TAARs and Neurodegenerative and Psychiatric Disorders

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Abstract

Trace amine-associated receptors (TAARs) are a family of G protein-coupled receptors expressed in the central nervous system and periphery. In humans, there are six functional members of the family with the TAAR1 being the best studied. In 2019, an agonist of TAAR1 successfully passed phase II of clinical trials and currently is being tested at phase III as a drug for the treatment of schizophrenia. Besides schizophrenia, drugs based on TAAR1 agonism are investigated for the treatment of depression, addiction, and neurodegenerative and metabolic disorders. In the brain, TAAR1 is involved in the regulation of the dopamine system acting as a neuromodulator. In the periphery, TAAR1 is implicated in the hormone secretion and immune system. Other five TAARs are known to be expressed in the olfactory system, but currently their role outside of the olfaction is being uncovered in the CNS and periphery. In this chapter, the role of TAARs in psychiatric and neurodegenerative diseases will be discussed.

Keywords

TAAR1 · Trace amines · Trace amine-associated receptors · Schizophrenia · Parkinson's disease

Abbreviations

3-MT	3-Methoxytyramine
6-OHDA	6-Hydroxydopamine
ADHD	Attention deficit hyperactivity disorder
cAMP	Cyclic adenosine monophosphate
CPP	Conditioned place preference
DA	Dopamine
DAT	Dopamine transporter
DDD	Dopamine-deficient DAT-KO mice
DRN	Dorsal raphe nucleus
GPCR	G protein-coupled receptor
L-AADC	Aromatic L-amino acid decarboxylase
L-DOPA	L-3,4-Dihydroxyphenylalanine
LTP	Long-term potentiation
MA	Methamphetamine
MAO	Monoamine oxidase
MDMA	Methylenedioxymethamphetamine
OCD	Obsessive-compulsive disorder
OUD	Opioid use disorder
PD	Parkinson's disease

PEA	β-Phenylethylamine
TA	Trace amine
TAAR	Trace amine-associated receptor
TAAR-KO	TAAR knockout
TH	Tyrosine hydroxylase
VTA	Ventral tegmental area

1 Introduction

Trace amines (TAs) are endogenous compounds found in the nervous system and peripheral tissues. They are chemically related to the classic monoamine neurotransmitters (dopamine, norepinephrine, and serotonin) and represented by biogenic amines with low tissue concentration. β-Phenylethylamine, p-tyramine, p-octopamine, and tryptamine are the main examples of TAs. Both trace amines and their associated receptors have been implicated in the etiology of an array of neuropsychiatric disorders and can be used as promising potential drug targets via modulation of the monoaminergic systems. However, their role in the mechanism associated with neurotransmission in mammalian systems is yet to be elucidated. In this chapter, the role of trace amine-associated receptors in psychiatric, neurodegenerative, and neurotoxicity processes and their possibility to be new drug targets for the treatment of brain disorders will be discussed.

2 Metabolism of Trace Amines

TAs are present in the CNS at a low concentration < 10 ng/g (Gainetdinov et al. 2018). In contrast to classic monoamine neurotransmitters, TAs are not stored in vesicles and readily diffuse across the plasma membrane, although some studies suggested a role for transporters in TA release. Lack of vesicular storage is considered to be the reason for their low concentration in tissues as the turnover rate of TAs is relatively rapid. TA biosynthesis starts from precursor amino acid decarboxylation by the enzyme aromatic L-amino acid decarboxylase (L-AADC). L-AADC is also involved in the synthesis of classic monoamine neurotransmitters. It is abundantly expressed in tissues and thus is not considered to be a rate-limiting enzyme. Degradation of TAs occurs primarily via monoamine oxidase enzyme (MAO). Almost all TAs do not show selectivity and are metabolized by both MAO-A and MAO-B. Accordingly, MAO inhibition leads to a rapid increase of PEA and tryptamine concentration in the brain (Gainetdinov et al. 2018).

