Cellular and Molecular Neurobiology (2020) 40:229–238
https://doi.org/10.1007/s10571-020-00792-8

ORIGINAL PAPER

TAAR1 and Psychostimulant Addiction

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Received: 2 July 2019 / Accepted: 13 January 2020 / Published online: 23 January 2020

Abstract
Trace amine-associated receptor 1 is one of the best-characterized receptors of trace amines. Growing evidence shows that TAAR1 negatively regulates the monoaminergic activity, including dopamine transmission in the mesocorticolimbic system. Neurochemical assays demonstrated that selective TAAR1 full and partial agonists were effective to prevent psychostimulants-induced dopamine transmission in vitro and in vivo. In the last decade, many preclinical models of psychostimulant addiction such as drug-induced behavioral sensitization, drug-induced conditioned place preference, drug self-administration, drug discrimination, and relapse models were used to assess the effects of TAAR1 agonists on psychostimulants' behavioral effects. In general, activation of TAAR1 attenuated while knockout of TAAR1 potentiated psychostimulant abuse-related behaviors. Here, we review the advances in TAAR1 and its agonists in modulating psychostimulant addiction. We discuss the similarities and differences between the neurochemical and behavioral effects of TAAR1 full and partial agonists. We also discuss several concerns including the abuse liability, sleep reduction, and species-dependent effects that might affect the successful translation of TAAR1 agonists from preclinical studies to clinical application. In conclusion, although further investigations are in need to address certain concerns and the underlying neural mechanisms, TAAR1 agonists appear to be a promising pharmacotherapy to treat psychostimulant addiction and prevent relapse.

Keywords Trace amine-associated receptor 1 · Agonists · Psychostimulants · Cocaine · Addiction

Introduction

Drug addiction is a chronic relapse disorder characterized by compulsive drug taking and drug-seeking (Nestler 2001). Psychostimulants/stimulants are a group of drugs that increase the activity of the central nervous system and the body. Indeed, some psychostimulants are prescribed as legal medications to treat disorders such as ADHD in the clinical setting because at appropriate doses, psychostimulants can increase the ability to focus and promote sociability and vigor (Moriyama et al. 2013). However, due to the high pleasurable and reinforcing properties of psychostimulants, they are used globally as creational drugs and become major drugs of abuse (Badiani et al. 2011).

Nevertheless, there is currently no FDA-approved medicine to treat psychostimulant addiction. Therefore, discovering potential targets and developing effective pharmacotherapies for treating psychostimulant addiction have been dire clinical needs (Badiani et al. 2011; Oliere et al. 2013). Recent studies from our laboratory and that of others demonstrated that trace amine-associated receptor 1 (TAAR1) is a promising druggable target for treating psychostimulant addiction. Here, we review recent advances of TAAR1 in addiction to psychostimulants, including amphetamines, cocaine, and nicotine. We also discuss the potential and our concerns for TAAR1 agonists as pharmacotherapies for treating psychostimulant addiction and relapse.

TAAR1 and Its Downstream Signaling Pathways

In 2001, two independent groups cloned a novel GPCR using primers designed based on transmembrane domains of a subset of 5-HT receptors and the G protein-coupled catecholamine receptor gene family (Bunzow et al. 2001; Borowsky

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et al. 2001). It was demonstrated that trace amines, a group of amines structurally similar to classic amines but expressed at a relatively low level in the mammalian brain, such as *p*-tyramine, *β*-phenylethylamine (PEA), and octopamine, can fully activate this novel receptor. Therefore, it was identified as a receptor of trace amines and initially named as TA_1 or TAR1 (Borowsky et al. 2001; Bunzow et al. 2001). However, the nomenclature of "trace amine-associated receptor 1" (TAAR1) has been adopted in most of the later studies partially because it was found that not all members of TAARs have a high affinity for trace amines (Lindemann et al. 2005).

