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Diminished Role for Dopamine D1 Receptors in Cocaine Addiction?

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Dopamine D1-like receptors are directly related to the generation of reward-related signals in the brain. In drug naïve animals, selective stimulation of D1 receptors is sufficient to support acquisition and maintenance of self-administration behavior (1). Blockade of D1 receptors strongly attenuates the rewarding effects of psychostimulants drugs like cocaine and amphetamine, and D1 receptor knockout mice fail to acquire cocaine self-administration (1). D1 receptors are positively coupled to stimulatory G proteins, adenylate cyclase, and can facilitate excitatory input to D1-expressing neurons in striatal reward regions. Hence, drug naïve rodents will self-administer direct optogenetic excitation of D1-containing striatal neurons, essentially bypassing D1 receptor effects (2). In contrast to D1 receptors, selective stimulation of D2-like receptors fails to engender primary rewarding effects in drug naïve rodents, but can facilitate the conditioned rewarding effects of environmental stimuli associated with prior drug self-administration (1, 3).

Given that D1 receptors mediate cocaine's rewarding effects, it may seem paradoxical that pretreatment with a D1 receptor antagonist actually causes an escalation of cocaine self-administration when animals are allowed relatively free access to intravenous cocaine injections. Under these conditions, it is thought that animals titrate their preferred optimal level of cocaine intake over time, and compensate for D1 receptor blockade by self-administering cocaine at a faster rate. This causes a greater elevation in brain dopamine levels that displaces the D1 antagonist from its receptor and yields a preferred level of D1 receptor stimulation. Escalation of cocaine intake also occurs in rats after prolonged daily access to self-administration, and is thought to reflect a transition to more addicted biological states (4), thereby emulating hallmark psychiatric criteria for substance use disorders in humans. These tolerance-like effects are reflected by reports of feeling less "high" and euphoria in long-term cocaine abusers when compared to earlier stages of drug use, and a similar blockade of cocaine-induced euphoria is produced by acute pretreatment with the D1 receptor antagonist ecopipam (5). Based on these findings, it is reasonable to hypothesize that the development of cocaine addiction involves an attenuation of reward

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signals mediated by D1 receptors, and this loss of D1 function contributes to reward tolerance along with compensatory escalation in the amount of cocaine self-administered.

In a previous study, Ahmed and Koob (4) found that pretreatment with a non-selective dopamine receptor antagonist fails to induce further compensatory escalation in cocaine intake in rats following extended access to cocaine self-administration, possibly due to ceiling effects of attenuated dopamine receptor function. These rats actually exhibited greater sensitivity to profound suppression of self-administration behavior seen at higher antagonist doses, again suggesting an inherent dopamine receptor deficit following the transition to addiction. Such alterations in D1 dopamine receptor levels are reported following chronic cocaine self-administration, but the results are discrepant across many studies and complicated by numerous factors including length of exposure, abstinence period and species.

Escalation of cocaine intake may be inversely related to some index of reduced reward strength or euphorogenic effect. In contrast, the motivation for cocaine is an entirely different aspect of self-administration behavior that is reflected by the amount of effort animals will exert to obtain the drug, rather than the actual amount of drug consumed. To assess motivation in animals, progressive ratio reinforcement schedules are often employed, where animals must perform a progressively greater number of responses to obtain each successive cocaine injection. Thus, for example, the ratio of lever-press responses for each successive cocaine injection may increase as follows (1, 2, 4, 6, 9, 12, 15, 20, etc.) At some point, often after animals achieve a response/injection ratio upwards of 100 lever presses per cocaine injection, animals will cease self-administration behavior altogether. The highest ratio of lever presses/drug injection achieved prior to cessation of self-administration behavior is referred to as the “break point”, and is an index of the maximal effort exerted, or motivation, for cocaine. Systemic pretreatment with D1 receptor antagonists decreases break points for cocaine self-administration on progressive ratio reinforcement schedules, consistent with reduced motivation for cocaine, and opposite to the compensatory increases in cocaine self-administration produced by D1 receptor antagonism with less demanding response requirements described above (1). Similar bidirectional effects on low and high effort cocaine self-administration are found when D1 antagonists are infused into the nucleus accumbens, a dopamine terminal region highly implicated in primary cocaine reward (1).

