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Cortico-Striatal Circuits: Novel Therapeutic Targets for Substance Use Disorders

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Abstract

It is widely believed that substance use disorder (SUD) results from both pre-alterations (vulnerability) and/or post-alterations (drug effects) on cortico-striatal circuits. These circuits are essential for cognitive control, motivation, reward dependent learning, and emotional processing. As such, dysfunctions in cortico-striatal circuits are thought to relate to the core features of SUD, which include compulsive drug use, loss of the ability to control drug intake, and the emergence of negative emotional states (Koob et al. 2010). While the brain circuits underlying SUD have been studied in human patients largely through imaging studies, experiments in animals have allowed researchers to examine the specific cell-types within these circuits to reveal their role in behavior relevant to SUD. Here, we will review imaging studies on cortico-striatal systems that are altered in SUD, and describe animal experiments that relate SUD to specific neural projections and cell types within this circuitry. We will end with a discussion of novel clinical approaches such as deep brain stimulation (DBS), repeated transcranial magnetic stimulation (rTMS), and pharmacological targeting of G protein-coupled receptor (GPCR) heteromers that may provide promising avenues for modulating these circuits to combat SUD in humans.

1. Introduction:

Substance use disorders (SUD) impose a dramatic toll on our society. For instance, cigarette smoking is described by the Center for Disease Control and Prevention as the “leading cause of preventable death in the US, accounting for approximately 1 of every 5 deaths... each year” (CDC 2011). Alcoholism and other drug use account for about another 75,000 deaths annually (Kochanek et al. 2011). SUD also impacts millions of people who are not addicted to drugs, due to crime, poverty, and infectious disease transmission (Leshner 1997).

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Presently, there is no cure for SUD, and the available treatment options do not reliably help addicts quit. Relapse rates range somewhere between 50% and 90% within the first year of treatment, and for certain drugs (particularly nicotine and opiates), this rate can approach 100% (Davstad et al. 2007, Dawson et al. 2007, Rohsenow et al. 2007, Sullivan et al. 2007, Kaskutas 2009, Gonzales et al. 2010, Powell et al. 2010). On the positive side, a handful of medications do help certain people abstain from drug use (Edens et al. 2010). While these medications do not cure SUD, they demonstrate that drug intake can be managed in certain patients, and that with further research this management may expand to larger populations. While the exact way this management will expand is not clear, recent studies employing novel technologies in both humans and animals have provided clues about novel approaches for treating SUD. In this review, we will discuss 1) imaging studies implicating cortico-striatal transmission in SUD, 2) optogenetic studies investigating cortico-striatal circuitry in drug exposed and addicted animals, and 3) novel clinical approaches for targeting cortico-striatal circuits to treat SUD.

2. Imaging Cortico-striatal Circuitry in SUD

Imaging studies have demonstrated strong links between SUD and dysfunction in cortico-striatal circuitry, and in particular dopamine (DA) function within this circuitry (Kalivas 2004, Volkow et al. 2005, Koob et al. 2008, Ikemoto 2010, Luscher et al. 2011). Positron emission tomography (PET) studies have demonstrated that SUD involves impaired DA receptor function in the striatum, such as decreases in DA D_2 receptor (D_2R) availability, as well as an associated reduction in baseline glucose metabolism in frontal and temporal cortices (Volkow et al. 1993) (Figure 1). Impairments in D_2R function have been demonstrated following drug exposure in animals (Nader et al. 2005), but could also manifest as a pre-existing vulnerability in certain people, such as those with polymorphisms in the gene coding for the D_2R (Noble 2000, Le Foll et al. 2009). On a finer temporal scale, function magnetic resonance imaging (fMRI) studies have shown that, while SUD initially affects striatal areas, it also propagates to cortical areas which are involved in attention, memory, motivation, executive function, mood and interoception (Ogawa et al. 1990, Volkow et al. 2014). Other pharmacological PET and fMRI studies demonstrated that enhancing tonic DA signaling through the use of methylphenidate can attenuate limbic brain responses to cocaine cues (Volkow et al. 2010) and normalize fMRI responses during an emotionally salient cognitive task (Li et al. 2010, Goldstein et al. 2011) in cocaine addicted individuals (Volkow et al. 2012).

More recently, PET and fMRI multimodality studies have documented an association between DA neurotransmission in the striatum and fMRI responses in the default mode network (DMN). The DMN is a collection of brain regions that are activated when an individual is not actively engaged with the world, but is at wakeful rest. These brain regions include the ventral PFC, the precuneus and the angular gyrus (Tomasi et al. 2009, Braskie et al. 2011). While it is unclear how endogenous DA affects the function of the DMN, fMRI studies that used stimulants (e.g., modafinil or methylphenidate) to enhance DA signals, have suggested an association between DA signaling and DMN function (Minzenberg et al. 2011, Tomasi et al. 2011). Specifically, these studies pointed to DA's possible role in boosting cognitive processing speed in part by reducing interfering activity from DMN.

