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Dopamine D2 receptors and striatopallidal transmission in addiction and obesity

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Abstract

Drug addiction and obesity share the core feature that those afflicted by the disorders express a desire to limit drug or food consumption yet persist despite negative consequences. Emerging evidence suggests that the compulsivity that defines these disorders may arise, to some degree at least, from common underlying neurobiological mechanisms. In particular, both disorders are associated with diminished striatal dopamine D2 receptor (D2R) availability, likely reflecting their decreased maturation and surface expression. In striatum, D2Rs are expressed by approximately half of the principal medium spiny projection neurons (MSNs), the striatopallidal neurons of the so-called “indirect” pathway. D2Rs are also expressed by cholinergic interneurons that influence MSN activity. This heterogeneity of D2R expression has hindered attempts, largely using traditional pharmacological approaches, to understand their contribution to compulsive drug or food intake. The emergence of genetic technologies to target discrete populations of neurons coupled optogenetic and pharmacogenetic tools to manipulate their activity have provided a means to dissect the contributions of defined neuronal populations in striatum to compulsivity. Here, we review recent evidence supporting an important role for striatal D2R signaling in compulsive drug use and food intake. We highlight advances in understanding the contribution of striatopallidal projection neurons to the reinforcing properties of food and drugs and their role in compulsivity. Finally, we identify opportunities for future obesity research using known mechanisms of addiction as a heuristic, and opportunities to leverage new tools to manipulate activity of specific populations of striatal neurons to understand their contributions to addiction and obesity.

The loss of control over food consumption in obese individuals who struggle and fail to control their body weight is similar in many respects to the compulsive drug taking observed in drug addicts [1,2]. Based on these similarities, it has been hypothesized that analogous or even homologous mechanisms may contribute to these compulsive behaviors [1,3–6]. Interestingly, human imaging studies have established that dopamine D2 receptor (D2R) availability is generally lower in the striatum of obese relative to lean individuals [7•, 8•, 9]. Similar deficits in D2R availability are also detected in those suffering from substance abuse disorders [10–12]. Individuals harboring the *TaqIA* A1 allele, which results in ~30–40

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% reduction in striatal D2Rs compared with those not carrying the allele [13–15], are over-represented in obese and drug-dependent populations [7••, 8••, 9, 16–18]. Hence, alterations in striatal D2Rs could potentially contribute to the emergence compulsive eating or drug use in obesity and addiction, respectively.

Dopamine D2 receptors in addiction and obesity

Recently, we investigated whether compulsive-like feeding behavior, as measured by palatable food consumption that is resistant to the suppressant effects punishment (or cues predicting punishment) emerges in rats with extended access to palatable diet that triggers hyperphagia and excessive weight gain. We provided rats with almost unlimited daily access to a “cafeteria diet” consisting of a selection of highly palatable energy-dense food products commercially available at most cafeterias and vending machines for human consumption, such as cheesecake and bacon, which induce obesity in rodents much like their human equivalents rats [19,20]. As these rats gained weight, they demonstrated eating behavior that was resistant to the suppressant effects of cues predicting the onset of aversive footshock [21••]. Similar compulsive-like intake is observed in rats responding for cocaine infusion after a period of extended access to the drug [22,23••].

In addition to their excessive adiposity and compulsive-like eating, cafeteria diet rats also had decreased D2Rs expression in striatum [21••]. We therefore assessed whether knockdown of striatal D2Rs could accelerate the emergence of compulsive-like intake in cafeteria diet rats. Considering that lentivirus undergoes very low rates of retrograde transport, this approach ensured that postsynaptic D2Rs on neurons in the striatum, and not those located presynaptically on dopamine inputs, were impacted by this manipulation [21••]. Striatal D2R knockdown indeed accelerated the emergence of compulsive-like consumption of calorically dense palatable food. However, striatal D2R knockdown did not trigger compulsive responding for standard chow, suggesting that animals had to experience a combination of D2R knockdown and even very limited exposure to the palatable food before compulsivity emerged [21••]. Surprisingly, the effects of disrupting striatal D2R signaling on compulsive-like patterns of drug intake have not yet been assessed.

Striatopallidal transmission and drug reward

The principal MSN projection neurons account for between 90–95 % of the neurons in the striatum. The MSNs are generally segregated into two discrete populations, termed the direct and indirect pathway neurons, although this characterization is almost certainly an over-simplification of the connectivity of striatal MSNs; for example, see Refs. [24–26]. The direct pathway MSNs, also known as striatonigral neurons, express dopamine D1 receptors (D1Rs) and project directly from the striatum to the substantia nigra pars reticulata (SNr) and internal segment of the globus pallidus (GPi). The indirect pathway MSNs, also known as striatopallidal neurons, express D2Rs and project indirectly from the striatum to the SNr/GPi via the external segment of the globus pallidus (GPe) and subthalamic nucleus (STN). Activation of striatonigral neurons generally facilitates forward locomotor behaviors, whereas the striatopallidal neurons exert an opposite inhibitory influence. In addition to the striatopallidal neurons, cholinergic interneurons in striatum also express D2Rs [27, 28••, 29]. This heterogeneity of D2R expression in striatum has complicated attempts to understand the mechanisms by which D2Rs may contribute to the development of compulsive drug and food intake. However, the development of mice that express Cre recombinase within defined populations of neurons, coupled with the emergence of Cre-dependent techniques to control the activity of Cre-expressing neurons, such as optogenetics [30•] and Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) [31,32•], is beginning to define the contribution of specific populations of striatal cells to

drug and food intake. As summarized below, these novel approaches are revealing key contributions of D2-expressing neurons in striatum to opposing the stimulant and rewarding properties of addictive drugs, and also opposing the emergence of inflexible, compulsive-like patterns of food or drug consumption.

