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Narrowing in on compulsions: Dopamine receptor functions

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Abstract

A series of experiments in rats explored the possibility that D3/D2 dopamine receptors are involved in behaviors that might be related to compulsion. A series of D3/D2 agonists and antagonists were shown to elicit yawning (D3-) and its inhibition (D2-receptor mediated). In rats with histories of cocaine exposure, D3-agonist-elicited yawning was enhanced, and quinpirole led to persistent operant responding only if conditioned-stimuli associated with cocaine were presented for responding. Finally, a more selective D3 partial agonist was reported that had a novel profile of activity that could have relevance to the suppression of dopamine-related compulsions.

Keywords

impulse control disorders; dopamine D2-like receptors

Impulse control disorders involve behaviors that occur excessively, seeming to be disconnected from the feedback normally imposed by the signaling, delivery, and consumption of reinforcers. Thus, whereas normal eating stops when the eater is sated, compulsive overeaters are not limited by food satiation. A similar lack of feedback restraint occurs with hypersexual behavior. On the other hand, compulsive behavior may continue even though the previously positive or pleasurable results of this behavior are no longer obtained. Compulsive shoppers may have little interest in the merchandise they seem unable to refrain from purchasing, and compulsive gamblers and drug abusers engage excessively in behaviors that can destroy their social, economic, and personal well being, yet provide precious little apparent enjoyment.

A possible connection between the dopamine receptors and impulse control disorders has been given a fascinating measure of support from a recently-described clinical condition in patients with Parkinson's Disease (PD) who are treated with dopamine agonists. As reviewed by Voon and Fox (2007), approximately 6% of these patients develop compulsive behaviors that include hypersexuality, compulsive gambling, overeating, shopping, or medication use. Although there is as yet no clear relation between these particular behaviors and a specific dopamine agonist therapy, and only occasionally has a clear dose-effect correlation been described in PD patients, a relation between dopamine agonists and these aberrant behaviors in predisposed individuals seems clear.

Two popular pharmacotherapies for PD that are implicated in impulse control disorder are pramipexole and ropinirole, used alone or in combination with the dopamine precursor, levodopa. Pramipexole and ropinirole are dopamine agonists with preference for the D3 receptor over the D2 receptor, and with low affinity for D1-like receptors (Piercey, 1998). In the doses used for treatment, it is probable that both D3 and the D2 receptors are activated by these drugs, and the case studies in which impulse control disorders are described do not permit determination of whether action at either or both of these sites is important either for treating the symptoms of PD or for producing impulse control disorders. In addition, it is not known what the impact of the neurochemical deficits produced by PD itself is on dopamine-agonist induced compulsive behavior, or why this effect is revealed in only a small proportion of patients. Much remains to be learned.

This points to need for preclinical approaches to evaluation of the role of D2 and/or D3 receptor activation, and potential setting conditions for the development of compulsive behavior. Two major impediments have restricted this research: one is the scarcity of drugs, either agonists or antagonists, that have the requisite selectivity for either the D3 or D2 receptor; the second is the lack of clear criteria that define behavior as compulsive. We have been evaluating the effects of D3-preferring D3/D2 agonists on a variety of behaviors in rats because of an interest in identifying D3-specific ligands. Our findings, as well as the clinical and preclinical literature, support the notion that compulsive behavior may indeed be linked to activity at the D3 receptor, and therefore potentially reduced by selective D3 antagonists or partial agonists.

