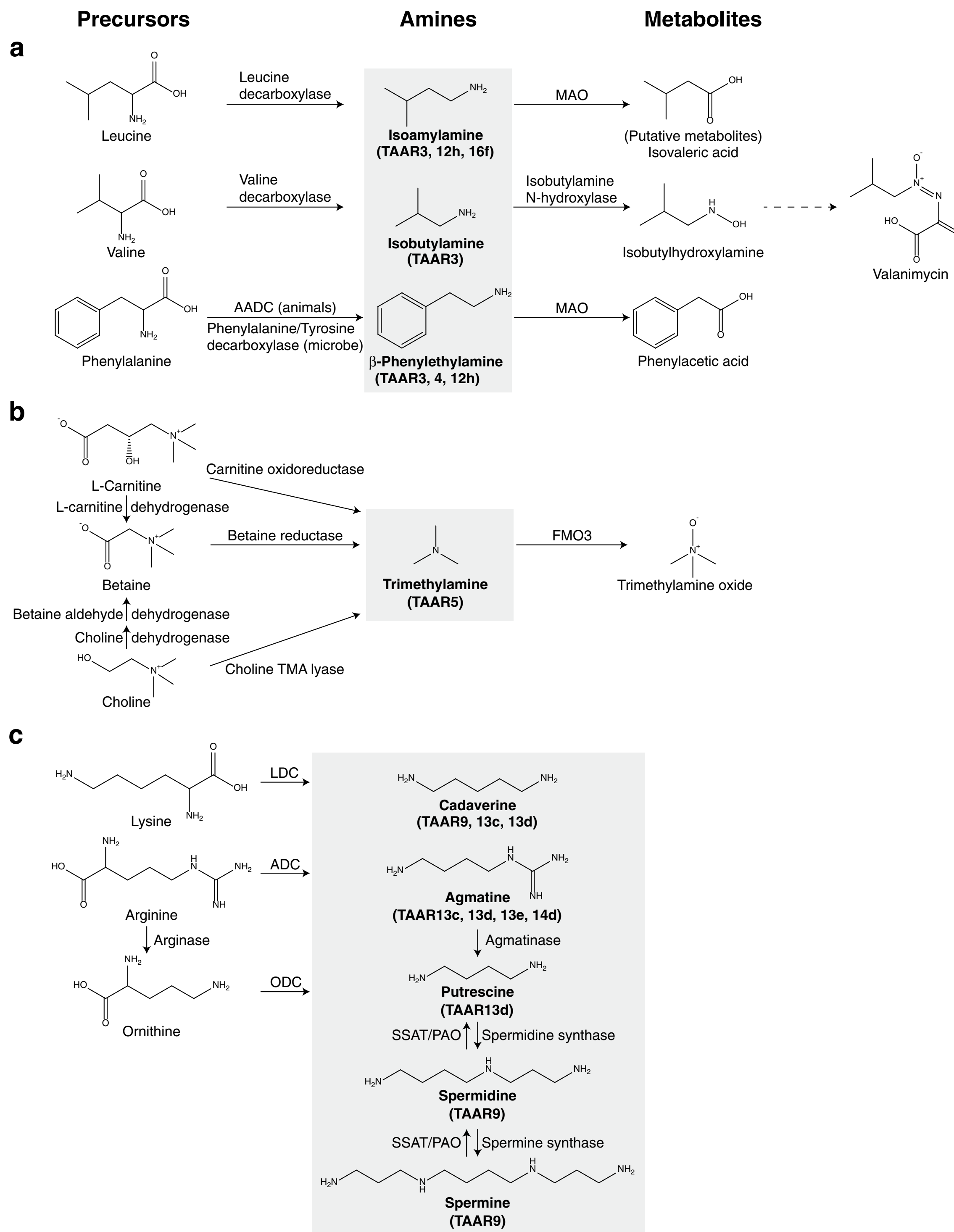


Fig. 4 Biosynthetic and metabolic routes for olfactory TAAR agonists. The precursors, amines, and metabolites in the biosynthesis pathways of olfactory TAAR agonists are listed. Amines are highlighted in the gray boxes. The known TAARs recognizing amines are listed underneath the ligands. **a** Biosynthesis pathways of TAAR3 and TAAR4 agonists. **b** Microbial metabolic routes of the TAAR5 agonist, trimethylamine, from food containing L-carnitine, betaine, and choline. **c** Biosynthesis pathways for diamines and polyamines, including cadaverine, agmatine, putrescine, spermidine, and spermine. *MAO* monoamine oxidases, *AADC* aromatic L-amino acid decarboxylase, *FMO3* Flavin-containing monooxygenase 3, *LDC* lysine decarboxylase, *ADC* arginine decarboxylation, *ODC* ornithine decarboxylase, *SSAT* spermidine/spermine acetyltransferase, *PAO* polyamine oxidase

Table 1 Comparison of EC_{50} values for recognition of TAAR/TAAR-like agonists determined in cell cultures, in TAAR OSNs, in TAAR glomeruli, and in behavior tests

Receptor	Ligands	In vitro	EC_{50} (M)		
			Electrophysiological recordings of OSNs	TAAR glomeruli imaging	Behavior test
Mouse TAAR3	*Isoamylamine*	*1.0×10^{-5}*	*1.5×10^{-8}*	*4.1×10^{-10}*	*5.9×10^{-10}*
	Cyclohexylamine	*7.0×10^{-6}*	*2.7×10^{-7}*		
	β-phenylethylamine	4.0×10^{-5}		1.9×10^{-10}	
	Trimethylamine	n.r.		7.9×10^{-7}	
Mouse TAAR4	*β-phenylethylamine*	*7.0×10^{-7}*	*1.0×10^{-12}*	*1.4×10^{-11}*	*5.0×10^{-12}*
	Cyclohexylamine	n.r.	7.7×10^{-10}		
	N-methylpiperidine	n.r.	5.1×10^{-10}		
	Isoamylamine	n.r.		9.9×10^{-9}	
	Trimethylamine	n.r.		4.7×10^{-7}	
Mouse TAAR5	*Trimethylamine*	*7.0×10^{-7}*		*3.1×10^{-8}*	*2.6×10^{-8}*
Sea lamprey TAAR348 (TAAR-like)	*Spermine*	*3.4×10^{-5}*			*$< 10^{-14}$*

The TAAR agonists solely determined by in vitro assays are not listed in the table. Agonists with the most high-affinity are given in italics. Data are taken from these papers (Dewan et al. 2018; Saraiva et al. 2016; Scott et al. 2019; Zhang et al. 2013)