3 Molecular and Cellular Biology of TAARs

Trace amine-associated receptors (TAARs) were discovered in 2001 by two independent groups (Borowsky et al. 2001; Bunzow et al. 2001). There are nine *Taar* genes in humans – three of them are pseudogenes, and six of them are functional

(TAAR1, TAAR2, TAAR5, TAAR6, TAAR8, and TAAR9). *Taar* genes are clustered on a single chromosome 6q23 in humans. Mouse and rat genomes contain 15 and 17 functional TAAR genes, respectively. TAAR1 expression was confirmed in several brain regions; TAAR1 mRNA and protein were found in the dopaminergic projections (ventral tegmental area, substantia nigra, dorsal and ventral striatum), glutamatergic projections (frontal cortex, amygdala, subiculum), and serotonergic projections (dorsal raphe nucleus (DRN)) (Gainetdinov et al. 2018). Other TAARs are expressed in the olfactory epithelium (Liberles and Buck 2006), but their expression was recently found in the central nervous system and periphery (Efimova et al. 2021; Espinoza et al. 2020; Gainetdinov et al. 2018).

TAARs belong to a large family of G protein-coupled receptors (GPCRs). GPCRs are located on the plasma membrane and mediate most intracellular responses to external stimuli (light, taste, odorant, hormone, neurotransmitter). Secondary messengers of GPCR may involve enzymes, receptors, ion channels, and ultimately transcription factors that control the gene expression. GPCRs are coupled to G proteins: $G_{\alpha s}$, $G_{\alpha i}/G_{\alpha 0}$, $G_{\alpha q}/G_{\alpha 11}$, and $G_{\alpha 12}/G_{\alpha 13}$. This classification is based on the properties of their α-subunits that determine functional properties of a heterotrimeric G protein. TAAR1 was found to be coupled to $G_{\alpha s}$, which increases the intracellular concentration of cyclic adenosine monophosphate (cAMP) and activates downstream signaling (Bunzow et al. 2001); therefore, TAAR1 activation in the cellular system was mostly studied using methods based on cAMP production (Barak et al. 2008; Miller et al. 2005; Revel et al. 2011). It was also shown that in response to amphetamine TAAR1 can recruit $G_{\alpha q}$ and $G_{\alpha 13}$ (Underhill et al. 2021). Activation of TAAR1 by agonist RO5166017 involves $G_{\beta\gamma}$ proteins and leads to outward K^+ current through G protein-coupled inwardly rectifying potassium (GIRK) channels in dopaminergic and serotonergic neurons (Revel et al. 2011). G protein-independent β-arrestin2 cascade is also implicated in the TAAR1 signaling (Harmeier et al. 2015). TAAR1 can modulate the firing activity of DA neurons in the ventral tegmental area (VTA) via potential interaction with dopamine D2 receptor (D2R) signaling (Lindemann et al. 2008). Accordingly, Espinoza et al. have shown that D2R antagonists enhanced TAAR1-mediated production of cAMP in response to an agonist β-PEA in a G protein-dependent and D2R-selective manner (Espinoza et al. 2011). In the olfactory system, TAARs are coupled to the olfactory type G_{olf} proteins that activate adenylyl cyclase type III and increase the cAMP production (Liberles and Buck 2006). Besides that, it was shown that TAAR5 signaling involves $G_{\alpha q/\alpha 11}$ pathway (Dinter et al. 2015).

4 TAARs as a Therapeutic Target in Psychiatry

4.1 Schizophrenia

Schizophrenia is a complex, heterogeneous behavioral and cognitive disorder involving both positive and negative symptoms. Schizophrenia is likely originated from a pathology of brain development caused by genetic or environmental factors