TAAR1 in the mammalian brain is expressed in the monoamine systems including the substantial niagra, ventral tegmental area (VTA), locus correlates, prefrontal cortex (PFC), dorsal striatum, and nucleus accumbens (NAc). Based on the anatomical pattern of TAAR1 expression, studies on TAAR1 have been focusing on monoamine transmissions and behavioral pharmacology. It has been shown that activation of TAAR1 reduces while knockout of TAAR1 potentiates dopamine transmission (Leo et al. 2014; Pei et al. 2014; Liu et al. 2018). Although the exact neural mechanism of TAAR1 in dopamine transmission remains unclear, many studies have provided some clues about the TAAR1-mediated signaling transduction. In vitro studies showed that TAAR was a G*s*- and G*q*-coupled receptor, and activation of TAAR1 could activate PKA- and PKC-dependent signaling pathways. However, the PKA or PKC pathways may not account for TAAR1-mediated decrease of dopamine transmission, because subeffective doses of PKA or PKC inhibitors did not block the effects of the TAAR1 full agonist RO5256390 (Asif-Malik et al. 2017). In the HEK-293 cells only transferred with TAAR1, activation of TAAR1 increased phosphorylation levels of ERK and CREB (PMID: 29,977,204). However, when TAAR1 was co-transfected with D2 receptors in the HEK293 cells, activation of TAAR1 did not alter the activities of ERK or CREB but inhibited the PI3K/AKT/GSK3 pathway instead. Presumably, the signaling transduction that mediates the effects of TAAR1 agonist could be more complicated in the in vivo conditions. First, there are potentially unknown receptors or molecules that can interact with TAAR1 and change the balance of downstream signaling. Second, TAAR1 could be under tonic activation in some brain regions. Thus, a TAAR1 agonist in the cultured cell studies could become an antagonist-like agent when applied to brain tissues or in vivo. More about this can be seen in the "TAAR1 full agonists vs. partial agonists" section below.

Interactions between TAAR1 and D2 receptors might be an important mechanism that mediates the inhibitory effect of TAAR1 activation on dopamine transmission. Although the TAAR1-dopamine transporter (DAT) interaction plays a role in the in vitro studies, DAT may not be necessary for the effects of TAAR1 in the in vivo context since TAAR1 agonists reduced the hyperactivity in DAT knockout mice (Revel et al. 2011). Evidence shows that TAAR1 could form a heterodimer with dopamine D2 receptors and interact with the presynaptic D2 receptors to negatively regulate dopamine transmission. A recent study showed that D2 antagonist blocked the activation of TAAR1-induced cAMP accumulation and reduction in dopamine accumulation, suggesting that the role of TAAR1 was dependent on D2 receptors (Xie and Miller 2007). On the other hand, TAAR1 may also interact with postsynaptic D2 receptors. TAAR1 knockout (TAAR1-KO) mice have an increase in D2High receptors (Wolinsky et al. 2007). It was also demonstrated that the D2/AKT/GSK3β signaling in the striatum was activated in TAAR1-KO mice, demonstrating a supersensitivity of postsynaptic D2 receptors (Espinoza et al. 2015a). More details regarding TAAR1 signaling can be found in our recent review paper and that of others (Liu and Li 2018; Gainetdinov et al. 2018; Pei et al. 2016).

TAAR1 Negatively Modulates Psychostimulants-Induced Neurochemical Alterations and Regulates Behaviors Associated with Psychostimulant Addiction

In the last two decades, the function of TAAR1 has been studied in different diseases, including cancer, diabetes, brain disorders such as schizophrenia, narcolepsy, and drug addiction (Grandy 2007; Liu and Li 2018; Tremmel et al. 2019; Raab et al. 2016; Michael et al. 2019). In particular, TAAR1 has been demonstrated to regulate the addiction-related behaviors to a broad range of drugs such as cocaine, caffeine, and alcohol, and palatable food addiction (Liu and Li 2018). Here, we focus on the role of TAAR1 in regulating the neurochemical and behavioral effects of psychostimulants that have been extensively examined so far, which primarily include amphetamines, cocaine, and nicotine.

Amphetamines

Amphetamine-like compounds, including amphetamine (AMPH), methamphetamine (METH), MDMA, 4-OH-amphetamine, and 4-Cl-amphetamine, could induce cAMP accumulation in the HEK-293 cells expressing TAAR1, indicating that amphetamines are potent agonists of TAAR1 (Bunzow et al. 2001; Miller et al. 2005). Importantly, it was shown that METH-induced dopamine efflux was dependent on TAAR1 and its downstream cascades, suggesting that TAAR1 is an essential mediator of the actions of METH (Xie and Miller 2009). Studies investigating the underlying mechanism consistently showed that the amphetamines-induced activation of TAAR1 was