nr no response

acid on the third transmembrane α-helix ($Asp^{3.32}$; Ballesteros–Weinstein indexing) forming a salt bridge with the ligand amino group, which is also highly conserved in biogenic amine receptors, while almost all of the teleost-specific clade III TAARs lack the $Asp^{3.32}$ residue and evolve a non-canonical ligand recognition motif on the fifth transmembrane α-helix ($Asp^{5.42}$). As a result, clade III TAARs can also recognize monoamines similar to clade I and II TAARs, but with an inverted recognition manner. In addition, there are several clade III TAARs that have both $Asp^{3.32}$ and $Asp^{5.42}$, and acquire the ability to detect diamines containing two amino groups (Li et al. 2015). Mammalian TAAR6 and TAAR8 family members also have a similar diamine binding site, $Asp^{3.32}$ and $Asp^{5.43}$ (Li et al. 2015). Consistent with this observation, a study based on homology modeling and molecular docking showed that diamines (putrescine and cadaverine) could bind to human TAAR6 and TAAR8 (Izquierdo et al. 2018). However, the experimental evidence is still lacking. It is not clear if $Asp^{5.43}$ in TAAR6 and TAAR8 is involved in interacting with the ligand amino group similar to $Asp^{5.42}$ in clade III TAARs. On the other side, TAAR9 is able to detect monoamines (*N*,*N*-dimethylcyclohexylamine, *N*-methylpiperidine, and triethylamine), diamines (cadaverine), and polyamines (spermidine and spermine) (Fig. 3) (Saraiva et al. 2016). TAAR9 retains the canonical $Asp^{3.32}$, but lacks either $Asp^{5.42}$ or $Asp^{5.43}$. It would be interesting to reveal the structural basis of TAAR9 that stabilizes multiple amino groups. A TAAR-like receptor in sea lamprey can also recognize polyamines (spermine, nap-spermine) and diamines (cadaverine) (Scott et al. 2019). Again, this receptor only has $Asp^{3.32}$, and other recognition motifs for the amino group are unknown.