or both. In preclinical models of psychosis-like hyperactivity induced by compounds elevating dopamine transmission such as cocaine or compounds decreasing glutamate transmission such as NMDA glutamate receptor antagonists PCP, L-687,414, or MK-801, TAAR1 agonists can decrease hyperlocomotion (Dorofeikova et al. 2018; Revel et al. 2012). Thus, TAAR1 agonists are effective in both major models of psychosis: hyperdopaminergic and hypoglutamatergic states (Carlsson et al. 2001). Recent clinical trials of a mixed TAAR1 and 5-HT1A agonist, SEP-363856, revealed that it can attenuate both positive and negative symptoms in schizophrenia patients (Koblan et al. 2020). However, it is important to note that some of the negative symptoms can be secondary to positive symptoms, but not negative or deficit symptoms per se. In this study, patients resistant to antipsychotic treatment were excluded. Adverse events with SEP-363856 included somnolence and gastrointestinal symptoms like nausea, diarrhea, and dyspepsia (Koblan et al. 2020). TAAR1 appears to be the first novel target for antipsychotic action from the beginning of the "antipsychotic era" in the 1950s because SEP-363856 has no measurable action on dopamine D2 receptors. In 2019, the US Food and Drug Administration (FDA) has granted Breakthrough Therapy Designation for SEP-363856 for schizophrenia. Importantly, the incidence of extrapyramidal symptoms was similar in SEP-363856 and placebo groups (Koblan et al. 2020). So, this treatment can become an alternative approach to extrapyramidal correctors and switch to atypical antipsychotics such as clozapine. This treatment could be also useful for future schizophrenia research as a drug with an alternative target to differentiate patients with similar diagnostic criteria but with different response to various drugs. Also, it could help to define different endophenotypes and can lead to better sorting of patients to find out the genetic basis of psychotic diseases.

Multiple studies linking TAAR1 genetic variants with schizophrenia have been recently reviewed (Rutigliano and Zucchi 2020). Association studies have linked schizophrenia also with variations in TAAR6, TAAR2, and TAAR5 (Dodd et al. 2021). SNP in TAAR2 seems to be slightly more frequent in patients with schizophrenia, as compared to healthy controls, although statistical significance is borderline. Intriguingly, it was shown that in mice TAAR2 is expressed in several brain regions, including the hippocampus, cerebellum, cortex, raphe nuclei, and habenula (Kuvarzin et al. 2020). Several studies have identified SNPs and other genetic variants in the TAAR6 gene in patients with schizophrenia, even though the results of these studies are somewhat conflicting. TAAR6 polymorphisms have also been reported to be connected with therapeutic responses to the antipsychotic aripiprazole, whereas a more complex relationship between TAAR6 and heat shock protein 70 polymorphisms has been associated with both the development of schizophrenia and treatment outcomes (Dodd et al. 2021).

4.2 Parkinson's Disease Psychosis

A search for clinical trials in the ClinicalTrials.gov database revealed one study by the company Sunovion evaluating the safety and tolerability of SEP-363856

(TAAR1 agonist) in subjects with PD psychosis, but results are not published yet. For now, the inverse 5-HT2A agonist pimavanserin is the first FDA-approved antipsychotic for the treatment of hallucinations and delusions associated with PD psychosis. As an alternative, doctors off-label use for this indication antipsychotics quetiapine and clozapine, but these atypical antipsychotics also have a "black box warning" for use in elderly people with dementia, which PD patients frequently have. The adverse effect profile of pimavanserin includes urinary tract infections, falls, peripheral edema, hallucinations, confusion, nausea, and headaches (Cruz 2017). So, alternative treatment options can be very useful.

4.3 ADHD

Attention deficit hyperactivity disorder (ADHD) is a developmental disorder presenting as a combination of impulsivity, hyperactivity, and inattention symptoms. The fact that family members of children with ADHD were at elevated risk for ADHD made ADHD an attractive target for genetic studies that revealed potential involvement of gene variants of dopamine receptors and dopamine transporter (DAT) (Faraone et al. 2005).

One of the useful animal transgenic models of ADHD is rodents without DAT gene (DAT-KO mice and rats) (Leo et al. 2018). In these animals, lack of DAT causing a five- to sevenfold elevation of extracellular dopamine levels pronounced novelty-induced hyperactivity and certain cognitive dysfunctions. This model has got a good face and predictive validity because most of the drugs, effective in ADHD, like d-amphetamine and methylphenidate are effective in this model and paradoxically decrease hyperlocomotion (Gainetdinov et al. 1999; Leo et al. 2018).

