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Viewpoint

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Trace Amines and Cocaine Abuse

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ABSTRACT: Cocaine addiction remains a clinical challenge with no effective pharmacotherapy available. Trace amine associated receptor (TAAR) 1 represents a promising drug target for the modulation of dopaminergic system and stimulant abuse. This Viewpoint discusses the emerging data which strongly suggest that TAAR 1 functions as a molecular "brake" that controls the addiction-related effects of cocaine and could be a novel drug target for the development of efficacious pharmacotherapy to treat cocaine addiction.

KEYWORDS: *Trace amine associated receptor 1, cocaine addiction, drug target, preclinical*

Cocaine abuse remains a medical and social challenge. Although decades of research has accumulated a large amount of knowledge on the neurobiology, biochemistry, and behavioral pharmacology of cocaine abuse, this information has not been translated to the discovery of efficacious medications. At present, there is no Food and Drug Administration approved medication for the treatment of cocaine addiction. Although multiple neurotransmitter systems involve the pharmacological effects of cocaine, dopamine is one of the most important players that mediate the addiction-related behavioral effects of cocaine. Several pharmacological approaches have been proposed to modulate the dopaminergic system to counteract the abuse-related effects of cocaine. For example, antagonists that target different dopamine receptor subtypes (e.g., D_1, D_2, and D_3) have been found to block some effects related to cocaine abuse. However, significant clinical success has not been demonstrated, largely due to the modest effectiveness and serious side effects. "Agonist replacement therapy" (e.g., methamphetamine or *d*-amphetamine for cocaine addiction) has been explored both in animals and in human subjects, which demonstrates some promising clinical outcomes. However, concerns about the abuse liability of the replacement drugs per se make this approach less appealing. In this context, exploring alternative approaches that indirectly modulate the dopaminergic system could be a fruitful strategy. Recent findings strongly suggest that trace amine associated receptor (TAAR) 1 could be such a promising new drug target to combat cocaine addiction.

Trace amines represent a small group of minute amounts of amines in the central nervous system that traditionally include *β*-phenylethylamine, *p*-tyramine, octopamine, and tryptamine. Although it has been known for decades the existence of trace mines in mammalian brain, their independent physiological roles have been controversial until the discovery of TAARs. In particular, TAAR 1 has been cloned from both rodent and primate brains and represents the most widely studied TAAR thus far. With the aid of genetically modified mice, we have learned that TAAR 1 participates in the modulation of dopaminergic activity. TAAR 1 knockout mice demonstrate a behavioral phenotype of supersensitivity to dopaminergic activation, with increased behavioral response to amphetamines. In contrast, brain-specific overexpression of TAAR 1 creates a behavioral phenotype that is hyposensitive to amphetamines. These results suggest a functional modulation of dopaminergic system by TAAR 1,[1] which raises the possibility of pharmacologically targeting TAAR 1 for the treatment of psychiatric disorders whose pathophysiology involves dysregulation of dopaminergic system, such as schizophrenia, depression and drug addiction.

Recently, several pharmacologically highly selective TAAR 1 ligands have been reported, and their effects in animal models of schizophrenia and depression and on the cognitive performance and feeding behaviors have been described.[2,3] Overall, it was found that TAAR 1 agonists demonstrate highly promising antipsychotic-like effects in preclinical studies and show superior therapeutic profiles than existing antipsychotics because they suppress feeding and decrease body weights in animals and thus lack the major adverse effect of body weight gain as seen in some existing antipsychotics. These data are consistent with the notion that TAAR 1 agonists could functionally modulate dopaminergic system and thus it is a natural hypothesis that these compounds may also alter stimulant abuse.

Two independent studies that were published simultaneously in *Neuropsychopharmacology* reported that TAAR 1 agonists can halt addiction-related effects of cocaine in rats.[4,5] In one study,[4] a TAAR 1 partial agonist RO5203648 and a TAAR 1 full agonist RO5256390 (Figure 1) dramatically reduced context cue- and cocaine-induced reinstatement to cocaine seeking behavior, a widely used animal model of cocaine relapse. Neurochemical measurement revealed that RO5203648 prevented cocaine-induced dopamine overflow in the nucleus accumbens, a key brain region in drug addiction. The other study employed more extensive behavioral analyses and examined the impact of a TAAR 1 partial agonist RO5263397 (Figure 1) on several abuse-related effects of cocaine.[5] It was found that RO5263397 significantly reduced both context cue- and a priming dose of cocaine-induced reinstatement of cocaine seeking behavior, which is consistent with the results using other TAAR 1 agonists (RO5203648 and

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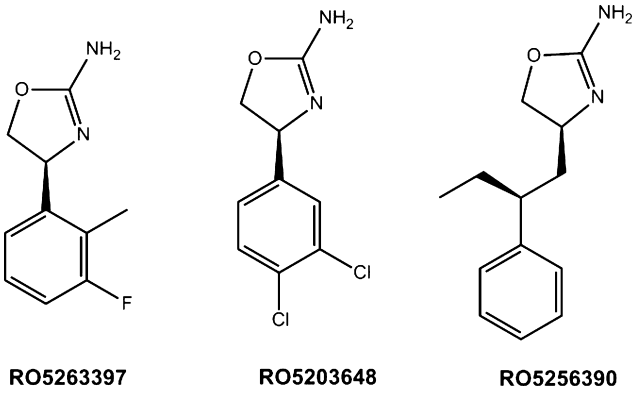

Figure 1. Structures of the three selective Roche TAAR 1 receptor agonists (RO5263397, RO5203648, and RO5256390).

RO5256390).[4] In addition, RO5263397 was found to significantly attenuate the expression of cocaine-induced behavioral sensitization and conditioned place preference, two commonly used paradigms for the study of drug-induced behavioral neuroplasticity. Lastly, behavioral economic analysis was used to assess the effect of RO5263397 on cocaine taking behavior. In the presence of RO5263397, rats stopped taking cocaine earlier when the workload for getting cocaine was progressively increased, suggesting that RO5263397 decreased the motivation of cocaine intake in animals.

These data are significant because they directly tested the notion that pharmacologically modulating TAAR 1 can reduce cocaine addiction using animal models with good translational and predictive values. In addition, medicinal chemistry has made great progress in identifying highly selective TAAR 1 agonists with good druggability. These timely studies reinforce the concept that TAAR 1 functions as a viable molecular "brake" to control dopaminergic activity whose activation reduces cocaine abuse and addiction. Future studies should focus on understanding the neural mechanisms underlying the antiaddiction effects of TAAR 1 agonists, which may eventually lead to novel TAAR 1 based pharmacotherapies that will refine and improve the status quo of treatment of cocaine addiction.

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