Based on these findings, alterations in striatal DA function, and ensuing dysfunction in cortico-striatal circuits are believed to play a core role in SUD.

2.1 Alterations in cortico-striatal connectivity.

The majority (~90%) of DA in the brain is released in the striatum (Bertler et al. 1959), which has repeatedly been implicated as a major brain site of dysfunction in SUD. Deficits in striatal D_2R function have been linked to multiple forms of drug addiction (including cocaine, nicotine, heroin, alcohol, and methamphetamine), and even non-drug consumptive behavior such as obesity (Volkow et al. 2009, Volkow et al. 2013). In addition, SUD has been associated with deficits in DA release in response to cues and events associated with drugs of abuse. One hypothesis for how these deficits in striatal DA function contribute to drug use in SUD is termed the “reward hypo-function” hypothesis. This hypothesis posits that due to dopaminergic impairments, addicts do not receive sufficient levels of DA stimulation from natural rewards or moderate quantities of drugs of abuse, and therefore must seek larger quantities of those drugs to achieve satisfaction. Despite the simple clarity of this hypothesis, and its validity in explaining certain behavioral features of SUD, it is clear that more complicated processing occurs in striatal circuitry of addicts, beyond simply seeking additional DA release.

The striatum is the primary input nucleus of the basal ganglia, a network of brain structures that integrate sensory and motivational information, and use it to guide the selection of goal-directed behaviors. Since the basal ganglia lies at the intersection of the anatomical loops linking many cortical and subcortical structures (Bornstein et al. 2011), it is hardly surprising to find cortical correlates of striatal DArgic deficits. Beyond the deficits mentioned above, recent resting state functional connectivity (RSFC) studies have found that cocaine addicted individuals display evidence of impaired functional connectivity along multiple pathways, including those linking the ventral tegmental area (VTA) and substantia nigra (SN) with the striatum and thalamus (Gu et al. 2010, Tomasi et al. 2010), the two hemispheres (Kelly et al. 2011), and the cortex with the striatum (Hanlon et al. 2011). RSFC studies are particularly useful because, by collecting data at rest, they avoid confounds associated with the performance of any task that requires the subject’s cooperation or motivation. As open access to large RSFC databases begin to successfully integrate datasets from multiple studies, RSFC results will achieve increased statistical power and sensitivity to characterize the connectivity of the human brain and its disruption in SUD (Biswal et al. 2010, Tomasi et al. 2011).

Such abnormal cortico-striatal connectivity may reflect a general phenomenon that applies to other forms of SUD beyond cocaine users. For example, abnormal functional connectivity between the dorsal prefrontal cortex (DPFC) and striatum predicts impairments in learning and the magnitude of alcohol craving among alcoholics (Park et al. 2010). In addition, decreased RSFC of anterior cingulate cortex (ACC) among chronic heroin users is associated with more drug-cue induced activation (Liu et al. 2011). Consistent with these results, a more recent comparative study of non-using vs using male prisoners (the latter being those who met criteria for SUD on any of several substances) found SUD to be associated with abnormal connectivity between cortical areas (a network of frontal cortical

regions including dorsal ACC, DPFC, and frontal operculum) and subcortical areas (ventral striatum) (Motzkin et al. 2014).

In addition to deficits in DA function itself, the picture that is emerging from RSFC studies in SUD is that of a faulty flow of information between the centers that process reward and those that govern cognitive-behavioral control (i.e., the PFC). The frontal cortex is crucial for the orchestration of adaptive behavior because of its preeminent role in shaping cognition, including inhibitory control and decision making among others. Thus, dysfunctions in frontal regions are likely to hamper control over compulsive drug intake (Volkow et al. 2006). Supporting this hypothesis, a recent meta-analysis of functional neuroimaging studies on alcohol, cocaine, methamphetamine, and marijuana users (Tomasi et al. 2013) revealed frontal abnormalities that were consistent with the correlations between striatal D_2R reductions and the decreased metabolic activity in ACC, orbitofrontal cortex (OFC) and dorsolateral prefrontal cortex (DLPFC, reviewed in (Tomasi et al. 2013)). The links between SUD and cortico-striatal function are likely to be both a risk factor for, and a consequence of, SUD (Belcher et al., 2014). Animal work (discussed in the next section) has also supported the role of these frontal structures in inhibitory control over drug intake, although it has revealed that this relationship is dynamic, and likely depends on the specifics of the task in which the animal is engaged.

