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Invited review

Dopamine D3 and 5-HT$_{1B}$ receptor dysregulation as a result of psychostimulant intake and forced abstinence: Implications for medications development

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ABSTRACT

Addiction to psychostimulants, including cocaine and amphetamine, is associated with dysregulation of dopamine and serotonin (5-HT) neurotransmitter systems. Neuroadaptations in these systems vary depending on the stage of the drug taking-abstinence-relapse cycle. Consequently, the effects of potential treatments that target these systems may vary depending on whether they are given during abstinence or relapse. In this review, we discuss evidence that dopamine D3 receptors (D3Rs) and 5-HT$_{1B}$ receptors (5-HT$_{1B}$Rs) are dysregulated in response to both chronic psychostimulant use and subsequent abstinence. We then review findings from preclinical self-administration models which support targeting D3Rs and 5-HT$_{1B}$Rs as potential medications for psychostimulant dependence. Potential side effects of the treatments are discussed and attention is given to studies reporting positive treatment outcomes that depend on: 1) whether testing occurs during self-administration versus abstinence, 2) whether escalation of drug self-administration has occurred, 3) whether the treatments are given repeatedly, and 4) whether social factors influence treatment outcomes. We conclude that D3/D2 agonists may decrease psychostimulant intake; however, side effects of D3/D2R full agonists may limit their therapeutic potential, whereas D3/D2R partial agonists have fewer undesirable side effects. D3-selective antagonists may not reduce psychostimulant intake during relapse, but nonetheless, may decrease motivation for seeking psychostimulants with relatively few side-effects. 5-HT$_{1B}$R agonists provide a striking example of treatment outcomes that are dependent on the stage of the addiction cycle. Specifically, these agonists initially increase cocaine's reinforcing effects during maintenance of self-administration, but after a period of abstinence they reduce psychostimulant seeking and the resumption of self-administration. In conclusion, we suggest that factors contributing to dysregulation of monoamine systems, including drug history, abstinence, and social context, should be considered when evaluating potential treatments to better model treatment effects in humans.

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1. Introduction

Several theories of addiction postulate that chronic intake of drugs of abuse challenges homeostatic regulation of the neurotransmitter systems that are directly affected by the drugs, resulting in compensatory changes that are likely at the heart of the pathology underlying the development of dependence (Ahmed and Koob, 1998; Antelman and Caggiula, 1996; Kalivas, 2009; Koob et al., 2004, 1997; McEwen, 2000). Because these changes are caused by drug-induced neurotransmission outside of the physiological range associated with natural stimuli, we refer to the process causing them as dysregulation. Neurons that are directly affected by a drug may cause dysregulation of downstream neurons, which then continues to cascade throughout interconnected neurons within brain circuits.

Monoamine transporters are primary sites of action of psychostimulants (Akimoto et al., 1990; Reith et al., 1997; Zetterstrom et al., 1983). Dysregulation of circuitries involving monoamine neurotransmitters occurs with repeated psychostimulant use and

Abbreviations: D3Rs, dopamine D3 receptors; 5-HT$_{1B}$Rs, 5-HT$_{1B}$ receptors; SA, self-administration; PR, progressive ratio; FR, fixed ratio; VI, variable interval; NAc, nucleus accumbens; NAcsh, nucleus accumbens shell; NAcc, nucleus accumbens core; A$_{2A}$Rs, adenosine A$_{2A}$ receptors; EPM, elevated plus maze; OCD, obsessive–compulsive disorder; VTA, ventral tegmental area; BLA, basolateral amygdala; CeA, central amygdala; dSt, dorsal striatum.

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may manifest as 1) changes that oppose the drug's effects resulting in tolerance and withdrawal syndromes (Ahmed et al., 2002); 2) changes that amplify the drug's effects leading to sensitization (Robinson and Berridge, 2000); and 3) gradual shifts in the relative activity among parallel circuits (e.g., mesolimbic versus nigrostriatal pathways) (Porrino et al., 2007). Escalation of drug intake is a hallmark sign of the development of addiction and continues to challenge homeostasis making the dysregulation progressively more pronounced and possibly distinct from that occurring with limited drug intake (e.g., Orio et al., 2010). Abstinence results in the loss of drug-induced input to these circuits, again challenging homeostasis and causing its own dysregulation. Abstinence-induced dysregulation may become more pronounced with time causing the emergence and strengthening of drug craving (Gawin and Kleber, 1986; Tran-Nguyen et al., 1998), a phenomenon known as the incubation effect (Grimm et al., 2001).

Dysregulation is dynamic with different changes occurring in the brain at different stages of the drug abuse–abstinence–relapse cycle. In this review, we discuss evidence of dysregulation involving two different monoamine receptor subtypes: dopamine D3 receptors (D3Rs) and 5-HT_{1B} receptors (5-HT_{1B}Rs). We then discuss evidence from psychostimulant self-administration (SA) animal models that supports the development of medications that target these receptors. To aid with interpretation of this literature, we first discuss how various measures of drug SA are differentially sensitive to the incentive motivation and reinforcement processes that are involved in addiction and how these measures may inform treatment efficacy that is dependent on the stage of the abuse–abstinence–relapse cycle. We conclude that both D3Rs and 5-HT_{1B}Rs are good targets for development of medications for psychostimulant dependence and emphasize that research in this area will benefit from considering the dynamic changes in monoamine neurotransmitter systems that have been identified from basic neuroscience research.