TAAR1 agonists have also shown the same calming effect on hyperactive DAT-KO mice and rats (Leo et al. 2018; Revel et al. 2011), and this effect occurs in a TAAR1-selective manner (Revel et al. 2011). Interestingly, the hyperlocomotor and neurochemical (striatal release of DA, serotonin, and norepinephrine) effects of amphetamine are enhanced under the condition of TAAR1 deficiency in TAAR1 knockout mice (Wolinsky et al. 2007). Similarly, MDMA increases locomotion more robustly in TAAR1 knockout than in WT mice (Di Cara et al. 2011). Thus, it might be expected that some ADHD patients with SNP variants in the TAAR1 gene, which could lead to decreased function of TAAR1 protein, can have hypersensitivity to psychostimulants. This information could be helpful for therapists to identify this sensitive group to treat them with another drug of choice.

4.4 Addictions

TAAR1 is widely expressed in brain regions involved in addiction formation: VTA, substantia nigra, dorsal and ventral striatum, frontal cortex, amygdala, subiculum, DRN (Gainetdinov et al. 2018). There is convincing evidence that TAAR1 agonists can be new potential antiaddictive drugs for several drugs of abuse. At the same

time, TAAR1 agonist RO5263397 alone did not induce conditioned place preference or conditioned place aversion in rats (Thorn et al. 2014). Rats did not self-administer RO5263397 when substituting RO5263397 for methamphetamine in the self-administration task (Pei et al. 2015). Moreover, other TAAR1 agonists (RO5262297 and RO5256390) did not decrease the response in the intracranial self-stimulation test (Pei et al. 2015). Thus, preclinical tests did not reveal abuse potential of TAAR1 agonists. However, preclinical models have certain limitations, and abuse potential in humans should be evaluated in upcoming clinical trials.

4.5 Stimulant Addiction

There are no medications against stimulant addiction with good evidence of effectivity, and no drug was approved for this indication yet. TAAR1 is a promising target for the treatment of stimulant addiction. TAAR1 agonists that have been reported in the literature are similarly potent at both human and rat TAAR1. Furthermore, the efficacy that has been reported in animal models is comparable to the efficacy that has been reported in in vitro expression systems, which may provide a basis for predicting effective doses in humans. The TAAR1 partial agonist RO5203648 effectively reduced cocaine self-administration and relapse to drug-seeking behavior in rats (Pei et al. 2015; Revel et al. 2012), although cocaine is not a TAAR1 ligand itself. The partial TAAR1 agonist RO5263397 blocked methamphetamine-primed reinstatement of methamphetamine seeking, decreased the motivation to self-administer methamphetamine, and prevented methamphetamine-induced dopamine elevations in the nucleus accumbens (Pei et al. 2017). Also, TAAR1 knockout mice in context-dependent sensitization experiment showed higher conditioned locomotor responses to amphetamine than wild-type mice, and in the conditioned place preference (CPP) test, TAAR1-KO mice were more sensitive to priming-induced reinstatement of amphetamine-induced CPP (Sukhanov et al. 2016).

4.6 Nicotine Addiction

It has been shown that nicotine treatment in rats results in downregulation of TAAR1 protein in the nucleus accumbens (NAc). Administration of TAAR1 agonist blocked nicotine-induced c-Fos expression in the NAc, and also reduced nicotine-induced dopamine release in the NAc. Injections of TAAR1 agonists attenuated the expression and development of nicotine-induced sensitization, nicotine self-administration, and the reinstatement of nicotine seeking. On the contrary, TAAR1 knockout rats showed augmented cue-induced and drug-induced reinstatement of nicotine seeking (Liu et al. 2018). The partial TAAR1 agonist RO5263397 decreased hyperactivity induced by nicotine in rats and prevented the development of sensitization to nicotine (Sukhanov et al. 2018). In summary, these findings demonstrated that TAAR1 regulates nicotine use and indicate that TAAR1 agonists could be novel pharmacological interventions for nicotine addiction.