Aside from the key acidic amino acids that form salt bridge with the ligand amino group, there are various important residues in the transmembrane domains of TAARs that constitute the ligand binding pockets. Combining homology modeling and mutagenesis experiments, Ferrero et al. found that the amino acid at 3.37 is another ligand contact site functioning as a selectivity filter. Swapping the corresponding amino acids at 3.37 together with 3.38 dramatically reversed the ligand responsiveness of TAAR7e and TAAR7f (Ferrero et al. 2012). In addition, a ligand-gating residue, $Asp^{6.58}$, has been reported to function as the key allosteric binding site in zebrafish TAAR13c. Single mutations from $Asp^{6.58}$ to other residues (Glu, Ala, and Asn) convert TAAR13c to supersensitive receptors with increased affinity to cadaverine. Surprisingly, those mutations could rescue the response of a $Asp^{3.32}$ mutant to cadaverine, suggesting the concomitant effect of orthostatic and allosteric binding sites (Sharma et al. 2016, 2018).

Animal Behaviors Elicited by Olfactory TAAR Agonists

Some olfactory TAAR ligands are volatile amines that are formed by decarboxylation of amino acids (Fig. 4). They can be found in decaying foods and animal body fluids. For instance, urine samples from many species can active a number of TAARs, such as TAAR3, TAAR4, TAAR5, TAAR7f, TAAR8c, and TAAR9 (Dewan et al.

2013; Ferrero et al. 2011; Li et al. 2013; Liberles and Buck 2006). Therefore, it is conceivable that those amines may mediate animal social communications through the TAAR olfactory subsystem. Indeed, several TAAR agonists can mediate instinctive animal behaviors, including sexual attraction, predator avoidance, and aversive response, which are critical for animal survival and reproduction. Furthermore, the TAAR olfactory system has been proposed to regulate migratory and homing behaviors in teleost fish, as the expression levels of teleost TAARs and projection patterns of TAAR-expressing neurons are developmentally and environmentally regulated (Churcher et al. 2015; Fatsini et al. 2016; Shao et al. 2017; Tessarolo et al. 2014). Intriguingly, some of the TAAR agonists even evoke species-specific behaviors. In this study, we will summarize the endogenous sources of different TAAR agonists and their induced animal behaviors.