dependent on the interaction between TAAR1 and DAT. For example, co-transfection with TAAR1 and DAT-enhanced AMPH- and MDMA-induced cAMP accumulation (Miller et al. 2005). METH-induced inhibition of dopamine uptake was displaced in cells co-transfected with TAAR1 and DAT and in the striatal synaptosomes of wild-type mice and rhesus monkeys, but not in DAT-only transfected cells or TAAR1 knockout mice (Xie and Miller 2009). A recent study showed that TAAR1 mediates AMPH-induced activation of the downstream RhoA and cAMP signaling in HEK293 cells expressing DAT but not cells without DAT (Underhill et al. 2019). Interestingly, two different G proteins G13 and Gs-regulated TAAR1 activation (Underhill et al. 2019). It was further shown that AMPH-induced activation of both TAAR1-G_{13}-RhoA and TAAR1-Gs-PKA signaling were dependent on DAT (Underhill et al. 2019). However, the TAAR1 agonist octopamine, which is not a substrate of DAT, did not activate RhoA signaling. Accordingly, it was suggested that these TAAR1/RhoA and TAAR1/PKA-signaling pathways might be particular cascades that mediate the effects of amphetamines and could not generalize to other TAAR1 agonists (Underhill et al. 2019).

Consistent with the in vitro studies, AMPH-induced locomotor activity and dopamine accumulation in the striatum in TAAR1 knockout (TAAR1-KO) mice was enhanced compared to their wild-type littermates (Wolinsky et al. 2007). The TAAR1-KO mice also showed an elevated level of context-dependent sensitization to AMPH (Miner et al. 2017). The effects of METH in the TAAR1-KO mice have also been reported (Achat-Mendes et al. 2012). Knockout of TAAR1-enhanced METH-induced hyperactivity and promoted the formation and retention of METH-induced conditioned place preference (CPP) (Achat-Mendes et al. 2012). In addition, TAAR1-KO mice and the DBA/2 J mice that have a non-functional allele of Taar1 consumed more METH compared to WT C57BL/6 J mice (Harkness et al. 2015).

Beside the TAAR1-KO mice, animals that overexpress *taar1* in the brain were also generated, which was named as *taar1* Tg mice (Revel et al. 2012a). Before discussing the behaviors of this line of *taar1* Tg mice, it should be kept in mind that *taar1* was expressed in all types of neurons in the whole brain of this mice strain, which is in contrast with the specific expression pattern of that in the wildtype animals (Revel et al. 2012a). The electrophysiological results showed that excitatory and inhibitory inputs into the VTA were altered in the *taar1* Tg mice (Revel et al. 2012a). Interestingly, although the basal levels of dopamine and norepinephrine in the nucleus accumbens (NAc) were elevated, amphetamine did not alter dopamine levels in the *taar1* Tg mice (Revel et al. 2012a). Consistently, behavioral test showed that AMPH led to hyperactivity in WT but not in *taar1* Tg mice (Revel et al. 2012a).

Several selective TAAR1 agonists have been developed and tested with amphetamines. In one study that systemically assessed the behavioral effects of TAAR1 agonist in METH addiction, the selective TAAR1 partial agonist RO5263397 attenuated METH-induced behavioral sensitization, METH self-administration, and cue- and drug-induced reinstatement of METH-seeking (Jing et al. 2014). A more recent study showed that RO5263397 also decreased the breakpoint for METH self-administration in a progressive ratio schedule of reinforcement and METH-induced dopamine overflow in the NAc (Pei et al. 2017). The inhibitory effects of RO5263397 on METH-associated behaviors were not due to a non-specific behavioral inhibition since the same dose of RO5263397 had no effect on cue-induced reinstatement of sucrose-seeking (Jing et al. 2014). In addition, RO5263397 was not self-administered by rats (Pei et al. 2017). In another study, the TAAR1 partial agonist RO5203648 also decreased METH-induced sensitization, METH self-administration, and dopamine overflow in the NAc but not striatum synaptosomes (Cotter et al. 2015).

