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Interaction of dopamine and adenosine receptor function in behavior: Studies with dopamine-deficient mice

Douglas S. Kim[1,2], Richard D. Palmiter[1,3,4]

[1]Molecular and Cellular Biology Program, University of Washington, Seattle, Washington 98195,[2]Department of Genetics, Harvard Medical School, Boston, Massachusetts 02115,[3]Howard Hughes Medical Institute, University of Washington, Seattle, Washington 98195,[4]Department of Biochemistry, University of Washington, Seattle, Washington 98195

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1. ABSTRACT

The interactive effects of dopamine and adenosine on various behaviors in mammals have been studied extensively. The observation that dopamine and adenosine receptors are expressed together in neurons of the striatum has been a major impetus for studying these neurotransmitters because the striatum has been implicated in regulating motor and reward-related behaviors. This article reviews recent work concerning how dopamine and adenosine receptor activity impinges on these behaviors in a genetically altered mouse which cannot produce dopamine in dopaminergic neurons. It considers evidence regarding the motor and reward-related behaviors regulated by adenosine and dopamine, the neuronal circuits that respond to adenosine and dopamine, and the signaling mechanisms by which adenosine and dopamine interact.

2. INTRODUCTION

Dopaminergic neurotransmission from midbrain afferents to the striatum modulates the excitatory input from cortical and thalamic glutamatergic neurons (reviewed in 1). Dopamine binds to G protein-coupled receptors, and signaling downstream from these receptors influences the effects of glutamatergic and other ionotropic inputs and aids in shaping voluntary movement and reward-related behaviors (reviewed in 2). Adenosine is another modulatory influence that activates G protein-coupled receptors in the striatum (reviewed in 3). Functional opposition of adenosine and dopamine has been observed in several models of dopamine depletion in terms of locomotor and feeding behavior, including dopamine neurotoxin-treated rodents and primates and genetically altered mice. Adenosine A2A receptors are co-expressed

with dopamine D2 receptor by striatopallidal medium spiny neurons that represent the indirect output pathway of the striatum, whereas adenosine A1 receptors are enriched in D1 receptor-expressing medium spiny neurons that consititute the direct striatonigral output pathway and are also found in striatopallidal neurons (reviewed in 3-4). A2A and D1 receptors are coupled to $G\alpha_{olf}$ (equivalent to $G\alpha_s$), whereas A1 and D2 receptors are coupled to $G\alpha_{o/i}$. Thus, within either the striatopallidal or striatonigral output pathways, adenosine and dopamine receptors can oppose each other at the level of intracellular signaling. The potential use of adenosine receptor antagonists to alleviate the motor deficits of Parkinson's disease patients, who exhibit loss of midbrain dopaminergic neurons, is currently being explored (reviewed in 5). The responsiveness of various models of dopamine depletion to adenosine receptor antagonists in motor, feeding, and reward-related behaviors is discussed in this article.

3. BEHAVIORAL RESPONSES TO ADENOSINERGIC DRUGS IN DOPAMINE-DEPLETED ANIMALS AND DOPAMINE RECEPTOR-DEFICIENT MICE

3.1. Motor behavioral responses to adenosinergic drugs in rats lesioned with 6-hydroxydopamine

In recent decades, researchers have paid considerable attention to the ability of adenosine receptor antagonists to reverse the hypoactivity and bradykinesia of dopamine-depleted animal models of Parkinson's disease, dopamine receptor antagonist-treated animals, and dopamine receptor-deficient mice (reviewed in 6-9). The response to adenosine receptor antagonists has been examined in adult rats in which the nigrostriatal projection has been treated unilaterally with the dopaminergic neurotoxin, 6-hydroxydopamine (6-OHDA). Removal of dopaminergic input to one side of the striatum has been shown to sensitize the responsiveness of ipsilateral postsynaptic striatal neurons, as evidenced by contralateral rotational locomotion of rats away from the lesioned side following treatment with a non-selective dopamine receptor agonist, apomorphine (10-12). Two different non-selective adenosine receptor antagonists, caffeine and theophylline, also induced contralateral rotations in lesioned rats (13) consistent with the notion that signaling via adenosine receptors opposes the action of striatal dopamine function in the regulation of motor behavior. Using this model, other investigators have documented the ability of more specific adenosinergics to induce contralateral rotations, including the adenosine A2A receptor antagonist, 3,7-dimethyl-l-propargylxanthine (DMPX; 14); the A2A receptor antagonists, KF17837 and KW-6002 (15); and the A1 receptor antagonist (1,3-dipropyl-8-(2-amino-4-chlorophenyl)-xanthine (PACPX; 14). Additionally, various adenosine receptor agonists were shown to block the acute effects of dopamine receptor agonists in terms of rotational behavior, including the A1 and A2A receptor agonist, N-ethylcarboxamido-adenosine (NECA; 16); and the A2A receptor agonist, CGS 21680 (17-18). Conflicting results have been reported when dopaminergic agonists and adenosine receptor antagonists were administered together. Specifc A2A receptor or non-selective adenosine receptor antagonists enhanced contralateral rotations induced by dopamine D1 or D2 receptor agonists (14). D1 receptor agonist-induced rotations were also augmented by administration of an A1 receptor antagonist (19-20) or an A2A receptor antagonist (20-21). D2 receptor agonist-induced rotations were increased with co-administration of an A2A receptor antagonist (22). Turning behavior induced by L-3,4-dihydroxyphenylalanine (L-DOPA) could be enhanced by A2A receptor antagonists, including SCH 58261, KF17837, KW-6002, or STI1535 (15, 23-24). In contrast, other investigators found that an A2A receptor antagonist failed to augment apomorphine-induced (18) or D1 receptor agonist-induced contralateral rotations (22). Taken together, the preponderance of the experimental evidence suggests that adenosine A1 and A2A receptors acutely oppose the action of dopamine receptors in this model of Parkinson's disease.