One of our most useful findings confirms the suggestion (Levant, 1997) that dopamine agonist-induced yawning in rats is specifically mediated by D3 receptor activation (Collins, Witkin et al., 2005; Collins, Newman, et al., 2007). Having a selective assay for D3 activity is critical for evaluation of effects of agonists and antagonists at this site. Drugs that are D3-preferring, with actions on D3 receptors at small doses and on D3 and D2 receptors at larger doses, produce an inverted U-shaped pattern of activity in the yawning assay. Dose-dependent increases in yawning are observed with small doses of D3-preferring agonists including pramipexole, quinpirole, PD-128,907, and 7-OH-DPAT, whereas dose-dependent decreases in yawning are observed at higher doses. Correlated with the decreasing limb of the yawning dose-response curve is a decrease in body temperature, an effect that appears to be due to agonist activity at the D2 receptor (Figure 1A - D). Antagonists selective for D3 over D2 receptors inhibit the induction of yawning produced by small doses of the agonists (Figure 1E) while having no effect on the inhibition of yawning, or induction of hypothermia produced by larger doses. D2-selective antagonists, on the other hand, do not affect the induction of yawning following small agonist doses, but reverse the inhibition of yawning (Figure 1F) and decrease in body temperature observed at larger doses (Collins et al., 2005; 2007). Analysis of these dose-response functions not only permits the characterization of agonists and antagonists with activity at the D3 and D2 receptors, but also allows for greater insight into the receptor(s) involved in the mediation of other behavioral effects of D3/D2 agonists and antagonists.

Following a finding by Nader and Mach (1996), who reported that a D3-preferring D3/D2 agonist like quinpirole does not maintain self-administration behavior in monkeys unless the animals have a history of cocaine self-administration, we evaluated the ability of quinpirole to serve as a reinforcer in rats. We replicated the findings of Nader and Mach (1996), but also observed that even in rats with a history of cocaine self-administration, quinpirole failed to maintain responding if the stimuli previously associated with cocaine were not presented (figure 2A). Furthermore, responding maintained by the stimuli previously paired with cocaine was observed if quinpirole was simply administered, noncontingently, prior to the session (figure 2B). In the absence of the cocaine-associated stimuli, quinpirole pretreatment

did not elicit responding (figure 2C). In the absence of quinpirole, the stimuli themselves did not maintain responding (figure 2C). What appeared to be quinpirole-maintained responding in cocaine-experienced rats actually was responding maintained by cocaine-paired stimuli that seemed to become salient in the presence of quinpirole.

Other investigators have also noted unusual effects of quinpirole administration. Amato, Milella, Badiani, and Nencini (2006), for example, have found that water-deprived rats, given quinpirole before daily sessions of water-reinforced responding, initially showed decreases in water-maintained responding, and subsequently showed marked increases in responding. However, the rats did not consume the reinforcers they earned, and in fact, continued to respond and receive water presentations even when water was freely available in their operant chambers.

The requirement that quinpirole be given for several days before a disconnection was observed between responding and consumption of the water reinforcer is not incidental. Neither was the requirement of several days of exposure to cocaine before quinpirole induced lever pressing for cocaine-paired stimuli, nor the daily administration of levodopa to PD patients long before compulsive behavior developed. Chronic administration of dopamine agonists or dopamine releasing compounds appears to be required to set the stage for the development of D3/D2-induced compulsive responding. The sensitized response involves, but is not necessarily limited to the D3 receptor, as indicated by our finding (Truong and Collins, unpublished observations) that pramipexole becomes more effective and potent in its capacity to elicit yawning in rats that have been exposed to a sensitizing regimen of cocaine injections (2 days of 15 mg/kg/day followed by 5 days of 30 mg/kg cocaine). Cocaine, itself, does not induce yawning, and this exposure to cocaine did not result in an immediate increase in the potency or effectiveness of pramipexole, but rather the sensitization increased gradually over a period of more than a week (Figure 3), suggesting that an incubation period may be a necessary component for the development of impulse control disorders.

These and other studies have led us to define compulsive behavior in terms of the setting conditions that appear to evoke it and the conditions that appear to maintain it. The setting conditions for compulsive behavior includes the presence of agonist actions on D3 and/or D2 receptors and a past history of exposure to these drugs or other dopamine agonists or dopamine releasing drugs. Once the setting conditions of previous dopamine exposure and current presence of D3 or D2 agonists are met, the compulsive behavior will appear as excessive (if the opportunity for excessive behavior is present) or as behavior that occurs regardless of whether that behavior is reinforced (i.e., in extinction) or the organism is sated. All that appears to be required is that the behavior generates stimuli that were previously paired with a "potent reinforcer".