3. Cell type specific manipulations of cortico-striatal circuitry in SUD

While the major brain systems that are altered in SUD have been extensively studied with imaging techniques in humans, modern techniques in animals are allowing the investigation of specific cell types within these circuits with unprecedented control. Two related technologies, optogenetics and chemogenetics, make it possible to selectively stimulate or inhibit particular cell types within a specific brain region by expressing either light-sensitive opsins, or Designer Receptors Exclusively Activated by Designer Drugs (DREADDs) in these cell types (Boyden et al. 2005, Atasoy et al. 2008, Dong et al. 2010). These techniques have been used to examine specific cell types in the structures relevant to SUD, including DA D_1R- and D_2R-expressing medium spiny neurons (termed D1-MSNs and D2-MSNs) in the striatum, and prefrontal cortical pyramidal neurons.

3.1 Optogenetic studies of the prefrontal cortex.

As described in the imaging studies above, the prefrontal cortex (PFC) is involved in executive control, decision-making and reinforcement learning and valuation (Jentsch et al. 1999, Goldstein et al. 2002, Goldstein et al. 2011). The prelimbic cortex (PLC), which corresponds to the dorsomedial PFC in humans, is critical for instrumental learning and goal-directed behavior (Corbit et al. 2003, Ostlund et al. 2005), and is involved in drug and cue induced drug-seeking and reinstatement (Capriles et al. 2003, Di Pietro et al. 2006, Di Ciano et al. 2007, Zavala et al. 2008). The infralimbic cortex (ILC), which corresponds to the ventromedial PDC in humans, is involved in stimulus-response learning and habitual behavior (Coutureau et al. 2003, Killcross et al. 2003). Optogenetic studies of the PFC have demonstrated that specific circuits within the PFC have different roles in modulating

behavior associated with SUD. Importantly, these effects depend on both the specifics of the task and the drug experience of the animal.

Optogenetically inactivating the ILC impaired habit learning (Smith et al. 2012), which could suggest that such a manipulation may prevent the development of compulsive drug seeking in patients with SUD. Indeed, inactivation of ILC inputs to the NAc abolished cocaine induced locomotor sensitization (Pascoli et al. 2012). Similarly, inhibition of ILC neurons during the expression of a cocaine contextual memory impaired recall of recent cocaine memory. Interestingly, activation of ILC neurons during this task facilitated the extinction of remote memory, suggesting a time-dependent switch in the ILC in regards to drug memories (Van den Oever et al. 2013). Photoinhibition of the PLC blunted the cue-induced reinstatement of cocaine-seeking (Stefanik et al. 2013). In apparent contrast, Chen and colleagues demonstrated that the intrinsic excitability of pyramidal neurons in the PLC is decreased following prolonged cocaine self-administration, and that *activating* these neurons can prevent compulsive cocaine seeking (Chen et al. 2013). While this result may seem at odds with those that suggest that inhibition of the PLC is effective at reducing drug use, the differences may be due to methodological differences (Jasinska et al. 2014). These results suggest that different stimulation parameters may attenuate drug-seeking in different contexts, or in animals with different drug exposure or abstinence histories. In both human and animal studies, it is important to recognize the complexity of neural information processing, and that dysfunction is rarely likely to be the result of homogeneous over-activation or under-activation across a wide range of conditions. Therefore, treatment options aimed at rebalancing these circuits will likely require complex manipulations.

3.2 Cell-type specific manipulations of the striatum.

A major projection of the pre-frontal cortex is to the striatum, where it follows a topographic organization such that different cortical regions preferentially innervate different areas of the striatum (Voorn et al. 2004, Humphries et al. 2010). Cortical afferents combine with those from thalamus, amygdala, and hippocampus to modulate the activity of striatal neurons. Approximately 95% of striatal neurons can be divided into two populations that exhibit distinct neurochemical expression patterns and anatomical projection targets (Albin et al. 1989, Gerfen et al. 1990), as well as differential expression of D_1R and D_2R. In the dorsal striatum, striatal neurons primarily expressing D_1R (D1-MSNs) largely overlap with the “direct pathway” striatal projection, while striatal neurons primarily expressing D_2R (D2-MSNs) largely overlap with the “indirect pathway” striatal projection, Figure 2 (Gerfen et al. 1990). D1-MSNs directly project to the internal globus pallidus (iGP) and substantia nigra pars reticulata (SNr), while D2-MSNs project indirectly to the SNr and iGP, by way of the external globus pallidus and subthalamic nucleus. In the ventral striatum (particularly in the shell), approximately 18% of medium spiny neurons express both D_1R and D_2R, and their projections can innervate both the ventral pallidum and the midbrain (Bertran-Gonzalez et al. 2008, Humphries et al. 2010).

