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RESEARCH****Research Report****Dopamine receptor modulation of repetitive grooming actions in the rat: Potential relevance for Tourette syndrome****Jennifer L. Taylor^{a,*}, Abha K. Rajbhandari^b, Kent C. Berridge^a, J. Wayne Aldridge^a**^aDepartment of Psychology, University of Michigan, Ann Arbor, MI, USA^bNeuroscience Training Program, Department of Psychiatry, University of Wisconsin-Madison, Madison, WI, USA

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ABSTRACT

Studies of rodent grooming can provide valuable insight for dopamine contributions to the initiation, organization, and repetition of motor patterns. This information is useful for understanding how brain dysfunctions contribute to movement disorders such as Tourette syndrome and obsessive compulsive disorder, in which patients are driven to reiterate particular movement patterns. In rodents, dopamine D1 receptor stimulation causes a complex behavioral super-stereotypy in the form of excessive production and rigid execution of whole sequences of movements known as syntactic grooming chains. Sequential super-stereotypy of grooming chains may be particularly advantageous for modeling movement sequences and treatments in Tourette syndrome and related disorders. Here, we report that co-administration of haloperidol, one available treatment for Tourette syndrome and primarily a D2 receptor antagonist, prevented D1 stimulation with SKF38393 from inducing sequential super-stereotypy, which manifests as an exaggeration of the tendency to complete all four phases of a syntactic chain in rigid serial order once the first phase has begun. In a separate experiment, we showed that in contrast to acute D1 agonist administration, 39 h withdrawal from chronic (3 weeks) administration of the D1 antagonist SCH23390 (which has been suggested to increase D1 receptor expression in the basal ganglia) did not elicit sequential super-stereotypy after drug cessation. Instead, rats suddenly removed from repeated SCH23390 spent more time performing simple stereotypies that included intense scratching and biting behaviors. Together, these results have implications for understanding how dopamine receptors facilitate particular stereotypies manifest in animal models of Tourette syndrome and obsessive compulsive disorder.

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1. Introduction

Dysfunction of the basal ganglia involving alteration in dopamine neurotransmission is proposed to contribute to a range of movement disorders (Albin et al., 1989; Albin, 2006).

Patients with Parkinson's disease, which is caused by destruction of nigrostriatal dopamine neurons, show deficiencies in performing movement sequences (Agostino et al., 1992; Benecke et al., 1987; Harrington and Haaland, 1991). In contrast, patients with Tourette syndrome experience

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repetitive undesired movements interjected into ongoing behavior known as tics (Berardelli et al., 2003). Simple tics are “repetitive stereotyped jerks” while complex motor tics “consist of a wide variety of muscle jerks and contractions in different muscle groups organized in sequence and coordinated movements resembling normal motor gestures” (Berardelli et al., 2003). The efficacy of anti-dopaminergic agents such as haloperidol in treating Tourette symptoms, along with other clinical and basic science findings, have contributed to the concept that abnormal dopamine signaling and aberrations in basal ganglia processing are important factors contributing to the pathophysiology of Tourette syndrome (Albin and Mink, 2006; Frey and Albin, 2006; Jimenez-Jimenez and Garcia-Ruiz, 2001; Mink, 2006; Segawa, 2003; Singer et al., 2002).

The biological basis of Tourette syndrome is thought to overlap that of obsessive compulsive disorder (OCD), a condition which is characterized by intrusive thoughts (obsessions) and urges to repeat rigid behavioral patterns (compulsions) (Goodman et al., 2006). Although the serotonin system is most often implicated in OCD, the dopamine system may be disrupted as well (Kim et al., 2003). Dopamine antagonists may need to be added to the treatment regimen for some OCD patients, especially when OCD is co-morbid with Tourette syndrome (McDougle et al., 1994). As dopamine and basal ganglia dysfunction likely contribute to Tourette syndrome and OCD, it is reasonable to use rodent models to elucidate whether basic dopamine receptor actions, such as interactions between receptors and changes in receptor number, can modulate abnormal repetition of specific movements or movement patterns. Grooming sequences and simple stereotypies are among the motor behaviors that can be used in animals to answer such queries.

