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Dopamine/adenosine interactions related to locomotion and tremor in animal models: Possible relevance to parkinsonism⋆

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Abstract

Adenosine A_{2A} antagonists can exert antiparkinsonian effects in animal models. Recent experiments studied the ability of MSX-3 (an adenosine A_{2A} antagonist) to reverse the locomotor suppression and tremor produced by dopamine antagonists in rats. MSX-3 reversed haloperidol-induced suppression of locomotion, and reduced the tremulous jaw movements induced by haloperidol, pimozide, and reserpine. Infusions of MSX-3 into the nucleus accumbens core increased locomotion in haloperidol-treated rats, but there were no effects of infusions into the accumbens shell or ventrolateral neostriatum. In contrast, MSX-3 injected into the ventrolateral neostriatum reduced pimozide-induced tremulous jaw movements. Dopamine/adenosine interactions in different striatal subregions are involved in distinct aspects of motor function.

Keywords

Dopamine; Basal ganglia; Neostriatum; Caudate; Putamen; Nucleus accumbens; Antipsychotic; Parkinson's disease; Motor; Motivation

1. Introduction

Interactions between diverse neurotransmitter systems in the basal ganglia are thought to regulate aspects of motor function related to parkinsonism. In addition to dopamine (DA), considerable research has implicated several other basal ganglia neurotransmitters, including acetylcholine, serotonin, glutamate and GABA, in aspects of motor function and dysfunction [1-4]. More recently, brain adenosine neurons have also been implicated in regulating the motor functions of the basal ganglia [5-7]. Anatomical studies have demonstrated that the adenosine A_{2A} receptor subtype is highly expressed in DA-rich striatal regions [7-11]. Adenosine A_{2A}

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receptors in the striatum are largely expressed on enkephalin-positive striatopallidal neurons, which also contain DA D_2 receptors [7-10]. Adenosine A_{2A} receptor antagonists produce motor effects in animal models, and it has been widely suggested that adenosine A_{2A} antagonists could be used as non-dopaminergic treatments for parkinsonian symptoms [4,5,11-17]. For all these reasons, it is important to characterize the effects of adenosine A_{2A} antagonists in animal models [18].

2. Studies of locomotor activity in rats

Adenosine A_{2A} antagonists have been assessed for their motor effects using a number of tasks that are suitable for rodents. Haloperidol-induced rigidity was reversed by the A_{2A} antagonist SCH 58261 [19]. Hauber et al. [20] observed that catalepsy induced by DA antagonists could be reversed by the selective A_{2A} antagonist MSX-3. In addition, several studies have focused on 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 [17]. The impairment of locomotion shown by D_2 receptor-deficient mice was rescued by the adenosine A_{2A} antagonist KW-6002 [21]. 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 [22].

In order to understand more fully the brain mechanisms mediating the effects of drugs acting on adenosine, it is important to identify the specific brain locus at which adenosine A_{2A} receptor antagonists act to increase locomotion in animals with impaired dopaminergic function. Adenosine A_{2A} receptors are present throughout the striatal complex, which includes the caudate/putamen (i.e., neostriatum) and also the nucleus accumbens [6,7,9,10]. Previous studies have indicated that adenosine A_{2A} receptors in the nucleus accumbens may be important for mediating the locomotor effects of drugs that act on adenosine A_{2A} receptors [23-25]. Moreover, there is considerable evidence indicating that interference with DA transmission in the nucleus accumbens leads to a suppression of spontaneous locomotion [26-29].

Recently, 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 [30]. Haloperidol is a DA antagonist that is known to suppress locomotion in rats (e.g., Ref. [22]) and to produce parkinsonian side-effects in humans [31,32]. 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 [33]. Therefore, we 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 [30]. Repeated administration of haloperidol was used because this procedure has been employed previously for studies of adenosine A_{2A} antagonists [22] and because repeated administration mimics the conditions seen when antipsychotic drugs such as haloperidol are used clinically. Additional experiments have studied the ability of intracranial injections of MSX-3 to increase locomotion in haloperidol-treated rats [30]. Three brain areas were studied: nucleus accumbens core, dorsomedial nucleus accumbens shell and ventrolateral neostriatum (VLS). The nucleus accumbens was investigated because this brain area is involved in the regulation of locomotor activity [23,24,26-28,30]. Although earlier studies examined the effects of intra-accumbens injections of MSX-3 on locomotor activity, these studies did not differentiate between core and shell subregions, and they 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 (see below) and skilled motor control [34-36], but is not thought to be important for locomotion [28,37,38].

In these studies, systemic injections of MSX-3 in a dose range of 2.5–10.0 mg/kg were capable of reversing the suppression of locomotion induced by either acute or repeated (i.e., 14 day) administration of haloperidol 0.5 mg/kg [30]. Bilateral infusions of MSX-3 into the nucleus accumbens core (2.5–5.0 μg per side) produced a dose-related increase in locomotor activity in rats treated with 0.5 μg/kg haloperidol either acutely or repeatedly [30]. There was no overall significant effect of MSX-3 infused into either the dorsomedial shell or the VLS. In addition, there were no significant effects of systemic or intra-accumbens injections of MSX-3 (10.0 mg/kg and 5.0 μg per side, respectively) in rats that were not treated with haloperidol. These results indicate that antagonism of adenosine A_{2A} receptors can reverse the locomotor suppression produced by DA antagonism and that a critical site for this effect is the nucleus accumbens core. Although Parkinson's disease is generally associated with depletions of DA in the neostriatum [39], this disorder is also characterized by nucleus accumbens DA depletions [40,41]. As with rodents, the nucleus accumbens of primates is also involved in locomotion [42]. Thus, it is possible that DA/adenosine interactions in the nucleus accumbens may be important for regulating behavioural functions, including locomotion, that are impaired in parkinsonism.

