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Research report

Injections of the selective adenosine A_{2A} antagonist MSX-3 into the nucleus accumbens core attenuate the locomotor suppression induced by haloperidol in rats

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Abstract

There is considerable evidence of interactions between adenosine A_{2A} receptors and dopamine D_2 receptors in striatal areas, and antagonists of the A_{2A} receptor have been shown to reverse the motor effects of DA antagonists in animal models. The D_2 antagonist haloperidol produces parkinsonism in humans, and also induces motor effects in rats, such as suppression of locomotion. The present experiments were conducted to study the ability of the adenosine A_{2A} antagonist MSX-3 to reverse the locomotor effects of acute or subchronic administration of haloperidol in rats. Systemic (i.p.) injections of MSX-3 (2.5–10.0 mg/kg) were capable of attenuating the suppression of locomotion induced by either acute or repeated (i.e., 14 day) administration of 0.5 mg/kg haloperidol. Bilateral infusions of MSX-3 directly into the nucleus accumbens core (2.5 μg or 5.0 μg in 0.5 μl per side) produced a dose-related increase in locomotor activity in rats treated with 0.5 mg/kg haloperidol either acutely or repeatedly. There were no overall significant effects of MSX-3 infused directly into the dorsomedial nucleus accumbens shell or the ventrolateral neostriatum. These results indicate that antagonism of adenosine A_{2A} receptors can attenuate the locomotor suppression produced by DA antagonism, and that this effect may be at least partially mediated by A_{2A} receptors in the nucleus accumbens core. These studies suggest that adenosine and dopamine systems interact to modulate the locomotor and behavioral activation functions of nucleus accumbens core.

Keywords: Dopamine; Basal ganglia; Neostriatum; Caudate putamen; Antipsychotic; Parkinson's disease; D2 receptor

1. Introduction

Interactions between diverse neurotransmitter systems in the basal ganglia are thought to regulate several aspects of motor function [22,82]. Neostriatal depletions of dopamine (DA) are the immediate cause of motor dysfunction in patients with idiopathic Parkinson's disease [35], while pharmacological blockade of DA transmission with DA receptor antagonists such as haloperidol leads to drug-induced parkinsonism [53]. The most common treatments for Parkinson's disease generally involve dopaminergic strategies, including the DA precursor L-DOPA, as well as DA agonists such as bromocriptine, pergolide, or ropinirole [10,47,48]. Nevertheless, considerable research has implicated several other neurotransmitters in motor processes related to the basal ganglia, including acetylcholine [67,68], serotonin [11], glutamate [58,60], and GABA [12,45,77,80,81]. Within the last few years, evidence has begun to emerge indicating that brain adenosine neurons play an important role in regulating the motor functions of the basal ganglia [24,25,28,76]. Although several subtypes of adenosine receptors are involved in motor function, anatomical studies have demonstrated that the adenosine A_{2A} receptor subtype is expressed to a high degree in striatal regions [15,27,33,49,76,78]. Adenosine A_{2A} receptors in the striatum are largely expressed on enkephalin-positive striatopallidal neurons, which also contain DA D_2 receptors [76]. Antagonism of adenosine A_{2A} receptors

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produces motor effects in animal models [13,29,74,75], and it has been widely suggested that adenosine A_{2A} antagonists could be used as an alternative for the treatment of parkinsonian symptoms [24,25,38,52,56,61]. Because of the interest in studying the neurochemical interactions involved in motor control, and identifying novel non-dopaminergic treatments for parkinsonism, it is important to characterize the effects of adenosine A_{2A} antagonists in both human clinical trials and animal models.

A number of tests in rodents are used to study motor function, and adenonsine A_{2A} antagonists have been assessed for their effects in various procedures. Haloperidol-induced rigidity was reversed by the A_{2A} antagonist SCH 58261 [79]. Hauber et al. [32] observed that catalepsy induced by either DA D1 or D2 antagonists could be reversed by the selective A_{2A} antagonist MSX-3. Drug-induced tremulous jaw movements, which are used as an animal model of parkinsonian tremor [67,69], were reduced by co-administration of adenosine A_{2A} antagonists [18,74]. In addition, several studies have focused upon the effects of adenosine A_{2A} antagonists on locomotor activity. The adenosine A_{2A} antagonist KW-6002 reversed the hypolocomotion induced by the DA depleting agent reserpine [73]. The impairment of locomotion shown by D_2 receptor deficient mice was rescued by the adenosine A_{2A} antagonist KW-6002 [3]. Systemic injections of the adenosine A_{2A} antagonist KF17837 (5.0–20.0 mg/kg) reversed the suppression of locomotion induced by subchronic injections of haloperidol [18].