Isoamylamine, the selective TAAR3 agonist, can be detected in male mouse urine and putrid meat (Barger and Walpole 1909; Nishimura et al. 1989). It is produced from leucine by leucine decarboxylase in commensal microbiota (Fig. 4a) (Haughton and King 1961). Another TAAR3 agonist, isobutylamine, is also found in male mouse urine (Nishimura et al. 1989). In female mice, the production of isobutylamine varies during the estrus cycle with a peak during estrus (Harmeier et al. 2018). Fish spoilage also produces isobutylamine, which may act as a key spoilage indicator (Bai et al. 2019). It can be produced from valine by valine decarboxylase and further metabolized to other derivatives such as isobutylhydroxylamine and valanimycin (Fig. 4a) (Garg et al. 2002, 2008). Isoamylamine and isobutylamine were reported to induce puberty in female mice, although this effect is still in debate (Nishimura et al. 1989; Price and Vandenbergh 1992). In the behavioral experiments, mice display avoidance to isoamylamine, which is abolished in the *Taar* cluster knockout mice (Dewan et al. 2013). Interestingly, the mouse behavior toward isoamylamine is concentration-dependent, showing attraction at lower concentrations less than 1 mM (Saraiva et al. 2016). Isobutylamine attracts male mice, and the attraction behavior is abolished in the *Taar* cluster knockout mice (Harmeier et al. 2018). A recent study showed that deletion of TAAR3 causes 6.3-fold decrease in detection sensitivity to isoamylamine in mice (Dewan et al. 2018). Unfortunately, the authors did not perform the valence behavioral tests on the TAAR3 knockout mice, so it is still unclear if the attraction/aversion behaviors induced by isoamylamine and isobutylamine are mediated by TAAR3. Interestingly, a study found that MHC-dependent mate choice for males is likely associated with TAAR3 genotype in female bats (Santos et al. 2016). And the same group reported that MHC-dependent mate choice in raccoons is also linked to the TAAR loci (Santos et al. 2018). However, it requires further studies to validate the casualty of mate choice behaviors and TAARs in different species.

β-phenylethylamine, the high-affinity TAAR4 agonist, is enriched in the urine of numerous carnivores with concentrations varying from 2 to 340 μM. The average β-phenylethylamine levels in urine samples from carnivores are > 500-fold higher than those from herbivores (Ferrero et al. 2011). β-phenylethylamine is synthesized from phenylalanine decarboxylation, which is catalyzed by enzymes involving AADC in animals, phenylalanine decarboxylase, and tyrosine decarboxylase in microbes (Fig. 4a) (Marcobal et al. 2012; Sim et al. 2015). Phenylalanine is an essential amino acid that is not synthesized de novo and can only be supplied in diet. Thus, the difference of β-phenylethylamine levels in the urine samples could be explained by the difference in diet and/or phenylalanine metabolism (Ferrero et al. 2011). Behaviorally, rodents avoid β-phenylethylamine to a similar extent as predator urine, and depletion of β-phenylethylamine from predator urine diminished the avoidance behavior (Dewan et al. 2013; Ferrero et al. 2011). Although β-phenylethylamine activates both TAAR1 and TAAR4, knockout of TAAR4 in mouse greatly decreases the detection sensitivity of β-phenylethylamine and is sufficient to eliminate the aversive behavioral response (Dewan et al. 2013, 2018). These data strongly suggest that β-phenylethylamine is a predator-associated odor activating TAAR4-expressing neurons to repel rodents. Interestingly, β-phenylethylamine has been proposed as a tiger pheromone (Brahmachary and Dutta 1979). However, it is unknown if β-phenylethylamine is indeed an agonist for tiger TAAR4 and could induce tiger social behaviors.

Trimethylamine, the most sensitive TAAR5 agonist, is secreted into the animal urine in a species- and sex-dependent manner. The levels of trimethylamine are more than 1000-fold higher in mouse than in rat and human. In addition, male mice produce about 30-fold higher levels of trimethylamine than female mice (Li et al. 2013). The trimethylamine biosynthesis pathway involves a two-step route. Trimethylamine is initially derived via metabolism of dietary choline, L-carnitine, and betaine by gut flora (Chhibber-Goel et al. 2016; Janeiro et al. 2018). Flavin-containing monooxygenase 3 (FMO3) expressed in the liver and kidney further oxidizes trimethylamine into the odorless trimethylamine oxide (Fig. 4b) (Cashman 2002; Fennema et al. 2016; Li et al. 2013). The species- and sex-dependent trimethylamine production can be explained by the varied expression levels of FMO3 in different species and sexes. In mouse, FMO3 is expressed at > 1000-fold higher levels in female than male, producing male-enriched trimethylamine and female-enriched trimethylamine oxide. In contrast, FMO3 is expressed at high levels in rat without sex difference. Humans normally produce very low or undetectable levels of trimethylamine. However, patients with the genetic