As D1-MSNs and D2-MSNs express different DA receptors, DA itself can exert different effects on each population. Although DA receptors are complex GPCRs with diverse function, under most conditions activation of the D_1R enhances excitability while activation

of the D_2R reduces excitability. Optogenetic experiments on these neurons provide a framework for how striatal DA promotes reinforcing effects of drugs of abuse. Optogenetically activating D1-MSNs is reinforcing, and animals will work for self-stimulation of these neurons (Kravitz et al. 2012). Activating these neurons also enhances the reinforcing value of cocaine (Lobo et al. 2010) and accelerates the development of opioid tolerance (Gaspari et al. 2014). D1-MSNs have also been implicated in cocaine (Bertran-Gonzalez et al. 2008) and opioid reward (Cui et al. 2014). Consistent with these results, inhibiting D1-MSNs activity impairs reward learning and cocaine sensitization (Hikida et al. 2010). As DA itself enhances the excitability of D1-MSNs, DA-dependent reinforcement may depend on signaling through these neurons. The reinforcing properties of drugs of abuse (all of which pharmacologically increase striatal DA) (Di Chiara et al. 1988), may therefore depend on D1-MSNs, which may underlie compulsive drug use seen in SUD.

Conversely, animals will avoid places associated with stimulation of D2-MSNs (Kravitz et al. 2012), and stimulation of D2-MSNs reduces the reinforcing value of cocaine (Lobo et al. 2010), and is generally involved in aversive behavior (Hikida et al. 2010). DREADD-mediated inhibition of D1-MSNs in the NAc diminished behavioral sensitization to amphetamine, with the opposite response seen when D2-MSNs were inhibited (Ferguson et al. 2011). As stimulation of D2-MSNs is aversive, and DA can reduce the excitability of these cells through its actions on the D_2R, another function of striatal DA may be to remove an otherwise pervasive aversive state. Finally, recent evidence indicates that striatal interneurons are also involved in DA function, as optogenetically inhibiting cholinergic interneurons in the NAc altered MSN activity and decreased cocaine-induced conditioned place preference, although optogenetic activation of cholinergic interneurons did not modify cocaine preference in this study (Witten et al. 2010). This latter result is somewhat surprising, as optogenetically activating cholinergic interneurons in the NAc strongly increased DA release, although again without reports of modifying behavior (Cachope et al. 2012). In the aggregate, these studies point to opposing roles for D1-MSNs and D2-MSNs in drug reward, and a role for interneurons in modulating the function of these output neurons (Table 1). Considering imaging studies that point to deficits in D_2R signaling in SUD, it is possible that the impaired DA signaling through D_2Rs reduces the ability of DA to remove this pervasive aversive state, which may relate to the inability of non-drug rewards to create pleasure in addicts. In addition, it is worth nothing that D2-MSN induced punishment is much more transient than D1-MSN induced reinforcement, which may relate to why both positive and negative reinforcement processes can be so persistent in SUD (Wise et al. 2014).

3.3 Cortico-striatal projections.

As demonstrated in human imaging studies, brain changes associated with SUD likely depend on connections between the cortex and striatum. The connections between the mPFC and NAc in particular have been suggested to be a final common pathway for eliciting drug seeking (Kalivas et al. 2005) and have been suggested to exert control over drug seeking at different phases during the development of SUD (Everitt et al. 2005). However, optogenetic studies investigating this connection have produced mixed results. While some studies have reported that stimulating the mPFC-NAc projections can support

self-stimulation and real time place preference (Britt et al. 2012), others have found no reinforcement from photostimulation of this pathway (Stuber et al. 2011). Both short term (1 day) and long-term (45 days) withdrawal from either contingent or non-contingent cocaine increased release probability of the ILC-to-NAc synapses, although it was greatest in long-term withdrawal from contingent cocaine (Suska et al. 2013). The authors suggest that this reflects an increase in ILC-to-NAc shell glutamatergic synaptic transmission after withdrawal from exposure to cocaine, which could result in more habitual drug seeking. Consistent with this idea, optogenetic inhibition of the ILC-to-NAc shell pathway abolished cocaine-induced locomotor sensitization (Pascoli et al. 2012) while inhibition of the PLC-to-NAc core pathway impaired the reinstatement of cocaine seeking (Stefanik et al. 2013). This suggests that both of these pathways are critical for cocaine-directed behaviors and both may be potential targets for therapeutics. This said, whether the PLC-to-NAc pathway should be stimulated or inhibited may depend on the task, the drug history, or the state of the individual, per the discussion in section 3.2 (Jasinska et al. 2014). In addition, optogenetic stimulation protocols often differ between studies, making direct comparisons difficult (Kravitz et al. 2013). That said, both human imaging and animal studies implicate connections between cortex and striatum in SUD. In the final sections of this review, we will explore two relatively novel approaches for rebalancing cortico-striatal circuits in SUD. These include neuromodulation with DBS and rTMS, and the pharmaceuticals that can act preferentially on specific cell types and circuits through actions on GPCR heteromers.