4.7 Opiate Addiction

Presently, only opioidergic strategy is approved as medication-assisted therapy for opiate use disorder (OUD). TAAR1 receptor can be a new target in the pharmacological treatment of the OUD. In the animal model of morphine self-administration, the selective TAAR1 agonist RO5263397 attenuated morphine intake and decreased the breakpoint under a progressive-ratio schedule of responding. RO5263397 does not affect morphine-induced CPP, naltrexone-induced conditioned place aversion, and naltrexone-precipitated jumping behavior in morphine-dependent mice. Also, RO5263397 did not affect the analgesic effect of morphine in the acute pain model in mice and the chronic pain model in rats. Moreover, there was no effect of RO5263397 on morphine-induced behavioral sensitization in TAAR1 knockout mice (Liu et al. 2021). Summing up these results, it can be suggested that the TAAR1 agonist RO5263397 selectively affects the reinforcing properties of morphine.

4.8 Alcohol Addiction

Some experimental data suggest that TAAR1 agonists potentially could reduce alcohol consumption in humans with alcohol use disorders. The TAAR1 agonist RO5263397 decreased the expression of ethanol-induced behavioral sensitization in mice; also, repeated injections of this drug prevented the development of behavioral sensitization to ethanol; these effects are TAAR1 selective because RO5263397 did not affect the same behavior in TAAR1 knockouts (Wu et al. 2020). Besides, TAAR1 knockout mice in the two-bottle choice test displayed greater consumption of ethanol than wild-type mice (Lynch et al. 2013).

4.9 Obsessive-Compulsive Disorder

Several studies suggested that patients with obsessive-compulsive disorder (OCD) display increased impulsivity, impaired decision-making, and reward system dysfunction. From a Research Domain Criteria (RDoC) perspective, these findings are prototypical for addiction and have led some authors to view OCD as a behavioral addiction. Some antipsychotics are effective as selective serotonin reuptake inhibitor augmentation therapy, so TAAR1 agonists, because they have antipsychotic activity, were tested as anti-compulsive drugs. Two compounds, a full agonist and a partial agonist, RO5166017 and RO5203648, respectively, were examined in a classic Skinner's schedule of reinforcement, FI-30 s in C57Bl/6J mice (Espinoza et al. 2015b). Premature correct responses and the post-reinforcement pause were scored as a measure of impulsivity. Pretreatment with both TAAR1 agonists decreased the number of correct premature responses. Furthermore, RO5203648 significantly decreased the premature correct responses and increased post-reinforcement pause in WT mice; however, it failed to exert any effect on both parameters in TAAR1-KO

mice (Espinoza et al. 2015a, b). Schedule-induced polydipsia, characterized by the development of excessive drinking under intermittent food-reinforcement schedules, has been proposed as a useful model of OCD. The partial TAAR1 agonist RO5263397 in a wide range of doses attenuated the polydipsia induced by two different schedules of food delivery in rats. The effect remained unchanged for the 7 days of repeated treatment. In general, the RO5263397 decreases specifically the adjunctive drinking, and this effect is maintained with repeated drug administration without the development of tolerance (Sukhanov et al. 2019). Taken together, these data suggest that pharmacological activation of TAAR1 in vivo modulates impulsivity in mice.

4.10 Binge Eating

Binge eating is seen as a core feature of types of obesity and eating disorders (binge eating disorder, bulimia nervosa, and anorexia nervosa of the binge/purge type) and can be interpreted as food addiction. It was shown that RO5256390 blocked binge-like eating in rats (Ferragud et al. 2017). Furthermore, RO5256390 fully blocked compulsive-like eating when the palatable diet was offered in an aversive compartment of a light/dark conflict box (Ferragud et al. 2017). These results provide the first evidence for TAAR1 agonism as a novel pharmacological approach for compulsive binge eating.