3.2. Motor behavioral responses to adenosinergic drugs in other dopamine-depleted animals and dopamine receptor-deficient mice

Other paradigms of dopamine depletion and dopamine receptor-deficient mice have also been studied in terms of responsiveness to adenosine receptor antagonists. Rats lesioned bilaterally with 6-OHDA, either as neonates or adults, undergo reversal of their hypoactivity after theophylline treatment (25). A2A receptor antagonists reverse the hypoactivity of primates treated with the dopaminergic neurotoxin, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP; 26-27). A2A receptor antagonists can also enhance the motor-inducing effects of a D2 receptor agonist, D1 receptor agonist, or L-DOPA in this model (26, 28). The hypoactivity of mice treated with the catecholamine vesicle-depleting agent, reserpine, is reversed by A2A receptor antagonist treatment (29). In addition to these chemically induced models of dopamine depletion, genetically altered mice that carry null mutations in dopamine receptor genes have also been studied. The motor deficits of D2 receptor-deficient mice are reversed by A2A receptor antagonists and caffeine (30-31). The results of these investigations are consistent with the model of dopamine/adenosine opposition in terms of motor behavior.

3.3. Motor behavioral responses to adenosinergic drugs in dopamine-deficient (DD) mice

Another genetically engineered mouse model of dopamine depletion is the dopamine-deficient mouse. These DD mice carry null mutations in the tyrosine hydroxylase gene, whose gene product synthesizes L-DOPA, and targeted replacement of tyrosine hydroxylase function in noradrenergic cells where L-DOPA and dopamine are precursors for noradrenaline and adrenaline production (32-33). DD mice display parkinsonism-like motor deficits, hypophagia, hypodipsia, and high sensitivity to dopamine receptor agonists (32, 34-35). Brain dopamine content of DD mice is <1% of normal levels, but dopamine can be partially restored by L-DOPA injection (35). Acute L-DOPA treatment induces hyperactivity in DD mice (32, 34). Similar to responses of other models of dopamine depletion, the hypoactivity of DD mice can be reversed by administration of caffeine; a non-methylxanthine, non-

selective adenosine receptor antagonist, CGS 15943; an A1 receptor antagonist, 8-cyclopentyl-1,3-dipropylxanthine (DPCPX); or an A2A receptor antagonist, 8-(3-chlorostyryl) caffeine (CSC; 36). The activity induced by these drugs was much less than that induced by L-DOPA treatment. The co-administration of L-DOPA with each of these drugs, except for caffeine, resulted in equal or greater induction of locomotor activity as compared with treatment with L-DOPA alone. Interestingly, caffeine treatment attenuated the L-DOPA response, which was unexpected. In general, DD mice respond to adenosine receptor antagonists in a manner largely consistent with results obtained from dopamine neurotoxin-treated animal models. Unlike dopamine receptor-deficient mice, however, DD mice could be used to make a direct comparison between the effects of adenosine receptor antagonism and dopamine signaling restoration. The ability of adenosine antagonists to induce activity in this extreme example of dopamine deficiency suggests that these drugs might be effective in ameliorating motor symptoms even in late-stage Parkinson's disease patients. Further, even with the very high sensitivity to dopamine that DD mice exhibit, which is correlated with increases in the levels of a high affinity form of the D2 receptor and the responsiveness of signaling downstream from D1 receptors in the striatum (34, 37-38), adenosine receptor antagonist treatment induced locomotor activity in mutants but not hyperactivity, suggesting that adenosine receptor antagonists could be used to relieve bradykinetic symptoms of Parkinson's disease patients while inducing less excessive motor behavior.