disease trimethylaminuria (also known as 'fish malodor syndrome') have an abnormally large quantities of trimethylamine excreted in urine, sweat, and breath, which strongly impacts the quality of their social life (Fennema et al. 2016). The underlying basis for this disease is a missense mutation in the catalytic domain of FMO3 (Dolphin et al. 1997). Coincident with its biosynthesis, trimethylamine evokes species-specific behaviors (Li et al. 2013). Trimethylamine is attractive to mice at physiological concentrations, but is aversive to mice at higher concentrations. Interestingly, deletion of TAAR5 decreases the detection sensitivity of trimethylamine and abolishes the attraction behavior in mice (Dewan et al. 2018; Li et al. 2013). However, the avoidance behavior to trimethylamine at high concentrations is retained in TAAR5 knockout mice. Collectively, those data suggest that TAAR5 is required for mouse attraction for trimethylamine and another unknown olfactory receptor (possibly a TAAR) may mediate mouse aversion for high concentrations of trimethylamine. On the other hand, trimethylamine is highly aversive to humans and rats. Human TAAR5 also recognizes trimethylamine, yet with much lower affinity than rodent TAAR5 (Horowitz et al. 2014; Wallrabenstein et al. 2013). The pairing between trimethylamine and TAAR5 might be the molecular basis for human avoidance behavior to trimethylaminuria patients. Therefore, identification of a specific high-affinity human TAAR5 antagonist would greatly benefit the patients. One such effort identified Timberol®, an amber-woody fragrance, that inhibits TAAR5 activation by trimethylamine and increases the detection threshold for trimethylamine in human by almost one order of magnitude (Wallrabenstein et al. 2015).

Diamines containing two amino groups include cadaverine, putrescine, and agmatine. Cadaverine and putrescine are death-associated odors enriched in decaying carcasses. Cadaverine is decarboxylated from lysine mainly by lysine decarboxylase, and putrescine can be derived from L-ornithine by ornithine decarboxylase. Agmatine is formed by decarboxylation of arginine via arginine decarboxylase. Agmatine is also a precursor of putrescine, and can be converted into putrescine by agmatinase (Fig. 4c) (Kusano et al. 2008; Rhee et al. 2007). Adult zebrafish show innate avoidance behavior to cadaverine and putrescine (Hussain et al. 2013). However, cadaverine and putrescine can activate both TAAR13c and TAAR13d (Li et al. 2015). However, it is unknown if either of the two zebrafish TAARs is required for the avoidance behavior. Interestingly, cadaverine also elicits species-specific behaviors: it is aversive to zebrafish and mice, while it is attractive to goldfish (Dewan et al. 2013; Rolen et al. 2003). In mouse, TAAR9 can recognize cadaverine in vitro, and could act as the functional receptor to mediate aversion to cadaverine (Saraiva et al. 2016). Agmatine is the agonist for several zebrafish TAARs including TAAR13c, TAAR13d, TAAR13e, and TAAR14d (Li et al. 2015). Unfortunately, the behavioral response to agmatine has not been characterized.

Polyamines have more than two amino groups and generally consist of spermine and spermidine. Spermine and spermidine are ubiquitously produced in all species. They are found in semen of many vertebrates from jawless fish, bony fish to mammals (Lefèvre et al. 2011; Scott et al. 2019; Tsilioni et al. 2019). Spermidine can be synthesized from putrescine by spermidine synthase and further converted into spermine by spermine synthase. In reverse, conversion of spermine to spermidine, and spermidine to putrescine can be achieved by acetylation through spermidine/spermine acetyltransferase and by subsequent oxidization through polyamine oxidase (Fig. 4c) (Miller-Fleming et al. 2015; Rhee et al. 2007). Mouse TAAR9 can be activated by spermine and spermidine, but only the latter could trigger attraction behavior (Saraiva et al. 2016). This raises an interesting question about the role of TAAR9 in mouse valence behavior. In sea lamprey, spermine activates the TAAR-like receptor, TAAR348, that is specifically expressed in the olfactory epithelium. It attracts ovulatory female lampreys and may function as a sex pheromone (Scott et al. 2019).