4.11 Anxiety Spectrum Disorders

TAAR1 agonists are known to reduce anxiety in mice in stress-induced hyperthermia tests (Revel et al. 2012). In other animal tests of anxiety, like Zero-Maze and Elevated Plus Maze (EPM), mice lacking TAAR5 were compared with their wild-type littermates. TAAR5 knockout mice demonstrate lower anxiety levels than WT mice: knockout mice spend more time in opened arms, central zone (EPM), and have an increased number of rearing and head dipping (Espinoza et al. 2020). Thus, the anxiolytic action of TAAR5 antagonists could be predicted.

5 Drug-Induced Neurotoxicity

5.1 Psychotropic Drugs of Misuse as TAAR1 Agonists

It was shown that many psychostimulants and hallucinogens show agonistic activity for TAAR1 receptor. The list of these drugs is impressive: amphetamine, 4- fluoroamphetamine, MDA, methamphetamine, MDMA, 7-APB, 4-APB, 2-AI, *N*-methyl-2-AI, 2C-B, 2C-P, 2C-H, and some others (Bunzow et al. 2001; Rickli et al. 2015; Simmler et al. 2016). However, most of these drugs activate human TAAR1 only at high micromolar concentrations. TAAR1 is not the main target for these drugs; they also have an affinity to different types of serotonergic, adrenergic,

dopaminergic, and histaminergic receptors and monoamine transporters. But, as described above, TAAR1 affinity can inhibit the response to psychotropic drugs. On the other side, some people might have a mutation in the TAAR1 gene that decreases its function, and negative consequences and adverse side effects may occur with lower doses.

5.2 MDMA

Methylenedioxymethamphetamine (MDMA; "ecstasy") is known to activate human TAAR1 (Bunzow et al. 2001; Simmler et al. 2016). MDMA-induced increase of dopamine level in the dorsal striatum was amplified in TAAR1-KO mice compared to WT mice (Di Cara et al. 2011). In VTA and DRN TAAR1 agonist, RO5166017 inhibited the firing rate of DA and 5-HT neurons, and this action was TAAR1 selective. Also, in the DRN, RO5166017 interacted with 5-HT1A autoreceptors: application of RO5166017 caused a twofold increase in potency of the 5-HT1A partial agonist ipsapirone, whereas the TAAR1 antagonist EPPTB induced a twofold decrease in ipsapirone potency (Revel et al. 2011). These data provide strong evidence that TAAR1 receptors modulate the activity of both DA and 5-HT neurons.

5.3 Methamphetamine

Methamphetamine (MA) is one of the most common recreational drugs. TAAR1 is activated by MA and modulates dopaminergic function. After MA treatment, DA and tyrosine hydroxylase (TH) levels were lower in TAAR1-KO mice compared to WT, suggesting that TAAR1 can ameliorate MA-induced neurotoxicity (Miner et al. 2017). Also, TAAR1-KO mice consume more MA and exhibit insensitivity to MA-induced conditioned taste aversion and hypothermia (Harkness et al. 2015). Furthermore, behavioral and physiological studies indicate that TAAR1 function increases sensitivity to aversive effects of MA and may thereby protect against MA use. A study of the common variant TAAR1 synonymous SNP V288V, a polymorphism that demonstrates a 40% increase in TAAR1 expression in cell culture, investigated the relation between V288V and symptoms in methamphetamine users. A heterozygous allele of V288V was associated with 1.55 times the mean response for drug craving in active methamphetamine users and 1.77 times the mean response for drug craving in methamphetamine users who were in remission (Dodd et al. 2021).