3.4. Adenosinergic drugs and dopamine receptor agonist-induced sensitization of dopaminergic signaling in dopamine-depleted animals

In addition to the ability of adenosine receptor antagonists to acutely reverse hypoactivity in disease models, the chronic effects of these drugs have also been examined. In particular, chronic A2A receptor antagonist treatment can help suppress excessive movements induced by repeated L-DOPA or dopamine receptor agonist administration after degeneration of dopaminergic neurons in animal models (39-41). These excessive movements, including contralateral rotational locomotion in rats lesioned unilaterally with 6-OHDA, could be related to dyskinesias observed in Parkinson's disease patients who have become sensitized after repeated L-DOPA treatment. However, measurement of abnormal involuntary movements (AIMs) of the torso, limbs, head, and mouth in addition to excessive locomotion has been suggested to be a more accurate way of modeling L-DOPA-induced dyskinesias in dopamine-depleted animals (42). The high sensitivity to L-DOPA and dopamine receptor agonists in terms of locomotor activity is apparent from the initial L-DOPA treatment and remains elevated throughout the lifespan of DD mice (32). Thus, DD mice do not serve as a good animal model for L-DOPA-induced sensitization of dopaminergic signaling. But perhaps the initial high sensitivity to dopamine observed in L-DOPA-naïve DD mice occurs because of the presence of adenosine receptor signaling during development. The long-term influence of adenosine signaling, unchecked in the absence of dopamine, could alter the sensitivity of striatal neurons through a gene transcriptional mechanism. The chronic effects of adenosine receptor antagonists on the responsiveness of DD mice to acute L-DOPA challenge in terms of both hyperlocomotion and AIMs will be interesting to examine in the future.

3.5. Feeding responses to adenosinergic drugs in dopamine-depleted animals

The role of adenosine and dopamine in reward-related behaviors has also been explored in DD mice. In terms of feeding behavior, the severe hypophagia of DD can be acutely reversed by treatment with caffeine or an A2A receptor antagonist (36). These results are consistent with experiments using bilaterally 6-OHDA-lesioned rats, in which methylxanthine adenosine receptor antagonists were also shown to induce feeding behavior (43-44). In DD mice, feeding in response to L-DOPA could be enhanced by administration of caffeine or an A2A receptor antagonist. Repeated caffeine treatment could induce feeding behavior for several days but ultimately became less efficacious as compared to L-DOPA treatment, which can support enough feeding for survival for the entire lifespan of mature DD mice. The dopamine/adenosine opposition thus extends to the regulation of behavior related to a naturally rewarding stimulus, like food.

3.6. Reward-related behavioral responses to adenosinergic drugs in DD mice

The function of adenosine in reward learning has also been tested in DD mice. A T-maze paradigm was used to assess the ability of saline-, caffeine-, and L-DOPA-treated DD mice to like, want, and/or learn about food reward (45-46). Saline- and caffeine-treated DD mice were trained over ten days to associate visual cues in one arm of a T-maze with a food reward. The amount of food consumed, latency to begin eating, and number of correct arm entries were measured. After the initial phase of training, the mice were all treated with L-DOPA, and training continued to determine whether any learning had occurred that might have been masked during the initial training phase. DD mice given saline were hypoactive and did not perform the task. When administered L-DOPA in the second phase of the experiment, they learned the task just as naïve mice had in the first phase. Caffeine-treated DD mice were active and explored the T-maze, but they made random choices even after 10 days of training. When they did make correct choices, they consumed the food rewards. However, when these mice were treated with L-DOPA during the second phase, they chose the correct arm of the maze, suggesting that they had learned the location of the food rewards in the presence of caffeine but in the absence of dopamine. Apparently, DD mice treated with caffeine alone liked and learned about the food reward but were not nearly as motivated to seek food reward as those treated with L-DOPA. The notion that DD mice can learn about rewards in the absence of dopamine was further confirmed in another experiment in which DD mice were tested for their ability to form a conditioned place preference for morphine (47). As in the previous experiment, it was necessary to treat the DD mice with caffeine during the preference testing phase because DD mice were too hypoactive to demonstrate a preference