If it is the case that the D3 receptor is especially critical to the development, either of the sensitization necessary for compulsive behavior, or for the expression of compulsive behavior, or both, it is possible that a selective D3 antagonist or partial agonists would be effective in reducing compulsive behavior as modeled in animals or in impulse control disorders in humans. Ongoing efforts to synthesize ever more selective D3 ligands has had some recent positive results, and evaluation of the compounds in animal tests of stimulus-bound compulsive disorder has been positive (Spiller, Xi, et al., 2008; Di Ciano, Underwood, Hagan, & Everitt, 2003). We have, in collaboration with Drs. Shaomeng Wang, Jianyong Chen, and Beth Levant synthesized and evaluated a selective D3 partial agonist, CJ-1037 (Chen et al., 2008). Unlike full agonists, such as pramipexole, or antagonists, such as PG01037, at the D3 receptor, which either produce significant increases in yawning with an inverted U-shaped dose-response curve, or do not induce yawning,

respectively, CJ-1037 displays a distinct behavioral profile with low levels of yawning observed over a wide range of doses resulting in a relatively flat dose-response curve (Chen et al., 2008). Moreover, the effects of CJ-1037 on pramipexole-induced yawning are easily distinguished from those of selective D3 (PG01037) or D2 (L-741,626) antagonists (Figure 1 E-F). As shown in Figure 4, CJ-1037 differentially affects the ascending limb of the yawning dose-response curve, enhancing the low levels of yawning observed with small doses, and inhibiting the high levels of yawning observed at peak doses of pramipexole. Importantly, these effects are observed at doses that do not affect the D2-mediated inhibition of yawning or induction of hypothermia which occur with larger doses of pramipexole, suggesting that CJ-1037 possesses a selective partial agonist activity at the D3 receptor.

It is important to point out some caveats in this presentation. Our definition of compulsive behavior accounts nicely for the experimental models described, and also for PD patients whose long treatment with levodopa may set the stage for D3/D2 agonist-induced compulsive responding that produces stimuli associated with gambling, sex, purchasing, food, or medication. It may also account for compulsive drug abuse, because drug abusers also have a history of exposure to drug-induced dopamine release, and then engage in excessive behavior related to obtaining the stimuli associated with drug taking. This conceptual framework does not necessarily surround all forms or aspects of compulsive behavior, however. Most individuals who engage excessively in some behaviors do not have PD and are not taking dopamine agonists. A very detailed history would be necessary to determine whether any previous exposure to increased levels of central dopamine can be documented in, otherwise normal, compulsive gamblers, shoppers, or eaters. It is possible that these individuals have idiosyncratically enhanced sensitivity to endogenous dopamine, and appropriate brain imaging might show this, but there is no certainty that this would be the case. This framework also does not account for the ability of antagonist treatments to treat drug abuse. The administration of a long acting opioid antagonist reduces heroin abuse through the process of extinction, and this can be quite effective treatment in some circumstances (Comer, Sullivan & Hulse, 2007). In our notion, compulsive behavior is very difficult to extinguish by simply removing the reinforcer unless the stimuli related to drug taking are also removed, or pharmacologically blunted. Again, careful evaluation of the behaviors and the stimulus conditions that exist during and following extinction might permit a more thorough evaluation of how this type of successful extinction is managed. We certainly have much to learn about how compulsive behaviors develop and how they might be treated, but some significant inroads have been made recently that offer considerable hope for future understanding and treatment of some of these conditions.

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Figure 1.