5.4 NBOMe Derivatives of 2C Drugs

N-2-methoxybenzyl-phenethylamines (NBOMe drugs) are relatively new substances, which pharmacodynamics is not well investigated yet. In comparison to their 2C prototypes (2,5-dimethoxyphenethylamine or 2C drugs), the TAAR1 receptor binding activities of NBOMe drugs were decreased (Rickli et al. 2015). It was

suggested that the lower TAAR1 activity associated with *N*-2-methoxybenzyl substitution may enhance psychostimulant and addictive drug properties (Rickli et al. 2015). Interestingly, drug users interviewed in the large survey study ($n = 22{,}289$) reported about greatest negative effects of NBOMes, compared with 2C drugs that were rated as less bad (Lawn et al. 2014). TAAR1-mediated "auto-inhibition" of hallucinogens is an interesting topic for further research.

5.5 Synthetic Cathinones

Synthetic cathinones began to be popular as an alternative to stimulants like amphetamine. The slang name of this class of drugs is "bath salts" because initially these substances were sold as salts for bath until they were prohibited. The most common cathinones on the market are methylenedioxypyrovalerone (MDPV), mephedrone, and α-pyrrolidinopentiophenone (alpha-PVP). Synthetic cathinones have a weak affinity to TAAR1 receptors. It can be one of the reasons for stronger cathinone effects on dopamine and serotonin systems compared with classic amphetamines (Simmler et al. 2016). The role of cathinone weak affinity to TAAR1 receptors in abuse potential and psychosis development is still unknown.

6 TAARs in Neurodegenerative Disorders

TAAR1 is known to be involved in the regulation of the dopamine system acting as a negative modulator (Revel et al. 2011). Brain dopamine is critically involved in movement control, and its deficiency is the primary cause of motor symptoms in Parkinson's disease (PD). Until now, DA precursor L-DOPA remains the most effective treatment for PD, but the efficacy of this treatment declines over time along with the development of psychotic reactions and dyskinesias. DA agonists and other types of drugs directly or indirectly affecting DA function (MAO inhibitors, catechol-*O*-methyltransferase inhibitors) have some effectiveness in PD patients at the early stages of the disease and mostly are used with L-DOPA. L-DOPA administration causes elevation of not only dopamine levels but also multiple other metabolites. Levels of the extracellular dopamine metabolite and TAAR1 agonist 3-methoxytyramine (3-MT), also a trace amine (Gainetdinov et al. 2018), are significantly elevated after chronic L-DOPA treatment (Rajput et al. 2004). These elevated levels of 3-MT in various brain regions may contribute to the L-DOPA-induced dyskinesia (Sotnikova et al. 2010). Using dopamine-deficient DAT-KO (DDD) mice as a novel model of parkinsonism with absolute DA depletion caused by the TH inhibitor, Sotnikova et al. showed that intracerebroventricular 3-MT administration leads to complex locomotor behavior in animals without dopamine (Sotnikova et al. 2010). Moreover, TAAR1 signaling appears to be involved in this effect of 3-MT (Sotnikova et al. 2010). It was also shown that the effects of L-DOPA are significantly increased in TAAR1-deficient DDD mice (Sotnikova et al. 2008). Another study showed "antiparkinsonian" effects of amphetamines and MDMA in

DDD mice (Sotnikova et al. 2005), although this effect was not confirmed in double DAT/TAAR1 knockout, suggesting that the effect of amphetamines does not involve TAAR1 (Sotnikova et al. 2008).

In another study, Alvarsson et al. showed a reduced loss of dopaminergic markers after intrastriatal neurotoxin 6-hydroxydopamine (6-OHDA) administration in TAAR1-KO mice. TAAR1-KO mice showed also elevated L-DOPA-induced rotations and dyskinesia compared to WT (Alvarsson et al. 2015). Conversely, TAAR1 agonist enhanced degeneration of dopaminergic neurons induced in WT mice by 6-OHDA (Alvarsson et al. 2015). Thus, it would be important to determine whether partial TAAR1 agonists ameliorate L-DOPA-associated side effects such as dyskinesia.