otherwise. However, the pairing sessions with morphine were performed in the absence of caffeine. The experiment demonstrated that DD mice can experience the hedonic effects of morphine and form a preference for the environment where morphine was administered in the absence of dopamine and remember it for at least 24 hr (47). In a third experiment, caffeine treatment of DD mice marginally enabled mutant mice to make food reward-related associations in an operant conditioning task, whereas when they were treated with L-DOPA they learned as well as wild-type mice (48). Furthermore, when DD mice were trained to a high degree of performance with L-DOPA and then switched to caffeine, their performance gradually declined (unpublished observations). These behavioral experiments suggest that while caffeine might enhance locomotion and reverse the hypophagia of DD mice and thereby allow these mice to explore and learn about various testing environments, caffeine treatment does not allow DD mice to manifest goal-directed learning. Learning about rewards can occur in the absence of dopamine, and caffeine can aid in acquisition and performance of tasks that reveal the learning, but it cannot reverse the motivational deficits of DD mice as well as dopamine replacement can.

4. NEURONAL SIGNALING AFFECTED BY ADENOSINERGIC DRUGS IN DOPAMINE-DEPLETED AND DOPAMINE RECEPTOR ANTAGONIST-TREATED ANIMALS

4.1. Neuronal signaling in response to adenosinergic and dopaminergic drugs

A large amount of work has focused on the effects of adenosine receptor drugs on the activity of neurons projecting to and from the striatum because adenosine and dopamine receptors are co-expressed in the striatum (reviewed in 1, 4, 49). Taken together, electrophysiological and *in vivo* microdialysis experiments in brain slices and rodents indicate that A2A receptor activation in the striatum activates inhibitory GABAergic neurons that project to the globus pallidus (50-52). Activation of A1 receptors inhibits transmission from cortical glutamatergic and midbrain dopaminergic inputs to the striatum through presynaptically localized receptors (53-54). Additionally, A1 receptors inhibit GABA release from striatal neurons that project to the substantia nigra pars reticulata (55). The hypothesized molecular basis of the dopamine/adenosine opposition is the co-localization of dopamine and adenosine receptors in striatal neurons and the coupling of the receptors to opposing G proteins (4). Unlike most neurotransmitters that are released from synaptic vesicles in an impulse-dependent manner, adenosine is generated extracellularly by breakdown of ATP and by transport out of cells (3). Extracellular adenosine binds to adenosine receptors that can oppose the effects of released dopamine acting through its receptors in a striatal output neuron. As a consequence, adenosine receptor antagonists are predicted to have similar effects as dopaminergic agonists. The modulation of expression of immediate early genes, like *c-fos*, in response to dopaminergic and adenosinergic drugs has been used to assess whether co-expressed, G protein-coupled receptors indeed oppose each other's actions. Induction of *c-fos* gene expression reflects acute elevations in cAMP/calcium-dependent signaling in neurons (56-57). By itself, immediate early gene induction is not a marker of neuronal activation, but it does indicate a concerted increase in cAMP and calcium levels over the period of minutes to hours. Acute dopamine depletion by reserpine treatment or administration of D2 receptor antagonists leads to *c-fos* induction in striatopallidal neurons (58). This induction is blocked by non-selective adenosine receptor antagonists or A2A receptor antagonists, indicating that D2 and A2A receptors oppose each other's actions in striatopallidal neurons. An A1 receptor antagonist can induce *c-fos* expression in both striatonigral and striatopallidal neurons (59), which suggests that A1 receptors inhibit cAMP-dependent signaling in striatonigral neurons where D1 receptor expression is enriched and in striatopallidal neurons where other $G\alpha_s$ protein-linked receptors are found. Non-selective adenosine receptor or A2A receptor antagonists can augment the effects of L-DOPA or D1 receptor agonists in terms of *c-fos* expression in 6-OHDA-lesioned rats (20, 24), consistent with the notion that dopamine and adenosine receptors oppose each other's actions. But the observations that A2A receptors are expressed in striatopallidal neurons and D1 receptors are enriched in their expression in striatonigral neurons indicates that these receptors can oppose each other's actions even within different types of striatal neurons. In addition to the opposition of receptors at the level G protein signaling, A2A receptors have also been shown to physically interact and heterodimerize with D2 receptors and lower their affinity for dopamine (4). A2A receptors can also interact with metabotropic glutamate receptor 5 (mGluR5) in striatopallidal neurons, and this synergistically increases responsiveness to both A2A receptor agonists and mGluR5 agonists in terms of *c-fos* expression (60).