In this issue of *Biological Psychiatry*, Ramôa, Lynch and colleagues utilized progressive ratio testing in rats to assess the ability of local D1 receptor blockade in the nucleus accumbens to reduce motivation for cocaine following extended access conditions that promote escalation and the development of addicted phenotypes (6). After initial acquisition of self-administration behavior, they split rats into one of two groups; 1) rats with short daily access that were allowed to self-administer a maximum of 20 cocaine injections a day, or 2) rats with extended 24-hour access to cocaine for a maximum of 96 injections available each day. After 14 days of abstinence from cocaine, rats were tested for break points in cocaine self-administration using the progressive ratio procedure, and either with or without intra-accumbens D1 antagonist pretreatment. They compared male and female rats, and found that both sexes show similar enhancement in the motivation for cocaine following extended

access cocaine self-administration, with break points tripling to ~90 responses/injection from the ~30 responses/injection found with short access cocaine self-administration.

In rats subjected to short access cocaine self-administration (male and female), the D1 antagonist SCH 23390 produced prominent, dose-dependent reductions in break points for cocaine self-administration to about one half of control levels, consistent with previous work. In stark contrast, animals allowed extended access to cocaine self-administration exhibited virtually no reductions in break points following intra-accumbens infusions of the D1 antagonist. This profound loss of sensitivity suggests that D1 receptors in the nucleus accumbens no longer play a role in motivating cocaine self-administration behavior once animals develop an addicted behavioral phenotype. The findings are paralleled by previous work showing reduced sensitivity to D1 receptor-mediated locomotion and regulation of cocaine-seeking behavior among individual rats with higher preferred levels of cocaine intake when compared to rats with lower preferred levels of cocaine intake (1, 7). Moreover, human cocaine abusers who avidly choose cocaine over money rewards in laboratory settings show lower striatal D1 binding potentials than those who choose money over cocaine, although no overall decrements in D1 receptors are apparent when cocaine abusers are compared to non-abuser controls (8).

While the D1 antagonist was ineffective following extended cocaine access in this study, it is possible that higher intra-accumbens doses of SCH 23390 ($> 3.0 \mu\text{g}$) would reduce motivation for cocaine, reflecting a tolerance-like rightward shift in sensitivity to D1 receptor blockade. It would be informative to determine whether systemic D1 antagonist treatment also loses efficacy in these animals, since D1 receptors located in other brain regions including medial prefrontal cortex and ventral tegmental area motivate cocaine use in animals with short access to cocaine self-administration (1).

Interestingly, the study found that ovariectomized female rats fail to exhibit enhanced motivation for cocaine following extended access self-administration, unless they were given estradiol replacement treatment (6). This suggests that estradiol is necessary for vulnerability to transit to more cocaine-addicted states in females. Ovariectomized females with extended cocaine access also maintained sensitivity to the D1 antagonist-mediated reductions in motivation for cocaine, similar to rats with short access to cocaine self-administration. However, estradiol replacement restored resistance to D1 blockade in the extended access females, indicating that loss of D1 receptor sensitivity may underlie the estradiol effect on vulnerability to cocaine addiction. The authors note several previous studies showing that female sex hormones confer higher initial responsiveness to psychostimulants, but their study establishes a role for estradiol in facilitating the development of addiction with prolonged cocaine use.

The results of this study are consistent with the hypothesis that cocaine addiction creates an imbalance in D1 and D2 dopamine receptor responsiveness, favoring D2 over D1 receptor function. This idea may seem contrary to long-lasting decrements in cortical and striatal D2 receptor levels found in long-term human cocaine abusers (9), but other studies in animals suggest that chronic cocaine use can enhance functional coupling and behavioral responsiveness of D2 receptors (7, 10), and D2 receptors mediate powerful relapse effects in

animals models of cocaine-seeking behavior (1). Given the prominent and often opposing influence of D1 and D2 receptors on cocaine-motivated behaviors (1, 7), a pathological imbalance involving reduced reward signals mediated by D1 receptors and/or enhanced craving responses mediated by D2 receptors, or alterations in the direct and indirect striatal circuits that preferentially express these receptors, the restoration of D1 receptor function may represent an important goal for treating cocaine and other addictions.

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