Dose-response curves for D2/D3 agonist-induced yawning ($\circ$), and hypothermia (Δ). Characterization of A) pramipexole, B) quinpirole, C) PD-128,907, and D) 7-OH-DPAT was conducted in different groups of rats, with data presented as mean ($\pm$ SEM), $n=8$, number of yawns during a 20 minute observation period, and mean ($\pm$ SEM), $n=6$, change in core body temperature as measured 30 min after, compared to 1 min before agonist injection. *, $p<0.05$, and **, $p<0.01$, symbols represent significant levels of yawning or hypothermia compared to vehicle-treated rats as determined by one-way, repeated-measure ANOVA with post-hoc Dunnett's tests. Effects of the E) D3-selective antagonist, PG01037, and F) D2-selective antagonist, L-741,626, on yawning induced by PD-128,907. Data are presented as mean ($\pm$ SEM), $n=8$, number of yawns during a 20 minute observation period. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$; Significant difference from vehicle-treated animals was determined by unbalanced, two-way ANOVA with post-hoc Bonferroni tests. Panels A-D are modified from Collins et al., 2007, and panels E-F are modified from Collins et al., 2005.

Figure 2.

Effects of contingent or non-contingent quinpirole on operant responding in rats with a history of cocaine self-administration. All animals were trained to respond for 0.56 mg/kg/inj cocaine during daily 90 min sessions under a FR1TO5 schedule of reinforcement. Black-filled circles represent the mean number of responses that resulted in cocaine injection during the last 3 sessions of baseline responding for cocaine. A) Responding maintained by 0.032 mg/kg/inj quinpirole during daily 90 min sessions under a FR1TO5 schedule of reinforcement following substitution from a cocaine baseline. Gray-filled triangles represent responding that resulted in quinpirole injection paired with the stimuli that were previously paired with cocaine injection, whereas white-filled triangles represent responding that resulted in the injection of quinpirole without the stimuli that were previously paired with cocaine. B) Effects of pretreatment with 0.56mg/kg quinpirole immediately prior to the start of 90 min sessions in which responding resulted in either the presentation of the stimuli that were previously paired with cocaine injection (gray-filled circles), or no stimuli change followed by an unsignalled 5 sec TO (white-filled circles). C) Effects of pretreatment with 0.56 mg/kg quinpirole (filled gray-circles) or saline (white-filled squares) on alternating days immediately prior to 90 min sessions in which responding resulted in the presentation of the stimuli that were previously paired with cocaine injection. All data represent the mean ($\pm$ SEM), $n=6$, number of responses during the 90 min sessions, but do not include responses made during the timeouts. Data for quinpirole-reinforced responding paired with the stimuli that were previously paired with cocaine presented in panel A are taken from Collins and Woods, 2007; all other data are previously unpublished.

Figure 3.

Effects of cocaine exposure (2 days of 15 mg/kg cocaine followed by 5 days of 30 mg/kg cocaine) on pramipexole-induced yawning. Dose-response curves for pramipexole-induced yawning were generated, using a multiple-dose procedure as previously described (Collins et al., 2008), 24 hr, 72 hr, and 10 days after the final day of cocaine exposure. Black-filled circles represent the mean ($\pm$ SEM), $n=8$, number of yawns during a 30 minute observation period for rats that were treated with 7 days of cocaine, whereas white-filled circles represent the mean ($\pm$ SEM), $n=8$, number of yawns for rats that were treated with 7 days of saline. **, $p<0.01$. Significant difference in the number of yawns compared to the number of yawns observed for the same group during the 24 hr timepoint as determined by two-way ANOVA with post-hoc bonferroni tests. +++, $p<0.001$. Significant difference between the number of yawns for saline-treated rats as compared to cocaine-treated rats during the same timepoint as determined by two-way ANOVA with post-hoc Bonferroni tests. Data are previously unpublished.

Figure 4.

Effects of CJ-1037 on pramipexole-induced yawning and hypothermia. Pramipexole-induced yawning and hypothermia were collected using a multiple-dose procedure as previously described (Chen et al., 2008) with data presented as the mean ($\pm$ SEM), $n=8$, number of yawns during a 30 minute observation period, and mean ($\pm$ SEM), $n=6$, change in core body temperature as measured 30 min after each injection compared to 1 min before vehicle or CJ-1037 injection. *, $p<0.05$; **, $p<0.01$; ***, $p<0.001$. Significant effects of CJ-1037 on the number of yawns and changes in body temperature as compared to vehicle-treated rats were determined by two-way ANOVA with post-hoc Bonferroni tests. Panels A and B were modified from Chen et al., 2008.