4. Novel therapeutic approaches for treating SUD: Neuromodulation

While clinical manipulations generally lack the cell-type specific and temporal precision of optogenetic experiments, novel approaches are beginning to close this gap. One approach that has been widely applied to treating movement disorders is DBS, which refers to the implantation of chronic stimulating electrodes in specific structures to modulate their activity. The mechanism of action for DBS is not fully understood, but it likely includes inhibition of the target structure, in addition to distributed effects throughout the brain (Benazzouz et al. 2000, Hammond et al. 2008, Lee et al. 2011). Another less invasive approach to neuromodulation that also shows promise for treating SUD is repeated trans-cranial magnetic stimulation (rTMS).

4.1 Deep Brain Stimulation.

Multiple groups have evaluated DBS for treating neuropsychiatric disorders including SUD (Wichmann et al. 2011). A number of case studies, often aimed at relieving other psychiatric symptoms, have reported that DBS to the nucleus accumbens (NAc) can be beneficial for reducing intake of alcohol (Kuhn et al. 2007, Muller et al. 2009, Kuhn et al. 2011), nicotine (Mantione et al. 2010, Zhou et al. 2011), and heroin (Zhou et al. 2011, Valencia-Alfonso et al. 2012). Trials of 3–10 patients also revealed beneficial effects of NAc DBS for treating alcoholism and nicotine abuse (Kuhn et al. 2009, Voges et al. 2013). DBS studies in animals are consistent with these results, while also providing some mechanistic insights. DBS of the NAc reduced alcohol (Knapp et al. 2009, Henderson et al. 2010, Wilden et al. 2014) and cocaine (Vassoler et al. 2008, Vassoler et al. 2013) intake in rats. The study by Wilden et al. (2014) suggested that the relevant mechanism for reduction of intake is inhibition of the

NAc, although other studies suggest the opposite (Vassoler et al. 2013). DBS of the PFC has been used to treat depression, chronic pain (Thomas et al. 2009, Boccard et al. 2014), and eating disorders. Although it has not been targeted to treat SUD in humans, optogenetic studies (described above) suggest that neuromodulation of the pre-frontal cortex may also be a promising approach for treating SUD. However, these studies do not provide consistent guidelines for stimulation parameters, which will likely depend on the drug experience and history of the patient, as well as state-dependent effects that are discussed below.

SUD is a complex disorder with symptoms that wax and wane over time. For example, stress and anxiety make addicts (and animals when using models of addiction) more vulnerable to relapse (or reinstatement of drug self-administration). Despite their importance in SUD, these states are often transient, lasting a few hours or days. As such, DBS manipulations may benefit from stimulation paradigms that modulate stimulation parameters in real time, based on the changing needs of the patient. Novel developments in DBS for movement disorders include “closed loop” stimulation, in which recordings from the DBS electrodes are used to optimize the stimulation parameters to best manage symptoms. Such approaches have shown promise in patients with movement disorders (Rosin et al. 2011, Carron et al. 2013, Beuter et al. 2014), and could be beneficial for treating SUD. For instance, as optogenetic work suggests that PFC inhibition can attenuate stress-induced relapse, physiological read-outs of stress (ie: heart rate, blood pressure, galvanic skin response) could inform a DBS stimulator to increase inhibition of the PFC during particularly stressful periods.

4.2 Repeated Transcranial Magnetic Stimulation.

Despite its promise, DBS requires an invasive brain surgery that is not ideal for many SUD patients. An alternative non-invasive neuromodulation technique that has shown promise in treating SUD is rTMS. rTMS refers to the repeated exposure to alternating magnetic fields to modulate brain activity (Burt et al. 2002). In general, low frequency (<1Hz) rTMS is believed to attenuate, while high frequency (>5Hz) is believed to potentiate, synaptic transmission and local brain activity (Lefaucheur 2008). While the direct effects of the magnetic stimulation are limited to cortical areas, rTMS can modulate the activity of deeper structures through cortical projections (Ben-Shachar et al. 1997, Post et al. 2001). Although the literature on the use of rTMS in the treatment of SUD is relatively sparse, it has shown promise for non-invasively modulating neural activity and treating SUD (Barr et al. 2011, Wing et al. 2013). Several studies have reported that high frequency rTMS of the left dorso-lateral prefrontal cortex (l-dlPFC) reduces cravings for tobacco (Eichhammer et al. 2003, Johann et al. 2003, Amiaz et al. 2009, Pripfl et al. 2014). Other studies have indicated that rTMS of the dlPFC reduces craving for cocaine (Camprodon et al. 2007, Politi et al. 2008) and alcohol (Mishra et al. 2010, De Ridder et al. 2011). While reductions in craving are promising, there are few demonstrations of reductions in intake following rTMS. Two studies reported transient reductions in intake of cigarettes (Amiaz et al. 2009) and alcohol (De Ridder et al. 2011), although these reductions were not tracked over long periods. Future work looking at longer-term rTMS, with the goal of reducing intake is necessary to evaluate the promise of turning reductions in craving into reductions in intake.