Psychostimulants-induced impulsivity is also critical for the development of addiction. In a fixed interval schedule of reinforcement paradigm, the TAAR1 full agonist RO5166017 and partial agonist RO5203648 reduced impulsivity in mice (Espinoza et al. 2015b). Furthermore, TAAR1 KO mice showed a high level of perseverative and impulsive behaviors in a fixed interval-peak interval test (Espinoza et al. 2015b). A recent study from our lab used the five-choice serial reaction time task (5-CSRTT) and the delay-discounting task to evaluate the effects of TAAR1 agonist RO5263397 on attention and impulsivity in rats (Xue et al. 2018). In the 5-CSRTT task, accuracy and omissions are parameters to evaluate attention, while premature responses are indice of impulsive control. The curve of delayed discounting was used to evaluate impulsive choice. RO5263397 significantly attenuated acute METH-induced omissions and premature responses but did not affect delay discounting, suggesting that TAAR1 agonists regulate METH-induced attention deficit and impulsive control but not impulsive choice (Xue et al. 2018).

Cocaine

Cocaine is not a ligand of TAAR1 since cocaine did not induce cAMP accumulation in cells expressing TAAR1 (Miller et al. 2005). However, TAAR1 negatively modulates cocaine-induced dopamine accumulation. It demonstrated that the TAAR1 full-agonist RO5256390 prevented cocaine-induced inhibition of DA clearance in the NAc of brain slices (Asif-Malik et al. 2017). The same study showed that a subeffective dose of D2 receptor antagonist L-741626 but not PKC or PKA inhibitors prevented the effects of

RO5256390 on cocaine-induced dopamine release (Asif-Malik et al. 2017). Activation of D2/TAAR1 heterodimers induces inhibition of its effector glycogen synthase kinase-3 (GSK3). Thus, the GSK3 inhibitor SB216763 reproduced the inhibitory effects of RO5256390 on cocaine-induced DA transmission (Asif-Malik et al. 2017). These results indicated that D2 receptors but not PKA or PKC-dependent pathways mediated the effects of RO5256390 on cocaine-induced dopamine accumulation (Asif-Malik et al. 2017).

Growing evidence shows that TAAR1 regulates a broad range of cocaine abuse-associated behaviors. The TAAR1 partial agonist RO5263397 inhibited cocaine-induced hyperactivity in mice (Revel et al. 2011). Our study also showed that RO5263397 attenuated the induction and expression of cocaine-induced sensitization, expression of cocaine-induced CPP, and cue- and drug-induced reinstatement of cocaine-seeking (Thorn et al. 2014a). RO5263397 also increased the elasticity of cocaine demand curve, suggesting that RO5263397 decreased the motivation to take cocaine when the availability of cocaine was reduced (Thorn et al. 2014a). Furthermore, it is demonstrated that RO5256397 dose-dependently attenuated cocaine self-administration and prevented cocaine-induced decrease in intracranial self-stimulation (ICSS) (Pei et al. 2015).

The TAAR1 full agonists RO5256390 and RO5166017 blocked cocaine-induced hyperactivity (Revel et al. 2011). The lack of RO5166017′s effects in the TAAR1-KO mice indicates that the inhibitory effects of RO5166017 on cocaine in WT mice was mediated by TAAR1 (Revel et al. 2011). Similar to the effect of the TAAR1 partial agonist RO5263397, Pei et al. showed that the full agonist RO5256390 also attenuated cocaine self-administration and reduced the ICSS-lowering effect of cocaine (Pei et al. 2015). By using the cocaine-induced CPP paradigm, our study showed that RO5166017 attenuated the expression of cocaine reward memory but did not disrupt the memory reconsolidation or retention (Liu et al. 2016).

The role of TAAR1 in cocaine relapse is anatomically distinct (Liu et al. 2017). Activation of TAAR1 in the VTA and the prelimbic area of the mPFC attenuated both cue- and drug-induced reinstatement of cocaine-seeking (Liu et al. 2017). Activation of TAAR1 in the NAc shell reduced drug- but not cue-induced reinstatement, while in the NAc core reduced cue- but not drug-induced reinstatement of cocaine-seeking. Furthermore, activation of TAAR1 in the infralimbic area of the mPFC did not affect either cue- or drug-induced reinstatement of cocaine-seeking (Liu et al. 2017).