3. Studies of tremulous jaw movements

There is considerable uncertainty about the neurochemical mechanisms that underlie tremor generation, despite the fact that resting tremor is one of the primary symptoms of parkinsonism. A few studies have examined the effects of adenosine antagonists on parkinsonian tremor in humans, and some positive effects have been reported [14,43]. One of the rodent procedures used as a model of parkinsonian resting tremor is drug-induced tremulous jaw movements (TJMs). TJMs are rapid vertical deflections of the lower jaw that resemble chewing but are not directed at any stimulus [44]. Studies using slow-motion or freeze-frame video analyses, as well as electromyographic methods, have shown that these movements occur largely in the 3- to 7-Hz range that is also characteristic of parkinsonian resting tremor [44-47]. TJMs can be induced by striatal DA depletions [37,45] and by centrally acting cholinomimetic drugs [2, 44,48-51]. They are also induced by typical antipsychotics, such as haloperidol [22,52], pimozide [46,48] and reserpine [47], but not by atypical antipsychotics [52,53]. Although chronic administration of antipsychotic drugs can result in oral movements that may be related to other movement disorders, such as tardive dyskinesia, considerable evidence indicates that the chewing-like jaw movements induced by acute or subchronic administration of typical antipsychotic drugs share many characteristics with parkinsonian symptoms [2,44,46,47,51]. TJMs have been used as a rodent model of parkinsonian tremor for assessing antiparkinsonian drugs with various pharmacological profiles [4,47,48,51]. The adenosine A_{2A} antagonist KF17837 (10.0–20.0 mg/kg) suppressed haloperidol-induced TJMs [22], and the TJMs induced by the acetylcholinesterase inhibitor tacrine were reduced by systemic or intrastriatal injections of the adenosine A_{2A} antagonists SCH 58261 and SCH BT2 [54].

In a recent series of experiments, the potential antiparkinsonian effects of the selective adenosine A_{2A} antagonist MSX-3 were assessed by using acute or subchronic administration of antipsychotic drugs to induce TJMs [55]. In the first group of studies, pimozide (Orap) was used to induce motor impairments. Pimozide is a typical antipsychotic drug, which has been shown to produce motor side-effects in patients with schizophrenia and to exacerbate the symptoms of Parkinson's disease [46,56]. Moreover, pimozide has been reported to be more likely to produce parkinsonian tremor compared with other typical antipsychotics [56]. In recent papers, it was demonstrated that pimozide could induce TJMs with acute or subchronic administration (i.e., 1, 7 or 13 days of injections) at doses up to 1.0 mg/kg [46], and that the TJMs induced by repeated pimozide were blocked by the antiparkinsonian anti-cholinergic drug atropine [48]. Based on these previous experiments, the first group of studies assessed the ability of adenosine A_{2A} antagonism to suppress tremulous movements and increase motor

activity in pimozide-treated rats [55]. In these studies, rats were injected with 1.0 mg/kg of pimozide for 7 days, and on the eighth day they received injections of pimozide plus various doses of the A_{2A} antagonists KW-6002 or MSX-3. After receiving these drug treatments, the rats were assessed with a battery of motor tests that included observations of TJMs, catalepsy and locomotor activity. Administration of both KW-6002 and MSX-3 suppressed pimozide-induced TJMs, and also reduced catalepsy and increased locomotion in the pimozide-treated rats [55]. Additional studies showed that MSX-3 suppressed the TJMs induced by haloperidol, as well as the DA-depleting agent reserpine [55]. An additional experiment investigated the effects of intracranial injections of MSX-3 into the VLS, in order to determine whether local injections of an adenosine A_{2A} antagonist could reverse the TJMs induced by pimozide [55]. The VLS was chosen because this brain area, which is thought to be the homologue of the ventral putamen in primates, has been strongly implicated in the control of TJM activity [34, 37,44,49,54,57]. This experiment demonstrated that injections of MSX-3 into the VLS were able to suppress pimozide-induced TJMs [55], which was consistent with an earlier study showing that injections of an adenosine A_{2A} antagonist into the VLS could reduce the TJMs induced by the cholinomimetic drug tacrine [54].

4. Discussion

Taken together, the results of these experiments indicate that adenosine A_{2A} antagonism can reverse locomotor suppression and tremulous movements induced by typical antipsychotics [22,30,55]. These effects are consistent with the hypothesis that blockade of adenosine A_{2A} receptors can produce antiparkinsonian effects in animal models. Adenosine A_{2A} antagonists may be useful clinically for their tremorolytic effects, and may help in treating both idiopathic and antipsychotic-induced parkinsonian symptoms [22,30,55]. Moreover, these experiments indicate that different striatal subregions are involved in distinct aspects of motor function. This principle has been demonstrated clearly in the substantial literature showing that DA depletions or antagonism can have regionally specific effects [28,37,58], and it has important implications for understanding the anatomical mechanisms underlying the motor effects of antiparkinsonian drugs, including adenosine A_{2A} antagonists. Although antiparkinsonian drugs are typically given systemically, with the intention of producing an improvement in several different motor symptoms, it is nevertheless reasonable to suggest that different therapeutic effects (i.e., increase in locomotion, decrease in rigidity or tremor) are related to actions on distinct striatal subregions. In addition to studying these specific aspects of motor function, future research should also investigate the potential role of adenosine A_{2A} receptors in motivational functions that are impaired in parkinsonism, such as psychomotor activation and effort-related processes [59].

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