While the sophistication of neuromodulation is increasing, these techniques inherently lack the cell-type specificity of optogenetics or chemogenetics. As such, some researchers have speculated that optogenetics or DREADD technology will be applied to humans to bring the benefits of cell-type specific manipulations to patients. Researchers are already applying optogenetics to the human retina to combat blindness (Garg et al. 2013, Jacobson et al. 2013), and while applying optogenetics to central brain structures involves additional hurdles, there is no theoretical reason that this is not possible. However, other approaches can take advantage of normal human biology to produce cell-type specific modulation of neural activity in a non-invasive manner. In the next section, we will discuss one promising approach for targeting specific cell types in cortico-striatal circuitry.

5. Targeting specific projections with GPCR heteromer-selective ligands

5.1 Allosteric properties of GPCR oligomers.

Since their discovery, receptors have mostly been considered as single functional units. However, in recent years, a fast growing list of GPCR forming receptor oligomers has emerged (Milligan et al. 2005, Pin et al. 2007, Ferré et al. 2009, Ferré et al. 2014). Receptor oligomers are defined as a macromolecular complexes composed of at least two (functional) receptor units (protomers) with biochemical properties that are demonstrably different from those of its individual components (Ferré et al. 2009). As such, if a specific cell type expresses a unique combination of receptors, it may form unique hetereomeric complexes that could be targeted with pharmaceuticals. A first important concept that arises from the new field of GPCR oligomerization is that the pentameric structure constituted by one GPCR homodimer and one heterotrimeric G protein provides a main functional unit, and oligomeric entities can be viewed as multiples of dimers (Ferré et al., 2014). More specifically, GPCR heteromers are being considered as heterotetramers, formed of two different homodimers, each able to signal with their preferred G protein (Guitart et al., 2004; Navaro et al., 2004).

In such heteromers, each GPCR molecular unit contributes to allosteric modulation of the complex, altering the function or ligand affinity of each GPCR. For example, a ligand binding to one GPCR unit in the complex can lead to changes in the properties of a ligand binding to a different GPCR unit. The best reported example of this phenomenon is the allosteric antagonistic interaction between adenosine A_{2A} receptor ($A_{2A}R$) agonists on D_2R agonists in the $A_{2A}R$-D_2R heteromer (Ferré et al. 1991, Dixon et al. 1997, Kudlacek et al. 2003, Navarro et al., 2014). The $A_{2A}R$-D_2R heteromer is selectively localized in D2-MSNs (Ferré et al. 2007, Azdad et al. 2009, Trifilieff et al. 2011) (Figure 2) and it has been hypothesized that the allosteric interactions between $A_{2A}R$ and D_2R agonists within the $A_{2A}R$-D_2R heteromer provide a main mechanism responsible for the behavioral depressant effects of adenosine analogues and for the psychostimulant effects of selective $A_{2A}R$ antagonists and the non-selective adenosine receptor antagonist caffeine, with implications for several neuropsychiatric disorders. In fact, the same mechanism provided the main rationale for the use of $A_{2A}R$ antagonists in Parkinson's disease (Armentero et al., 2011; Jorg et al., 2014). A compound that selectively activated D_2Rs only when bound into $A_{2A}R$-D_2R heteromers could have a higher affinity for D_2Rs on D2-MSNs than D_2Rs on other cell

types in the brain and also be potentially useful as asntiparkinsonian agent. But, based on the important role of D2-MSNs in SUD (described in section 2 and 3.2), D_2R agonists or $A_{2A}R$ receptor antagonists with preferential affinity or functional response in $A_{2A}R$-D_2R receptor heteromers could could also constitute a promising approach for preferentially targeting these cells with a systemically delivered pharmaceuticals.

5.2 GPCR heteromers for targeting circuits involved in SUD.

The proof of concept of using GPCR heteromers to dissect distinct subpopulations of receptors came from experiments that compared the effects of several $A_{2A}R$ antagonists for their ability to produce locomotor activation or to block glutamate release induced by cortical stimulation (Orru et al. 2011). Locomotor activation depends on postsynaptic $A_{2A}R$, which form heteromers with D_2R on D2-MSNs. Blockade of presynaptic cortico-striatal neurotransmission depends on presynaptic $A_{2A}R$ which form heteromers with adenosine A_1 receptors (A_1Rs) localized in terminals of cortical neurons (Ciruela et al. 2006, Quiroz et al. 2009) (Figure 2). Therefore, assays of locomotor activation and cortico-striatal neurotransmission can reveal whether post-synaptic $A_{2A}R$-D_2R heteromers or presynaptic $A_{2A}R$-A_1R heteromers are preferentially activated. Based on their potency for blocking striatal glutamate release and potency for inducing locomotor activation in rats, two $A_{2A}R$ antagonists, SCH-442416 and KW-6002, were found to have preferential pre or post-synaptic activities, respectively (Orru et al. 2011). Parallel experiments in transfected cells demonstrated that the pre- and postsynaptic effects of these $A_{2A}R$ antagonists depend on their differential affinity for binding to $A_{2A}R$ heteromers. SCH-442416 bound with much less affinity to $A_{2A}R$ when co-expressed with D_2R than with A_1R. KW-6002 showed the best relative affinity for $A_{2A}R$ co-expressed with D_2R. The expected differences in affinity of SCH-442416 for $A_{2A}R$ in the presence and absence of D_2R have been reproduced in striatal tissue from wild-type mice and conditional striatal D_2R knock-out mice (results in preparation). The relative affinities for the different receptor heteromers may explain the behavioral actions of these compounds.

