The Trace of Non-classical Biogenic Amines: A New Road to Addiction Recovery

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Stimulant abuse is prevalent according to recent global epidemiological studies. Research into treatment for problematic stimulant abuse has yet to find a suitable pharmacotherapeutic agent to assist with detoxification, withdrawal and relapse prevention. The newly discovered trace amine-associated receptor 1 (TAAR1) constitutes a novel receptor target for medication development with significant potential to treat the pathological changes produced by chronic drug exposure, especially stimulant abuse. Here, I briefly review evidence indicating that TAAR1 modulates the activity of the dopamine system and strongly influences the neurochemical and behavioral actions of psychomotor stimulants. The evidence discussed confirms the view that TAAR1 is a promising candidate receptor for the design of new effective addiction therapies.

The Classical Direct Approach

The classical biogenic amines have been under the spotlight in the fields of neuropharmacology and neuropsychiatry for the past 50 years. Historically, the search for treatments for psychopathological disorders such as depression, anxiety and schizophrenia has focused on the receptors, transporters and metabolic pathways for three catecholamines—dopamine (DA), norepinephrine and epinephrine—histamine and serotonin, and to a lesser extent on amino acid transmitters and their receptors. Biogenic amines play a fundamental role in modulating a wide variety of physiological and behavioural processes, including autonomic function, hormone regulation and motor control, and are believed to contribute critically to emotional and cognitive function, neurotoxicity and mental disease [1-3]. The advent of drugs aimed at these classical targets to treat affective and psychotic disorders remains to this date the single most relevant advance in pharmacotherapy but the discovery of these drugs was serendipitous. It did not derive from the identification of the neuronal and circuit-level alterations underlying psychiatric illness. This lack of mechanistic understanding hampered the progress and further development of therapeutic agents. An area in which development of pharmacological treatments has been particularly difficult is addiction and addictive-related disorders, most notably addiction to cocaine and amphetamine-type substances. Stimulant addiction is widely recognized for its treatment challenges [4,5]. Although several forms of non-specific pharmacology are currently in use, including anti-depressants and anti-epileptic drugs, there are no specific and proven medications that can be used to facilitate detoxification, enhance retention in psychotherapy and generally promote quicker recovery from chronic stimulant abuse.

Changes in DA transmission are critical for understanding the acute and long-term effects of chronic stimulant exposure. The ability of cocaine-like drugs to maintain self-administration in rodents is correlated with their potency in inhibiting the dopamine transporter (DAT) [6]. Moreover, the self-reported “high” induced by stimulants in humans appears to be a function of both the rate of DAT occupancy by the stimulant and the speed of stimulant delivery into the brain [7]. It is therefore not surprising that significant efforts have long been devoted to identifying molecules designed to have dopaminomimetic actions but weak cocaine-like effects. Drug discovery has focused on drugs that could either act as a substitute for the stimulant drug or exert antagonistic actions by preventing the binding of the stimulant to the DAT. Part of the search has examined molecules that mimic the DAT-binding properties of a stimulant, such as cocaine, but are less stimulating and act with a slower receptor onset and offset than cocaine. Recent data showed that binding to the DAT and subsequent transport inhibition does not invariably produce stimulant-like effects [8]. This means that the design of DAT inhibitors with low abuse profile to treat stimulant addiction remains possible, even if these molecules impede dopamine transport [9]. The rationale for targeting the DAT in stimulant abuse is fuelled by the existence of slow-onset, long-acting DAT inhibitors with weak stimulant and reinforcing effects [10-12] and have the ability to inhibit sensitization [13,14] and reinstatement of cocaine seeking [15]. The dopamine replacement approach in cocaine addiction is based on the same principles guiding the replacement approach that has been implemented to treat opiate addicts and manage nicotine addiction. Although this a promising avenue that we are still exploring actively, compounds that act directly at the DAT (e.g., slow-acting DAT blockers) are more likely to have abuse potential or produce long-term unwanted effects, which may complicate substitution therapy.