It appears that PD and other neurodegenerative diseases cause alteration in TA metabolism. D'Andrea and colleagues developed a sensitive method of TA detection and conducted a series of experiments measuring plasma levels of TA in PD patients (D'Andrea et al. 2010, 2019). Using this method, they detected the presence of TA (tyramine, octopamine, and synephrine) in the plasma of healthy subjects as well as mRNA transcripts of TAARs in platelets. It was also shown that mean levels of octopamine are lower in PD patients (D'Andrea et al. 2010). Furthermore, it was found that the plasma of PD patients contains higher levels of tyramine compared to healthy control; other TA levels (synephrine and β-phenylethylamine) were also altered (D'Andrea et al. 2019). It should be noted that multiple lines of evidence suggest that gut microbiota can influence L-DOPA treatment effectiveness. For example, treatment with antibiotics improves L-DOPA effectiveness. Some *Lactobacillus* species in gut microbiota can produce tyramine, and an increase of Lactobacillaceae was noted in PD patients (Zheng et al. 2020). Thus, alterations of TA levels might occur during PD progression as well as after treatment. Some members of the TA family may represent putative biomarkers for early-stage detection and progression of PD.

Regarding the fact that the majority of TAARs are expressed in the olfactory epithelium, it should be noted that olfactory dysfunction is noted in early non-motor "preclinical" stages of PD as well as other neuropsychiatric disorders such as Alzheimer's disease (AD), schizophrenia, and related disorders (Doty 2012). Olfactory bulb, the brain region in which TAARs are expressed (Liberles and Buck 2006), is an area where Lewy bodies are found even in patients with a short history of PD (Cersosimo 2018). Interestingly, recent studies revealed TAAR5 expression not only in limbic brain areas receiving olfactory input but also in neurogenic zones (subventricular zone and subgranular zone). Moreover, an increase in the number of dopamine neurons and elevated adult neurogenesis process were found in TAAR5-KO mice suggesting a possible role of TAAR5 in adult neurogenesis as well as the potential of TAAR5 antagonist to be an antiparkinsonian drug (Efimova et al. 2021). Therefore, investigation of potential TAAR involvement in neurodegeneration might be an important point to investigate.

Alzheimer's disease is one of the leading causes of dementia. Elevated levels of amyloid-beta (Ab) peptide, the main component of amyloid plaques in the brain in pathology, are considered to be the main factor of the disease process. Long-term potentiation (LTP), a form of synaptic plasticity, is involved in memory and learning

processes; it is known that Ab decreases LTP. 3-Iodothyronamine (T1AM) is considered to be a derivative of thyroid hormone and endogenous agonist of TAAR1 found in every tissue studied (Zucchi et al. 2014). Preliminary evidence suggested that intracerebroventricular administration of T1AM improves learning and has an anti-amnestic effect in mice (Laurino et al. 2015). Accorroni et al. provided direct evidence of TAAR1 agonists (3-iodothyronamine and RO5166017) to affect LTP restoration in a mouse model of AD. An antagonist of TAAR1 abolished this effect, further proving the involvement of TAAR1 in learning and memory (Accorroni et al. 2020). Pro-cognitive effects of TAAR1 agonist were also shown in behavioral studies (Revel et al. 2013). It has been shown that Ab decreases the concentration of NMDA receptors on the synaptic membrane of glutamatergic neurons, thus possibly causing a decrease in synaptic plasticity. In this light, it is worth noting that TAAR1 agonist increases NMDA receptor surface expression in vitro in primary cortical cultures (Leo et al. 2019). Accordingly, TAAR1-KO mice seem to have reduced glutamate NMDA receptor activity (Espinoza et al. 2015a, b).

7 Conclusion

In summary, the TAAR family is a perspective drug target for various brain disorders. It appears that TAAR1 is involved in effects of various psychoactive substances possibly via modulation of dopamine and serotonin systems. Multiple evidence from human and animal studies indicates the potential role of TAARs in the pathogenesis of PD and other neurodegenerative disorders. Further studies are needed to elucidate their functional role in physiology and pathology.

8 Cross-References

- ▶ Methamphetamine and MDMA Neurotoxicity: Biochemical and Molecular Mechanisms
- ▶ Psychiatric Disorders in Animal Models of Schizophrenia

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