Nicotine

A recent study from our group demonstrated that TAAR1 also negatively regulates nicotine addiction (Liu et al. 2018). Chronic treatment of nicotine reduced the expression of TAAR1 in NAc but not the dorsal striatum or PFC (Liu et al. 2018). The full agonist RO5166017 attenuated nicotine-induced neural activation, indicated by the marker of neural activation, c-Fos, in the NAc (Liu et al. 2018). In addition, using in vivo Fast-scan Cyclic Voltammetry technique, we showed that RO5166017-attenuated nicotine-induced dopamine release in the NAc (Liu et al. 2018). Consistent with the neurochemical results, TAAR1 partial agonist RO5263397 dose-dependently attenuated nicotine-induced behavioral sensitization, nicotine discrimination, and motivation to nicotine intake assessed by nicotine demand curve (Liu et al. 2018). Both RO5263397 and RO5166017 decreased nicotine intake (Liu et al. 2018). In the extinction-reinstatement model, RO5166017 reduced cue- and drug-induced reinstatement of nicotine-seeking, while knockout of TAAR1 augmented the reinstatement. Furthermore, microinjection of RO5166017 into the NAc attenuated the reinstatement of nicotine-seeking without causing locomotor deficit, indicating that the NAc was one of the critical brain areas where TAAR1 regulates nicotine addiction (Liu et al. 2018). Consistently, Sukhanov et al. also showed that RO5263397 prevented nicotine-induced hyperactivity in nicotine-naïve and nicotine-sensitized mice (Sukhanov et al. 2018). Together, these results indicate that TAAR1 agonists are promising agents to treat nicotine addiction.

Figure 1 demonstrates a schematic summary of how TAAR1 agonists modulate the addiction-related effects based on the current mechanistic understanding of the interaction between TAAR1 and the dopaminergic system. Table 1 provides a summary of the pharmacological studies using TAAR1 agonists in animal models of drug abuse and addiction.

TAAR1 Full Agonist Versus Partial Agonists

As mentioned above, several full and partial agonists of TAAR1 were developed in the last decade (Revel et al. 2011, 2012b,2013). The major difference between full and partial agonists is that the maximal levels of TAAR1 activation induced by full agonists are similar to the endogenous TAAR1 agonist PEA while the partial agonists showed lower efficacy. For example, compared to PEA, the full agonist RO5256390 and partial agonist RO5263397 induced 107% and 76% cAMP accumulation in HEK-293 cells transfected with TAAR1, respectively (Revel et al. 2012b, 2013). Despite the different efficacies, behavioral studies demonstrated high similarities between TAAR1 full and partial agonists. For example, our study showed that both RO5166017 and RO5263397 were effective in attenuating nicotine-associated addictive behaviors (Liu et al. 2018, 2017, 2016). Based on the behavioral tests, it seems that

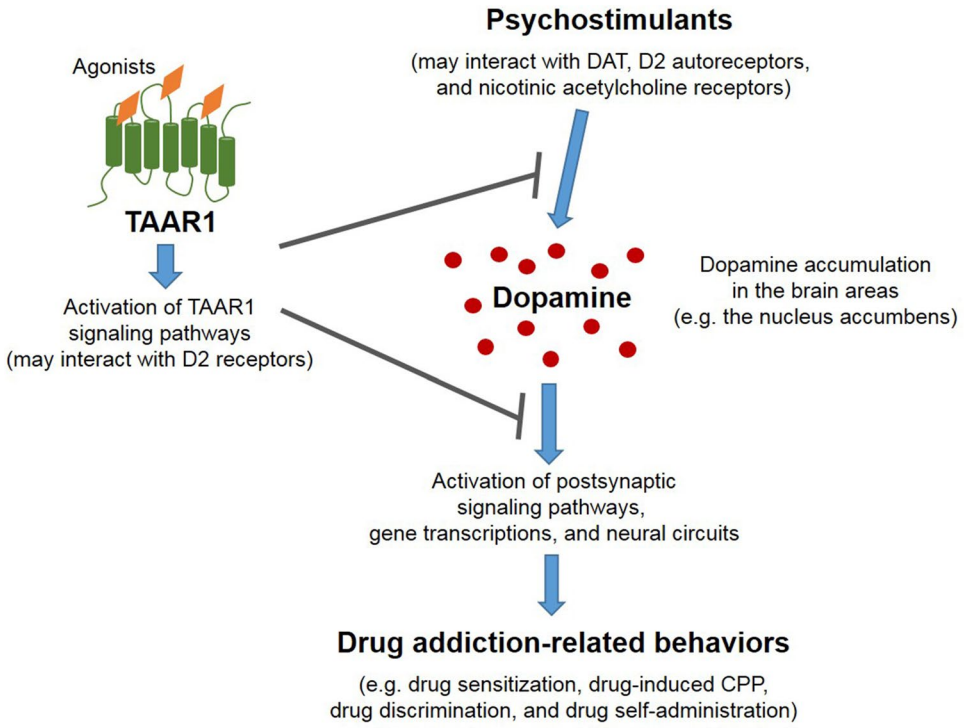

Fig. 1 A schematic diagram of the mechanism underlying the role of TAAR1 in regulating psychostimulant addiction