Grooming involves an innate set of movements used by many mammalian species to care for the body (Berridge, 1990; Richmond and Sachs, 1978; Young and Thiessen, 1991). During grooming bouts, rodents perform facial strokes, lick and scratch the body, and gnaw at the extremities (Bolles, 1960; Richmond and Sachs, 1978). These movements are usually executed in a fairly flexible arrangement, but on regular occasions rats perform a series of grooming movements in a highly predictable order (13,000 times greater than chance) (Berridge et al., 1987). This rigid sequential pattern is known as a “syntactic grooming chain” (Berridge et al., 1987). The basal ganglia are important for the regulation of syntactic grooming chains (Aldridge, 2005). For example, an intact striatum is necessary for the correct implementation of grooming chains, as lesions of the dorsolateral striatum impair the completion of syntactic grooming chains (Berridge, 1989a; Berridge and Whishaw, 1992; Cromwell and Berridge, 1996). Extracellular recordings of neural activity in the same region of dorsolateral striatum in rats have demonstrated that neurons in those regions code the entire grooming sequence pattern as a whole, especially firing in terminal phases. Those neurons also discriminate between the sequential pattern and those same grooming movements produced in different orders outside of the syntactic chain (Aldridge et al., 1993; Aldridge and Berridge, 1998; Meyer-Luehmann et al., 2002). By comparison, neural activity in the pars reticulata region of the substantia nigra appears to code the initiation of the pattern, responding especially to the onset of chains (Meyer-Luehmann et al.,

2002). This suggests that the basal ganglia play coordinated roles both in the initiation and organization of sequential patterns, rather than in just the elementary component movements within a pattern.

In rodents, dopamine is a crucial neurotransmitter for implementation of the sequential grooming pattern (Berridge, 1989b). Rodent studies have revealed that 6-hydroxydopamine lesions of dopaminergic neurons impair the correct completion of grooming chain patterns, similar to neostriatal lesions (Berridge, 1989b). In contrast, excessive dopamine neurotransmission caused by knockdown of the dopamine transporter expression in transgenic mice triggers sequential super-stereotypy in the form of exceedingly rigid execution of syntactic grooming chains (Berridge et al., 2005). There seems to be an especially important function for the dopamine D1 receptor in this dopamine contribution to grooming chain implementation in rodents. First, mutant mice lacking D1A receptors are less likely to complete grooming chains than normal mice (Cromwell et al., 1998). In contrast, peripheral or central administration of D1 receptor-specific agonists increase grooming chain initiation and the probability that grooming chains will be completed (i.e., “sequential super-stereotypy”), whereas a D2 agonist does not (Berridge and Aldridge, 2000a,b). The apparently excessive repetition of grooming sequences observed in the D1 agonist-treated rat has been speculated to be a potential model for complex tics observed in Tourette syndrome and for OCD (Albin and Mink, 2006).

Dopamine and its receptors are clearly implicated in super-stereotypy, but some of the details of that involvement and how they may lend insights into Tourette syndrome and OCD remain unclear. The current set of studies was undertaken to further investigate the idea that sequential super-stereotypy is induced by excessive activation of dopamine D1 receptors, and that it could be modulated by co-treatment with a D2 receptor antagonist. In doing so, we aim to better understand how dopamine influences the extent to which organized movements are carried out and reiterated. This is crucial for developing hypotheses about the brain pathologies that lead to disorders involving compulsive movements and for developing animal models of those aberrant behaviors.

For the first experiment, we were interested in clarifying the potential remaining role of endogenous stimulation of dopamine D2 receptors in sequential super-stereotypy. That is, normal co-activation levels of D2 receptors by endogenous dopamine might be important in supporting the production of super-stereotypy by D1 receptor over-stimulation, even if D2 over-stimulation by a D2 agonist is not sufficient by itself to cause the stereotypy (Berridge and Aldridge, 2000a). This role for endogenous D2 receptor participation is suggested by the clinical efficacy of neuroleptics in reducing tics and related symptoms in human Tourette patients (Jimenez-Jimenez and Garcia-Ruiz, 2001). Since the mechanism of action for neuroleptics is likely in part due to D2 receptor blockade, examination of this issue would provide insight into potential mechanisms underlying the motor tics of Tourette syndrome and its treatment (Arnt and Skarsfeldt, 1998; Robertson and Stern, 2000). Such information could also be advantageous in assessing whether the rodent syntactic chain pattern of repetitive movement sequences is truly relevant to modeling

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