1.1. Relevance of animal models to the chronic relapsing cycle of dependence

Drug SA involves incentive motivation, the process by which organisms are energized to seek drug, and reinforcement, the process by which response-contingent delivery of drug increases the probability of performing the response (Markou et al., 1993). There are procedures that can increase sensitivity to detecting effects of a manipulation on incentive motivation, such as requiring high workloads or testing under extinction conditions so that drug reinforcement is not available. This review focuses on four approaches to testing potential therapeutics: 1) psychostimulant SA under low demand schedules of reinforcement, 2) SA under progressive ratio (PR) schedules of reinforcement, 3) reinstatement of extinguished drug-seeking behavior either by acute stress, drug-associated cues, or drug priming injections, and 4) resumption of drug SA after a period of abstinence. Extinction and reinstatement of drug seeking reflects incentive motivational effects of the reinstating stimulus, and when response-contingent cues are used, also reflects conditioned reinforcing effects of the cues. There are many parallels between psychostimulant-seeking behavior measured in this model and self-reports of craving (Fuchs et al., 1998; Markou et al., 1993; Stewart, 1983), supporting the predictive validity of the model as a screen for anti-craving effects of medications. Resumption of psychostimulant SA after a period of abstinence is less commonly used to screen potential treatment effects, but in our view, offers a model with strong face validity for screening anti-relapse effects. Screening treatment effects during maintenance of SA is a common approach. The use of PR schedules to assess effects of a treatment on maintenance of SA is more sensitive to motivation than low ratio or interval schedules because the work demand increases across successive reinforcers (Markou et al., 1993; Salamone and Correa, 2012). With low ratio or interval schedules, the psychostimulant dose–effect function is typically an inverted U-shaped function whereas on PR schedules it is typically linear within non-toxic dose ranges. Typically, treatment-induced shifts of the psychostimulant SA dose–effect function to the left reflect facilitation of a pharmacological action at a receptor involved in drug reinforcement, shifts to the right reflect blockade of a pharmacological action at a receptor involved in drug reinforcement, upward shifts reflect enhancement of drug reinforcement, and downward shifts reflect attenuation of drug reinforcement (Mello and Negus, 1996). The latter outcome is optimal for a potential treatment because drug intake is reduced regardless of the self-administered dose.

2. Dysregulation of dopamine D3 receptors

One interesting characteristic of D3Rs that make them particularly relevant in addiction is their localization. D3R expression is primarily restricted to structures in the mesolimbic pathway, including the nucleus accumbens shell (NAc_{sh}), islands of Calleja, olfactory tubercle, and the ventral tegmental area (VTA) (reviewed by Heidbreder et al., 2005; Sokoloff et al., 2006). Importantly, the mesolimbic pathway is strongly implicated in drug addiction (Kalivas and Volkow, 2005; Wise, 2004). D3Rs are expressed on dopaminergic cell bodies where they may function as autoreceptors (Diaz et al., 2000). They are also expressed postsynaptically in the NAc_{sh} on medium spiny GABAergic neurons (Ridray et al., 1998). Convergent evidence suggests that psychostimulant use up-regulates D3Rs and that this effect is related to an increase in motivation for drug. In humans, psychostimulant overdose increases D3R binding in the ventral striatum (Boileau et al., 2012; Segal et al., 1997; Staley and Mash, 1996). In rodents, an increase in D3R binding in the ventral striatum emerges during the course of abstinence from a chronic cocaine regimen (Collins et al., 2011; Conrad et al., 2010; Marcellino et al., 2007; Neisewander et al., 2004) in parallel with the time-dependent enhancement of cocaine-seeking behavior (Morgan et al., 2002a; Neisewander et al., 2000; Tran-Nguyen et al., 1998). Furthermore, chronic administration of the D3/D2R agonist 7-OH-DPAT during abstinence from cocaine SA normalizes the elevated striatal D3R levels and reduces cocaine-seeking behavior (Fuchs et al., 2002; Neisewander et al., 2004). These findings suggest that there is a positive relationship between D3R binding and motivation for cocaine. Interestingly, the D3R up-regulation may depend on learning. Rats that have learned to associate a distinct environment with cocaine, as revealed by the expression of conditioned locomotor hyperactivity, have increased D3R levels in both the nucleus accumbens core (NAc_C) and shell (NAc_{sh}) in the ventral striatum (Le Foll et al., 2002). Such an increase is absent in rats exposed to cocaine in a familiar environment (home cage).

2.1. Limitations and complexities in evaluating potential D3R-targeted treatments

One complication in classifying D3R compounds into agonist, partial agonist or antagonist categories is that some compounds show functional selectivity. Functional selectivity describes the phenomenon that a ligand can have different intrinsic activities on different second messenger signaling systems that are coupled to the same receptor (Mailman, 2007; Urban et al., 2007). For example, the D3/D2R compound BP 897 acts as a partial agonist at the D3R in signaling pathways of mitogenesis (Pilla et al., 1999) but acts as an antagonist in GTPγS-dependent pathways (Gyertyán