The specific brain areas at which adenosine A_{2A} receptor antagonists act to increase locomotion in animals with impaired dopaminergic function are unclear. There are A_{2A} receptors present throughout the striatal complex, including subregions of neostriatum as well as nucleus accumbens [15,33,76,78]. Although Parkinson's disease is generally associated with depletions of DA in the neostriatum [35], it also has been demonstrated that this disorder is accompanied by depletions of DA in nucleus accumbens [9,50]. Previous evidence indicates that adenosine A_{2A} receptors in nucleus accumbens may be important for mediating the locomotor effects of A_{2A} antagonists. The adenosine A_{2A} agonist CGS 21680 was shown to suppress locomotion when injected directly into the nucleus accumbens [6,7,31]. Infusions of the adenosine A_{2A} antagonist MSX-3 directly into the nucleus accumbens produced a dose-related increase in locomotor activity [59]. Moreover, there is considerable evidence indicating that interference with DA transmission in nucleus accumbens leads to a suppression of spontaneous locomotion [5,16,19,46].

The present experiments were conducted to study the ability of systemic or intra-accumbens injections of the selective adenosine A_{2A} antagonist MSX-3 to reverse the locomotor effects of acute or subchronic administration of haloperidol in rats. Haloperidol was selected for these studies because it is a DA antagonist that is known to suppress locomotion in rats (e.g., ref. [18]), and to produce motor side effects in humans [8,53]. MSX-3 is a water-soluble pro-drug that is rapidly cleaved by phosphatases in vivo into MSX-2, which is the active antagonist of A_{2A} receptors [30,34,57,71]. Experiments 1 and 2 studied the ability of systemic injections of MSX-3 to reverse the suppression of locomotion induced by acute or repeated subchronic administration of 0.5 mg/kg haloperidol. Repeated administration of haloperidol was used because this procedure has been employed previously for studies of adenosine A_{2A} antagonists [18], and because repeated administration mimics the conditions seen when antipsychotic drugs such as haloperidol are used therapeutically. Experiments 3 and 4 studied the ability of intracranial administration of MSX-3 to increase locomotion in haloperidol-treated rats. Three brain areas were studied: nucleus accumbens core, dorsomedial nucleus accumbens shell, and ventrolateral neostriatum (VLS). Nucleus accumbens was investigated because, as described above, this brain area is involved in the regulation of locomotor activity. Although previous studies have examined the effects of local nucleus accumbens injections of MSX-3 on locomotor activity [59], these studies did not differentiate between core and shell subregions, and did not assess the effects of A_{2A} antagonism in the presence of a DA antagonist. The VLS site was chosen as a control striatal site because this striatal subregion is thought to be involved in motor functions such as tremor [20,21,39,54,67,74] and skilled motor control [20,65,66], but is not thought to be important for locomotion [19,39,42]. The fifth experiment studied the effects of systemic and intracranial injections of MSX-3 in animals not treated with haloperidol, tested under the same conditions that were used in the previous experiments.

2. Materials and methods

2.1. Animals

A total of 417 male Sprague Dawley rats (Harlan Sprague Dawley, Indianapolis, IN) were used in the present experiments. The rats had no prior drug experience, and weighed 315–480 g at the beginning of the experiment, with ad libitum access to lab chow and water. The rats were group-housed in a colony that was maintained at approximately 23 °C and had a 12-h light/12-h dark cycle (lights on at 07:00 h). These studies were conducted in accordance with University of Connecticut and NIH guidelines for animal care and use.

2.2. Drugs

Haloperidol was obtained from Sigma Chemical Co. (St. Louis, MO). It was dissolved in 0.3% tartaric acid, which also was used as the vehicle control for haloperidol injections. MSX-3 free acid ((*E*)-phosphoric acid mono-[3-[8-[2-(3-methoxyphenyl)vinyl]-7-methyl-2,6-dioxo-1-prop-2-ynyl-1,2,6,7-tetrahydropurin-3-yl]propyl] ester disodium salt) was synthesized in the Müller laboratory (Pharmazeutisches Institut, Universität Bonn, Bonn, Germany). MSX-3 was dissolved in 0.9% saline, and the pH of the MSX-3 solution was adjusted by adding 1.0N NaOH until the drug was completely in solution (pH 7.1–7.4) as the disodium salt. Solutions of 0.9% saline also were used as the vehicle solution for control injections. The dose of haloperidol used (0.5 mg/kg), and the 14 day repeated administration procedures, were selected based upon previous studies [18,81]. The doses of MSX-3 were chosen based upon pilot experiments, as well as the results of previously published studies [30,59].

2.3. Locomotor activity

Locomotor activity was assessed in an automated motor activity chamber (28 cm × 28 cm × 28 cm) that was placed inside a sound-proof shell. The floor of each chamber consisted of two movable wire mesh panels (27 cm × 13 cm) mounted above the base of the chamber, which were balanced on a metal rod