Striatopallidal neurons but not cholinergic interneurons express adenosine 2A receptors (A2AR). Based on this fact, Durieux and colleagues used A2AR-Cre mice to drive expression of diphtheria toxin receptor in (DTR) in striatopallidal neurons, then injected the animals with diphtheria toxin to induce highly specific lesions of these neurons [33•]. This manipulation triggered profound hyperlocomotion and a marked increase in sensitivity to the rewarding effects of amphetamine [33•]. Lobo and colleagues subsequently reported that targeted deletion of Tropomyosin-related kinase B (TrkB), the receptor for brain-derived neurotrophic factor (BDNF), in striatonigral diminished the rewarding properties of cocaine, whereas TrkB knockout in D2-expressing MSNs enhanced cocaine reward [34•]. Moreover, TrkB knockout in D2-expressing MSNs increased their excitability, with optogenetic stimulation of these neurons similarly decreasing cocaine reward [34•]. More recently, Neumeier and colleagues used DREADDs to show that inhibition of striatonigral neurons blocked the emergence of sensitized locomotor responses to amphetamine, whereas inhibition of striatopallidal neurons enhanced sensitization [35•]. These findings suggest that striatopallidal signaling opposes reward-related processes and may protect against addiction-relevant neuroplasticity.

Striatopallidal transmission and compulsive drug use

More recent findings have implicated striatopallidal signaling in “flexible” responding – the ability to cease responding when persisting in the behavior may result in negative consequences – disruption in which likely drives the emergence of compulsivity. Kravitz and colleagues found that optogenetic stimulation of striatopallidal neurons resulted in punishment-like responses in animals, reflected in avoidance of the optical stimulation [36•]. Using cell-specific expression of tetanus toxin to block neurotransmitter release, Nakanishi and colleagues found that disruption of striatopallidal signaling abolished the ability of animals to learn an inhibitory avoidance behavior (avoidance of an environment in which electric footshocks were delivered) [37•]. Using this same tetanus toxin-based approach, Nakanishi and colleagues also found that disruption of striatopallidal transmission induced inflexible-like behaviors in mice in which they were unable to alter their behavior in response to alerted task contingencies [38]. These findings are consistent with a role for striatopallidal neurons in regulating behavioral flexibility, a key role that facilitates the switching between different behavioral strategies in order to maximize reward opportunities [38]. Hence, drug-induced plasticity in striatopallidal neurons that results in their diminished activity could potentially precipitate inflexible, compulsive-like, patterns of drug-taking behavior. Consistent with this possibility, Alvarez and co-workers have recently shown that synaptic strengthening onto D2-expressing MSNs in nucleus accumbens occurs in mice with a history of intravenous cocaine self-administration [39•]. This synaptic strengthening was inversely correlated with the emergence of compulsive-like cocaine responding [39•]. Moreover, DREADD-mediated inhibition, or optical stimulation, of striatopallidal neurons increased or decreased, respectively, compulsive-like responding for cocaine in mice [39•].

Striatopallidal transmission and compulsive eating

These above findings provide direct evidence in support of a key role for D2-expressing MSNs in compulsive cocaine responding. This raises the important question of whether striatopallidal neurons are also involved in compulsive consumption of palatable food in obesity. Surprisingly, this possibility has not yet been investigated and this represents a

major gap in knowledge. Nevertheless, there are intriguing hints that this may in fact be the case. As noted above, A2ARs are densely expressed by striatopallidal neurons [40]. As such, pharmacological agents that modulate A2AR activity are expected to preferentially influence striatopallidal transmission. A2AR agonists, which increase striatopallidal transmission, reduced consumption of both highly palatable and standard chow in rats [41], and reduced lever-pressing for food rewards [42]. Conversely, pharmacological blockade of A2A receptors increased palatable food consumption when administered alone, and enhanced palatable food intake triggered by intra-accumbens administration of a μ -opioid receptor agonist (DAMGO) [43]. These findings are reminiscent of the inhibitory effects of indirect pathway stimulation on drug reward described above, and suggest that D2-expressing indirect pathway MSNs may regulate food intake in much the same way that they regulate drug rewards.

Conclusions and future directions

The above findings support a contextual framework in which prolonged drug use or weight gain drives adaptive responses in striatopallidal neurons, resulting in inflexible patterns of intake that become progressively more compulsive in nature. Hence, a major area of future activity in obesity research is likely to be defining the precise role for striatopallidal neurons in regulating the emergence of compulsive eating. It will also be important to determine if ameliorating this type of inflexible eating may form the basis of effective strategies to achieve long-term weight loss. Another area of research likely to be of considerable interest in both the addiction and obesity fields will be better defining the role for D2 receptors located on cholinergic interneurons. Optical inhibition of cholinergic interneurons in striatum abolishes the rewarding effects of cocaine [44]. D2 receptors on cholinergic interneurons regulate the characteristic pause-burst patterns of firing of these cells in response to salient stimuli through interactions with nicotinic acetylcholine receptors (nAChRs) located presynaptically on dopamine terminals [28]. Interestingly, antagonism of nAChRs blocks compulsive-like escalation of cocaine intake in rats with extended access to the drug [45]. Hence, it will be important to determine if D2 receptor signaling in striatal cholinergic interneurons also contributes to compulsive drug use and feeding behavior.

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Highlights

- Obesity and addiction result in diminished D2 receptor availability in striatum.
- D2 receptors control compulsive eating.
- DREADDs and optogenetics have revealed a key role for striatopallidal neurons in compulsive drug use.