4.2. Immediate early gene expression studies in DD mice

The neural substrates in DD mice that are responsible for adenosine receptor antagonist-mediated behavioral effects have been examined by assessing *c-fos* expression following drug treatment. Striatal *c-fos* expression is induced in DD mice by L-DOPA or D1 receptor agonist administration (34). At doses that evoke locomotor and feeding behavior in DD mice, caffeine does not induce striatal *c-fos* expression (36). Caffeine treatment does lead to increases in *c-fos* expression in cortical regions, but it is unclear whether adenosine receptor antagonism in the cortex could directly drive locomotor and feeding behavior. Unexpectedly, caffeine administration blocked L-DOPA- or D1 receptor agonist-induced *c-fos* expression in the striatum of DD mice, in the same way that it dampened the L-DOPA-induced hyperlocomotor response. It remains to be explained how the antagonistic action of caffeine on adenosine receptors could lead to these observations because caffeine was expected to augment *c-fos* expression in striatonigral neurons. Nonetheless, it is evident that locomotor activity by DD mice is closely related to levels of *c-fos* expression in the striatum. Determining the brain loci which respond

to adenosine receptor antagonists to drive feeding and other reward-related behavior in DD mice could be explored in the future by delivering adenosinergic drugs directly into selected brain regions. Previous studies showed that restoring dopamine production in the central or lateral striatum of DD mice by viral-mediated gene therapy completely reverses the hypophagia and promotes the survival of these mice (61-62). Additionally, localized bilateral dopamine denervation of the ventrolateral striatum of rats reduces feeding and drinking behavior (63). Adenosine receptors found in these striatal regions could play a role in feeding behavior of DD mice.

5. SUMMARY AND PERSPECTIVE

DD mice are another animal model for understanding the etiology of and testing the efficacy of treatments for Parkinson's disease, drug addiction, and other dopamine-related disorders. The dopamine depletion in these mice is stable in that the genetic lesion is permanent, severe because dopamine production is completely eliminated in dopaminergic neurons, and specific as dopaminergic neurons are intact except for the loss of dopamine synthesis. Dopamine can be restored in DD mice by L-DOPA administration, which permits investigators to determine whether behavioral deficits can be rescued. Adenosine receptor antagonists reverse the hypoactivity and hypophagia of DD mice, largely consistent with other studies using different models of dopamine depletion, dopamine receptor-deficient mice, and dopamine receptor antagonist-treated animals. Additionally, the non-selective adenosine receptor antagonist, caffeine, can allow certain aspects of reward-related behavior to proceed that are lacking in DD mice. The extent of reversal of motor and reward-related behaviors was not as great as with L-DOPA treatment. Future studies might shed light on the causes underlying this difference. One explanation could be that the regulated release of dopamine and phasic activation of downstream neurons in the striatum and elsewhere is more effective at evoking appropriate behaviors than blocking the relatively tonic influence of adenosine, which is produced extracellularly from the catabolism of ATP released from synaptic vesicles and by diffusion across cell membranes through adenosine transporters (64). This idea is consistent with the observation that L-DOPA can elicit feeding by DD mice, but dopamine receptor agonists (either D1-like, D2-like, or non-selective agonists) do not support sufficient feeding to keep DD mice alive. A second possibility is that the signaling efficacy of a dopamine receptor is greater than that of a co-localized adenosine receptor in each striatal neuron. Another alternative is that dopamine receptors are expressed in more striatal neurons than adenosine receptors are. Determining which of these possibilities, if any, is most reflective of the neurobiology of dopamine and adenosine signaling will aid in understanding how adenosine receptor antagonists can be most effectively used in the treatment of Parkinson's disease and other disorders. Other types of G protein-coupled receptors expressed in striatal neurons, such as muscarinic and cannabinoid receptors, also modulate dopamine receptor action. Investigation of the strength of these inputs relative to that of dopaminergic neurotransmission will shed light onto which receptors should be targeted in future drug development.

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Abbreviations: 6-OHDA: 6-hydroxydopamine; DD: dopamine-deficient; DMPX: 3,7-dimethyl-l-propargylxanthine; PACPX: (1,3-dipropyl-8-(2-amino-4-chlorophenyl)-xanthine; NECA: N-ethylcarboxamido-adenosine; L-DOPA: L-3,4-dihydroxyphenylalanine; MPTP: 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine; DPCPX: 8-cyclopentyl-1,3-dipropylxanthine; CSC: 8-(3-chlorostyryl) caffeine; AIM: abnormal involuntary movement; cAMP: adenosine-3',5'-cyclic monophosphate; mGluR5: metabotropic glutamate receptor 5

Key Words: Adenosine, Dopamine, Dopamine-deficient mice, Feeding, Motor, Reward, Review

Send correspondence to: Richard D. Palmiter, Howard Hughes Medical Institute, Department of Biochemistry, Box 357370, University of Washington, Seattle, Washington 98195, Tel: 206-543-6064, Fax: 206-543-0858, E-mail: palmiter@u.washington.edu

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