Although the TAAR agonists mainly elicit innate behaviors, the induced behaviors can be context-dependent. When presented together, the attractive and aversive TAAR agonists block one another's behavioral effects, resulting a combinatorial behavioral output. The attractive TAAR5 agonist, trimethylamine, can block aversion to the aversive TAAR3 and TAAR4 ligands, isoamylamine and β-phenylethylamine (Saraiva et al. 2016). This may be due to the combination of distinct olfactory inputs from different activated TAARs, since it occurs without receptor antagonism. Consistent with this model, different agonists for the same TAAR could evoke varied behaviors because of unknown activated receptors. For instance, both trimethylamine and pyrrolidine active TAAR5; however, trimethylamine is attractive to mice and pyrrolidine elicits a neutral response (Saraiva et al. 2016). Those results suggest that the instinctive olfactory behaviors induced by the TAAR agonists are context-dependent and modulated by the combination of inputs from different receptors.

Conclusion and Future Perspectives

The discovery of TAAR1 and its ligands has provided a unique avenue to study the monoaminergic system and its related disorders. The in vitro heterologous cellular work has identified trace amines, T_1AM, amphetamines, and monoamine metabolites as potent TAAR1 agonists. Recent studies also successfully designed specific agonists and antagonists for TAAR1. Future research should focus on the therapeutic potential of TAAR1 agonists and antagonists in different diseases caused

by dysregulation of monoaminergic systems. A thorough analysis of animal behavioral phenotypes after application of TAAR1 agonists and antagonists in a variety of contexts will further provide valuable insights into the physiological function of TAAR1.

Mammalian olfactory TAARs detect volatile amines and teleost TAARs detect water-soluble amine compounds. Although significant progress on deorphanization of olfactory TAARs has been achieved since the finding of TAARs in the olfactory system, many basic questions remain to be answered. Besides $Asp^{3.32}$ and $Asp^{5.42}$, what are other key residues in the transmembrane α-helices or extracellular loops that may constitute the agonist entry tunnel or agonist binding pocket? In addition, agonists for majority of TAARs from different species are still unknown. What is the physiological relevance of those TAAR agonists? What are the roles of the identified agonists and the corresponding TAARs in animal olfaction and social behaviors? Considering that some TAAR agonists could potentially cross cell membrane and circulate around the body, conditional knockout of TAARs in the olfactory epithelium might be necessary to elucidate their roles in olfactory behaviors. Also TAAR OSNs have been shown to project a distinct dorsal domain in the olfactory bulb, but the dedicated olfactory circuits beyond the bulb for the TAAR subsystem are largely unknown. Understanding the nature and feature of TAAR agonists will provide invaluable tools for us to explore the physiological roles of both non-olfactory and olfactory TAARs.

Acknowledgements This work was supported by National Natural Science Foundation of China (to Q.L., Award Number 31771154, 31970933), Shanghai Brain-Intelligence Project from the Science and Technology Commission of Shanghai Municipality (18JC1420302), Shanghai Pujiang Program (to Q.L., Award Number 17PJ1405400), Program for Young Scholars of Special Appointment at Shanghai Institutions of Higher Learning (to Q.L., Award Number QD2018017), Innovative research team of high-level local universities in Shanghai, Fundamental Research Funds for the Central Universities (Shanghai Jiao Tong University, to Q.L., Award Number 17X100040037), the Project of Invigorating Health Care through Science, Technology and Education (ZDXKB2016015).

Author Contributions ZX and QL conceived and wrote the paper.

Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical Approval This article does not contain any studies with human participants or animals performed by any of the authors.

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