the potency of the partial agonist RO5263397 is higher than the full agonist RO5166017. Studies showed that 3.2 mg/kg RO5263397 (i.p.) was effective to attenuate addictive behaviors of cocaine, METH and nicotine, whereas the minimal dose of RO5166017 that produced similar behavioral effects was 10 mg/kg (i.p.) in rats (Liu et al. 2018, 2017, 2016; Jing et al. 2014; Thorn et al. 2014a). It also showed that the same doses of the full agonist RO5256390 yielded less brain exposure than the partial agonist RO5263397 in rats (Revel et al. 2013). However, these do not prove that partial activation of TAAR1 is more effective than full activation of TAAR1 in reducing psychostimulant addiction. The TAAR1 partial agonist RO5203648 and the full agonist RO5256390 showed similar potency in the cocaine self-administration (Pei et al. 2015). The TAAR1 full agonist RO5256390 revealed higher potency than the TAAR1 partial agonist RO5263397 in preventing the cocaine-induced decrease in intracranial self-stimulation in rats (Asif-Malik et al. 2017). Besides, the behavioral effects of these TAAR1 agonists depend on their potencies on TAAR1 activation as well as other factors such as the distribution of these compounds in the key brain regions that regulate psychostimulant addiction (Revel et al. 2013).

Unlike the similarities in behavioral properties, the TAAR1 partial and full agonists produced distinct effects in the electrophysiological assays. The full agonist RO5166017 and RO5256390-attenuated firing rates of dopaminergic neurons in the VTA and 5-HT neurons in the DRN (Revel et al. 2011, 2013). In contrast, the partial agonist RO5263397 and RO5203648 increased the firing rates of these neurons, similar to the TAAR1 antagonist EPPTB (Revel et al. 2013, 2011; Bradaia et al. 2009). A hypothesis is that the TAAR1 partial agonists cannot overcome tonic activation of TAAR1 by endogenous trace amines in the VTA, thus TAAR1 in the VTA neurons could only be activated at lower level when exogenous partial agonists were present due to competitive inhibition. As a consequence, the partial TAAR1 agonists would inhibit TAAR1 activation in vivo, which in turn reduce the firing rates of VTA neurons. However, although the partial agonist RO5203648 increased firing rate of dopaminergic neurons in the VTA, which presumably would increase the dopamine release in the dopaminergic-projecting areas such as the NAc, the partial agonist RO5203648 prevented cocaine-induced dopamine release in the NAc of rat brain slice (Pei et al. 2014). Based on these similarities and differences of chemical and electrophysiological properties of TAAR1 partial and full agonists, we hypothesize that different neural mechanisms may account for the different behavioral effects. Alternatively, the dopaminergic neuron-projecting areas such as the NAc rather than the VTA where the bodies of dopaminergic neurons reside in are the common neuroanatomical sites of TAAR1 in regulating psychostimulant addiction.

Epidemic surveys demonstrated a high rate of co-occurrence/comorbidity between drug addictions and other mental disorders, including anxiety, depression, and schizophrenia (Compton et al. 2007; Ross and Peselow 2012). Evidence shows that TAAR1 agonists have antipsychotic,

Table 1 Pharmacological activation of TAAR1 on the neurochemical and behavioral effects of psychostimulants