The possibility of targeting A_1R-$A_{2A}R$ heteromers was also used to identify an important contributor to the reinforcing effects of cannabinoids (Justinova et al. 2011, Justinova et al. 2014). A paradoxical result reported that the $A_{2A}R$ antagonist MSX-3 decreases THC and anandamide self-administration in squirrel monkeys at a relatively low dose, while a three-fold higher dose produced the opposite effect (Justinova et al. 2011). Based on results obtained in rats (Orru et al. 2011), it was hypothesized that the different dose-dependent effects of MSX-3 could be related to a slightly selective presynaptic effect at lower doses with an overriding postsynaptic effect at larger doses. This hypothesis was confirmed by testing the effects of SCH-442416 and KW-6002 (Justinova et al. 2014). SCH-442416 produced a significant shift to the right of the THC self-administration dose-response curves, consistent with antagonism of the reinforcing effects of THC. On the other hand, KW-6002 produced a significant shift to the left, consistent with potentiation of the reinforcing effects of THC. These results show that selectively blocking presynaptic $A_{2A}R$ could provide a pharmacological approach to the treatment of marijuana dependence, and underscore cortico-striatal glutamatergic neurotransmission as a possible main mechanism involved in the rewarding effects of THC. At a more general level, these results also show that while

the concept of using GPCR heteromers to target specific cell types is relatively new, it is a promising approach for targeting specific cell types to modulate specific symptoms of SUD.

6. Conclusion

SUD is associated with alterations throughout the brain, including cortical and striatal circuits. Imaging studies in humans have demonstrated multiple alterations in these circuits, and animal studies are beginning to unravel the function of specific neuron types in these circuits with unprecedented precision. Ultimately, there is a need for new therapies that target these cells and ameliorate the symptoms of SUD. Based on data from human and animal work, new brain stimulation approaches are starting to make headway in targeting these structures in addicted patients. Novel pharmacological development involving GPCR heteromer-selective ligands represents another approach for targeting these circuits and alleviating the symptoms of SUD. While both brain stimulation and GPCR heteromer technologies are in their infancy, we believe that they represent promising new approaches for treating SUD.

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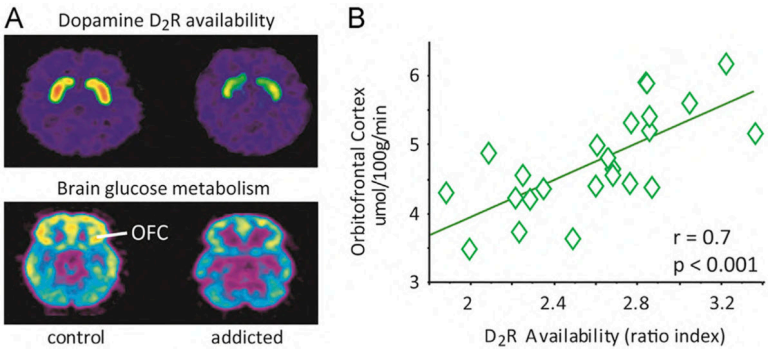

Figure 1.

Association between low DA D_2R availability and low cortical glucose metabolism in SUD. **A.** Examine PET scan images of a control and a SUD patient demonstrating lower 11C-raclopride binding to the D_2R (top), and reduced orbitofrontal (OFC) glucose metabolism (bottom). **B.** D2R availability is positively correlated with OFC metabolism in a group of patients.