Paving an Indirect Path to Treat Addiction

The opportunity has now emerged to modulate the dopamine system indirectly through the recently discovered trace amine (TA) receptor system, paving the way to new forms of pharmacological intervention in stimulant addiction. TAs, including β-phenylethylamine, p-tyramine, octopamine and tryptamine, constitute a group of endogenous amines intimately related to classical neurotransmitters such as DA [16]. TAs evoke “amphetamine-like”, sympathomimetic effects at high nanomolar to low micromolar concentrations, whereas in the low nanomolar range, TAs may have neuromodulatory actions and contribute to monoamines’ homeostasis [17]. After a long search, brain receptors for TAs were recently discovered [18,19] and the first ever developed tools to study their function have very recently become available. Two receptors, named the TAAR1 and TAAR4 subtypes, have been found to be sensitive to TAs at physiological concentrations, but only TAAR1 has been identified and cloned in the human, monkey, rat and mouse genomes. Thus TAAR1 is the only subtype phylogenetically conserved in the mammalian brain [20]. Interestingly, Taar1 is expressed throughout the limbic and monoaminergic systems [21,22], thus providing a unique opportunity to modulate ascending aminergic systems specifically, particularly DA and serotonin. Studies with transgenic mice lacking Taar1 (Taar1−/− mice) revealed that TAAR1

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negatively regulates dopaminergic neurotransmission. Taar1−/− mice displayed elevated discharge rate of DA neurons [23], suggesting that TAAR1 is tonically active or constitutively activated to downregulate the firing frequency of midbrain DA neurons. This is in agreement with the finding that both the endogenous agonist p-tyramine and the selective TAAR1 agonist ROS166017 suppressed the firing frequency of DA neurons [23,24], whereas the selective antagonist EPPTB increased it [25]. However, the partial agonist, ROS203648, increased the firing rate of DA neurons [26], suggesting that TAAR1 can control DA transmission in opposite ways depending on ambient levels of trace amines. This unique feature of TAAR1 may be highly relevant for the treatment of stimulant addiction.

There is also evidence of TAAR1-mediated regulation of DAT activity, which could be an important process sub-serving psychomotor stimulant action. The effects of methamphetamine on dopamine uptake require the interaction of methamphetamine with TAAR1 [27], suggesting that this novel receptor could contribute to the long-lasting pathophysiological neuroadaptations produced by psychomotor stimulants. The possible implication of TAAR1 in the psychopharmacological effects of stimulant drugs is further reinforced by the fact that several psychoactive substances, including amphetamine, methamphetamine, MDMA (3,4-methylenedioxymethamphetamine), and lysergic acid diethylamide are themselves agonists of TAAR1 [18,28].

Similarly, it has become apparent that TAAR1 activation strongly modulates the neurochemical and behavioral effects of psychomotor stimulants. Mice lacking Taar1 showed augmented amphetamine-elicted locomotor activity [23], whereas transgenic mice overexpressing TAAR1 displayed hyposensitivity to amphetamine in both parameters [29]. Moreover, the selective full agonist, ROS166017, reduced the locomotor- and stereotypy-stimulating effects of cocaine [24]. Recently, we have provided the first evidence that TAAR1 regulates stimulant self-administration. The TAAR1 partial agonist, ROS203648, dose-dependently reduced cocaine intake in a self-administration paradigm [26]. Our preliminary observations also indicate that TAAR1 activation prevents relapse to cocaine seeking (unpublished observations).

These observations highlight the remarkable potential of TAAR1 to modulate the pathological neuroadaptations that abused drugs produce on the DA system. Indeed, chronic stimulant exposure is associated with long-lasting deficits in DA transmission, which may partially account for the anhedonia and dysphoria that follows drug withdrawal. Our main hypothesis is that TAAR1 stimulation may “normalize” DA neurotransmission by reducing excessive DA activation following stimulant intake, while re-activating the DA system during drug withdrawal. The state-dependent regulation of DA physiology and metabolism by TAAR1 provides a unique opportunity to regularise DA transmission in the different stages of the addiction cycle, including not only the abuse or “high” phase (high DA, euphoria) but also the withdrawal phase (low DA, dysphoria). Given that the metabolites considered by most to be trace amines derive from standard aromatic amino acids, our hypothesis is consistent with allied views supporting a role for amino acid therapy (i.e., the KB220Z neuroadaptogen amino acid therapy) in addiction [30].

The jury is out on whether TAAR1 can become a real medicinal target in addiction but the experimental machinery is at work fuelled by promising findings. We can look forward to new and exciting discoveries related to TAAR1 that will help us pave a new road to recovery in stimulant addiction in the years to come.

References


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