Psychostimulants	Agonists	Neurochemical alterations		Behaviors	References
		In vivo	In vitro		
METH	RO5263397 (partial)	RO5263397 prevented METH-induced DA overflow in slices of the NAc, while having no effect on DA transmission by itself	N/A	RO5263397 attenuated METH sensitization, METH self-administration, cue- and drug-induced reinstatement of METH-seeking, and breakpoint of METH self-administration in rats	Jing et al. (2014) and Pei et al. (2017)
	RO5203648 (partial)	RO5203648 did not affect METH-mediated DA efflux and uptake inhibition in striatal synaptosomes	RO5203648 transiently inhibited METH-induced DA release in the NAc	RO5203468 reduced METH-induced locomotor activity, development of METH sensitization, METH self-administration. RO5203648, at the high dose, cross-sensitized with METH	Cotter et al. (2015)
AMPH	RO5073012 (partial)	N/A	N/A	RO5073012 did not significantly affect AMPH-induced hyperactivity	Revel et al. (2012a)
Cocaine	RO5263397 (partial)	N/A	N/A	RO5263397 attenuated cocaine-induced sensitization, CPP, cocaine-induced lowering of ICSS reward thresholds, cue-and priming-induced reinstatement of cocaine-seeking	Thorn et al. (2014b; Thorn et al. (2014a) and Pei et al. (2015)
	RO5203648 (partial)	N/A	N/A	RO5203648 reduced cocaine-induced hyperactivity, cocaine self-administration, and drug-induced reinstatement of cocaine-seeking	Pei et al. (2015) and Pei et al. (2014)
	RO5256390 (full)	RO5256390 inhibited cocaine-induced DA overflow without changing DA transmission by itself in slices of NAc	N/A	RO5256390 reduced cocaine-induced hyperactivity, cocaine self-administration, cocaine-induced lowering of ICSS reward thresholds	Revel et al. (2013), Asif-Malik et al. (2017) and Pei et al. (2015)
	RO5166017 (full)	N/A	N/A	RO5166017 suppressed the expression of cocaine cpp, had no effect on retention or reconsolidation, and prevented formation of cocaine extinction memory RO5166017 into the ventral tegmental area, prelimbic cortex, and the NAc inhibits cue- and drug-induced reinstatement of cocaine-seeking	Liu et al. (2016) and Liu et al. (2017)

Table 1 (continued)

Psychostimulants	Agonists	Neurochemical alterations		Behaviors	References
		In vivo	In vitro		
Nicotine	RO5263397 (partial)	N/A	N/A	RO5263397 attenuated nicotine-induced hyperactivity and nicotine sensitization RO5263397 attenuated nicotine discrimination, nicotine intake, and nicotine demand curve	Sukhanov et al. (2018) and Liu et al. (2018)
	RO5166017 (full)	N/A	RO5166107 decreased DA release in the NAc and prevented nicotine-induced DA release in the NAc	RO5166017 attenuated nicotine intake, cue- and drug-induced nicotine-seeking Microinjection of RO5166017 into the NAc reduced the reinstatement of nicotine-seeking	Liu et al. (2018)

METH methamphetamine, *AMPH* amphetamine, *DA* dopamine, *NAc* nucleus accumbens, *ICSS* intracranial self-stimulation, *N/A* not applicable

antidepressant-like, and pro-cognitive properties (Revel et al. 2013). The partial agonists RO5203648 and RO5263397 and full agonist RO5256390 improved performance of monkey in the object retrieval task, suggesting these compounds improved cognition (Revel et al. 2013, 2012b). RO5203648 and RO5263397 but not RO5256390 reduced immobility time in the forced swimming test. RO5263397 and RO5256390 showed antidepressant-like properties in the differential reinforcement of low-rate behavior paradigm in the monkey (Revel et al. 2012b, 2013). Taken together, both the full and partial TAAR1 agonists are potentially effective to treat comorbidity of psychostimulant addiction and other mental disorders.

Concerns on TAAR1 Agonists for Treating Psychostimulant Addiction

The Abuse Potential of TAAR1 Agonists

Before concluding that TAAR1 agonists are promising therapeutic candidates for treating psychostimulant addiction, the addictive properties of TAAR1 agonists should be addressed. TAAR1 agonist RO5263397 alone did not induce CPP or conditioned place aversion in rats (Thorn et al. 2014a). Rats did not self-administer RO5263397 when substituting RO5263397 for METH in the self-administration task (Pei et al. 2017). In addition, RO5262297 and TAAR1 agonist RO5256390 did not decrease the responding in the intracranial self-stimulation (Pei et al. 2015). Taken together, current data suggest that RO5263397 has no abuse potential in the examined preclinical models. It should be noted that using preclinical models to assess the abuse potential of compounds in humans have its limitations and their true abuse liability can only be determined in humans.