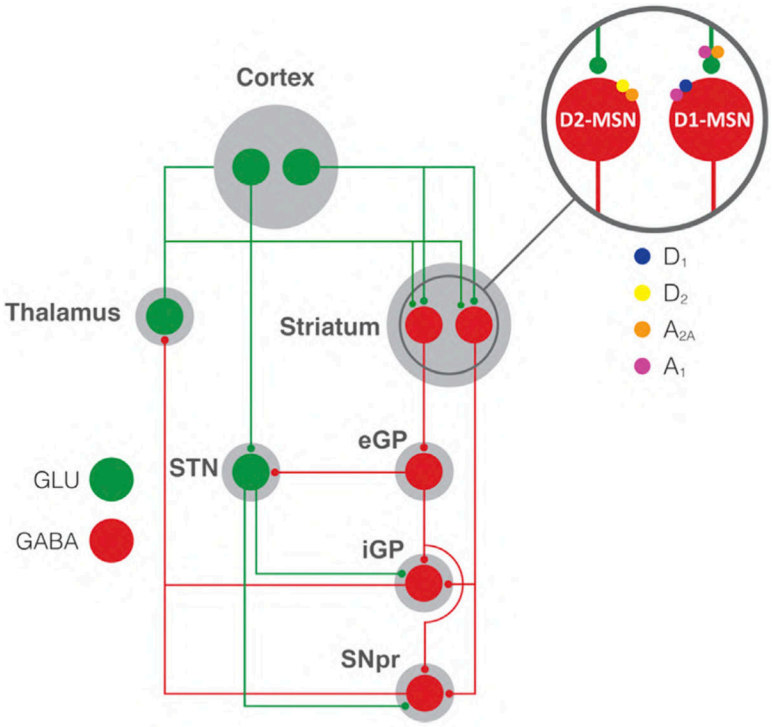

Figure 2.

Basal ganglia circuitry and localization of pre- and postsynaptic adenosine and DA receptor heteromers in the D1-MSNs and D2-MSNs, as possible targets for SUD. D1-MSNs directly connect the striatum with the output structures of the basal ganglia: the internal segment of the globus pallidus (iGP) and substantia nigra pars reticulata (SNpr). D1-MSNs connect with the output structures by relays in the external segment of the globus pallidus (eGP) and the subthalamic nucleus (STN). DA induces a strong thalamo-cortical disinhibition by acting on stimulatory D_1R localized in the D1-MSN, which form heteromers with A_1R, and on inhibitory postsynaptic D_2R localized in the D2-MSN, which form heteromers with $A_{2A}R$. $A_{2A}R$ forming heteromers with A_1 receptors are localized in cortico-striatal glutamatergic terminals that contact D1-MSN.

Table 1.

Optogenetic/chemogenetic studies implicating cortico-striatal circuitry in substance use disorder

	Publication	Brain region/ circuit	Manipulation	Effect on behavior
Striatum/NAc	Lobo et al., 2010	NAc	Pairing cocaine with optogenetic activation of D_1R-MSNs or D2-MSNs	D1-MSN: ↑cocaine reward D2-MSN: ↓ cocaine reward
	Witten et al., 2010	NAc	Optogenetic activation or inhibition of cholinergic interneurons	Inhibition during cocaine exposure: ↓ cocaine CPP Activation: no effect
	Cachope et al., 2012	NAc	Optogenetic activation of cholinergic interneurons	↑ NAc DA release
	Ferguson et al., 2011	NAc	Inhibitory DREADD in D1-MSNs or D2-MSNs	D1-MSN: ↓ amphetamine sensitization D2-MSN: ↑ amphetamine sensitization
	Kravitz et al., 2012	Dorsal striatum	Operant responding for D1-MSNor D2-MSN optogenetic stimulation	D1-MSN: ↑ reinforcement D2-MSN: ↓reinforcement
	Cassataro et al., 2014	NAc	Inhibitory or excitatory DREADD in NAc neurons	excitation: no effect inhibition: ↓ alcohol consumption
	Gaspari et al., 2014	NAc	Optogenetic activation of D1-MSNs, D2-MSNs, or *RGS9*-expressing neurons	D1-MSN: ↑ RGS9–2 levels ↑ morphine tolerance D2-MSN: ↓RGS9–2 levels RGS9: ↑ morphine tolerance
Prefrontal cortex	Chen et al., 2013	PLC (dmPFC)	Optogenetic activation or inhibition after cocaine was paired with footshock	Activation: ↓cocaine seeking inhibition: ↑cocaine seeking
	Stefanik et al., 2013	PLC (dmPFC)	Optogenetic inhibition	↓cue-induced reinstatement
	Van den Oever et al., 2013	ILC (vmPFC)	Optogenetic activation or inhibition of pyramidal neurons during expression of cocaine-contextual memory	Activation: ↑ extinction of remote cocaine memory Inhibition: ↓recall of recent cocaine memory
PFC-to-NAc projections	Stuber et al., 2011	mPFC-to-NAc projections	Optogenetic activation	No self-stimulation
	Britt et al., 2012	mPFC-to-NAc projections	Optogenetic activation	↑real-time place preference and self-stimulation
	Pascoli et al., 2012	ILC-to-NAc projections	Optogenetic inhibition	↓cocaine induced locomotor sensitization
	Stefanik et al., 2013	PLC-to-NAc projections	Optogenetic inhibition	↓cue-induced reinstatement