TAAR1 Agonists Promote Wakefulness and Reduce Sleep

The TAAR1 partial agonists RO5263397 and RO5203648 dose-dependently increased the latency to sleep onset and promoted wakefulness without affecting locomotor activity in rats and mice (Pei et al. 2017; Revel et al. 2012b, 2013). RO5263397 also promoted wakefulness without affecting the locomotor activity or producing a cognitive deficit in Cynomolgus macaques (Goonawardena et al. 2019). In contrast to TAAR1 partial agonists, the full-agonist RO5256390 did not affect the amount of wakefulness or architectures of sleep components (Revel et al. 2013). RO5256390 and RO263397 showed therapeutic effects in reduction of cataplexy in the Alm-pretreated Atax mice and DTA Dox(−) mice, two different mouse models of narcolepsy (Black et al. 2017). It should be noted that RO5256390 is a full agonist

in rats, monkeys, and humans, but may be likely a partial agonist in mice, since the intrinsic activity of RO5226390 in mice is relatively low (79%) (Revel et al. 2013). These studies strongly suggested that TAAR1 agonists, especially the partial agonists, are promising wake-promoting therapeutics.

However, although the wake-promoting properties of TAAR1 agonists would benefit patients with narcotic, it could be a serious problem when applying the TAAR1 agonists to treat psychostimulant addiction. It is common that patients abusing drugs have sleep problems and suffer insomnia, especially in the abstinence period (Grau-Lopez et al. 2016; Chakravorty et al. 2018). The TAAR1 agonists that increase waking and reduce sleep could worsen sleep problems of patients with psychostimulant addiction. Since the TAAR1 full agonists showed little or no effects on wakefulness, we suggested that TAAR1 full agonists are more appropriate than partial agonists to treat psychostimulant addiction in patients suffering insomnia.

Species-Dependent Stereoselectivity of TAAR1

The role of TAAR1 in the development of psychostimulant addiction and relapse may be species-dependent. Evidence showed that the TAAR1 shows species-dependent stereoselectivity for its ligands (Reese et al. 2007). For example, the isomers of AMPH, METH, and hydroxyamphetamine induced different levels of cAMP accumulation in HEK293 cells expressing mTAAR1, rTAAR1, and hTAAR1 (Reese et al. 2007). Presumably, less potent the isomers of amphetamines on TAAR1, more dependent on their other targets to produce their effects. Furthermore, dopamine is also an agonist of TAAR1 (Bunzow et al. 2001). Therefore, the species-dependent stereoselectivity of TAAR1 may affect the role of dopamine and the development of amphetamines addition. Accordingly, the different potencies of amphetamines on TAAR1 across species may cause slight different functions of TAAR1 in amphetamines addiction.

This species-dependent stereoselectivity may also be important for developing TAAR1 agonists to treat psychostimulant addiction. Espinoza et al. showed that RO5263397 shows 392-fold higher potency at the mTAAR1 compared to hTAAR1 in vitro (Espinoza et al. 2018). As mentioned above, the TAAR1 full-agonist RO5256390 may not always be a full agonist across species (Revel et al. 2013). Thus, the species-dependent stereoselectivity of TAAR1 might result in translational discrepancies from preclinical studies to clinical application. Based on this consideration, future studies are required to clarify the correlation between TAAR1 activation and psychostimulant addiction in humans. Moreover, other species such as rhesus monkeys that is genetically close to human could be considered in assessing the efficacy of TAAR1 agonist in the future.

In Conclusion

Growing evidence strongly shows that TAAR1 plays an important neurophysiological role in regulating monoaminergic activity and psychostimulant addiction. Although the detailed mechanisms of TAAR1 and its agonists' actions remain unclear, considerable preclinical studies have demonstrated the effectiveness of TAAR1 agonists in treating psychostimulant addiction. Although there is currently no clinical trial to test the potential of TAAR1 agonist in treating psychostimulant addiction, the TAAR1 agonist SEP363856 (Sunovion) and RO6889450 (Hoffmann-La Roche) are under phase 2 clinical trials for the treatment of patients with schizophrenia. It is predicted that a great deal of critical information could be obtained from these clinical trials for the translation of TAAR1 agonists to treat psychostimulant addiction. It should also be noted that there are several potential concerns such as species-dependent effects, abuse liability, and potential sleep deprivation about the clinical use of TAAR1 agonists.

Author Contributions JL and JXL planned and prepared the original draft. All authors revised the manuscript and agreed on the finalized version of the manuscript.

Funding This work was funded by the National Institutes of Health National Institute on Drug Abuse [Grants R21DA040777 and R01DA047967]. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Compliance With Ethical Standards

Conflict of interest All the authors decalred 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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