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Adenosine A_2 receptor-mediated modulation of contralateral rotation induced by metabotropic glutamate receptor activation

Jennifer A. Feeley Kearney, Roger L. Albin *

Neuroscience Program and Department of Neurology, University of Michigan, 1103 E. Huron Street, Ann Arbor, MI 48104-1687, USA

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Abstract

Systemic pretreatment with the adenosine receptor antagonist theophylline significantly decreases contralateral rotation induced by unilateral intrastriatal 1-aminocyclopentane-1*S*,3*R*-dicarboxylic acid (1*S*,3*R*-ACPD). Intrastriatal or intrasubthalamic nucleus coadminstration of theophylline and 1*S*,3*R*-ACPD significantly decreases contralateral rotation suggesting that metabotropic glutamate (mGlu) receptors and adenosine receptors interact locally. These appear to be adenosine A_2 receptor effects as the adenosine A_2 receptor antagonist 8-(3-chlorostyryl)caffeine (CSC) also decreases contralateral rotation induced by unilateral intrastriatal and intrasubthalamic nucleus administration of 1*S*,3*R*-ACPD, while the adenosine A_1 receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX) has no effect. Pretreatment with the adenosine A_2 receptor agonist 2-*p*-(2-carboxyethyl)phenethylamino-5′-*N*-ethylcarboxamido adenosine hydrochloride (CGS 21680) potentiates contralateral rotation induced by unilateral striatal 1*S*,3*R*-ACPD, whereas pretreatment with the adenosine A_1 receptor agonist N^6-cyclopentyl-adenosine (CPA) has no effect. These results suggest that mGlu receptor effects may be due, in part, to modulation of adenosine action.

Keywords: Adenosine A_2 receptor; Basal ganglia; Metabotropic glutamate receptor; Striatum; Subthalamic nucleus

1. Introduction

Excitatory amino acids are important neurotransmitters in the basal ganglia. The metabotropic glutamate (mGlu) receptors are a major class of excitatory amino acid receptors. Eight mGlu receptor subtypes have been cloned, with $mGlu_1$, $mGlu_2$, $mGlu_3$, $mGlu_4$, $mGlu_5$ and $mGlu_7$ receptors expressed in brain, $mGlu_6$ receptor expressed in retina, and $mGlu_8$ receptor expressed primarily in retina and olfactory bulb. These subtypes have been subcategorized into three groups based on their amino acid sequence homology, pharmacological profiles and effector systems. When expressed in transfection systems, activation of group I receptors ($mGlu_1$ and $mGlu_5$) results in stimulation of phosphoinositide hydrolysis. Activation of group II receptors ($mGlu_2$ and $mGlu_3$) and group III receptors ($mGlu_4$, $mGlu_6$, $mGlu_7$, $mGlu_8$) results in inhibition of forskolin-stimulated cAMP accumulation (for reviews, see Schoepp and Conn, 1993; Pin and Duvosin, 1995). In nervous tissue mGlu receptors are coupled to a variety of other effector systems as well, including stimulation of phospholipase D (Boss and Conn, 1992), inhibition of Ca2 + currents (Sayer et al., 1992), modulation of K + currents (Pin and Duvosin, 1995), and increased release of arachidonic acid via phospholipase A_2 activation (Dumuis et al., 1990). In addition, activation of mGlu receptors by the selective agonist 1-aminocyclopentane-1*S*,3*R*-dicarboxylic acid (1*S*,3*R*-ACPD) increases cAMP accumulation in hippocampal slices by potentiating cAMP responses to other neurotransmitter receptors coupled positively to adenylyl cyclase, notably adenosine A_2 receptors (Winder and Conn, 1992, 1993).

Ligand binding studies have shown that the striatum and subthalamic nucleus possess a high density of mGlu receptor binding sites (Albin et al., 1992) and several mGlu receptor subtype mRNAs are expressed by basal ganglia neurons (Testa et al., 1994). Unilateral intrastriatal and intrasubthalamic nucleus injection of the selective mGlu receptor agonist 1*S*,3*R*-ACPD in-

* Corresponding author. University of Michigan, 1014 Neuroscience Laboratory Building, 1103 E. Huron Street, Ann Arbor, MI 48104-1687, USA. Tel.: (313) 764-1347; fax: (313) 764-2189.

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duces vigorous contralateral rotation in rats (Sacaan et al., 1991; Kaatz and Albin, 1995). The basis for this behavioral change appears to be increased activity of dopaminergic nigrostriatal neurons on the injected side, secondary to activation of the subthalamonigral projection (Sacaan et al., 1992; Kaatz and Albin, 1995). The mechanism(s) underlying the effect of unilateral striatal and subthalamic nucleus mGlu receptor activation have not yet been identified.

There is a high density of adenosine A_2 receptors in the striatum (Jarvis and Williams, 1989), and some of the effects of striatal and subthalamic nucleus mGlu receptor activation may be mediated by modulation of adenosine action. We performed a series of experiments to determine if the contralateral rotation induced by unilateral striatal mGlu receptor activation can be modified by blockade or activation of adenosine receptors.

2. Materials and methods

2.1. Intracranial injections

Male Sprague-Dawley rats (Harlan, Indianapolis, IN, USA) weighing 200–300 g were used in all experiments. Intrastriatal and intrasubthalamic nucleus injections were performed under ether anesthesia. Animals were mounted in a Kopf stereotaxic frame and injected with a 5 μl Hamilton syringe. Drugs were injected in a 2 μl total volume over 4 min. The syringe was left in place for 5 min after injection, withdrawn, and the incision was closed with wound clips. Animals were allowed to recover for 4 h in bedded cages before rotational behavior was measured. Since inhalation anesthetic was used, animals were fully awake 30–40 min postsurgery. Coordinates for intrastriatal injection were AP +1.0 mm, ML 2.6 mm, DV −5.7 mm. Coordinates for intrasubthalamic nucleus injection were AP −3.7 mm, ML 2.3 mm, DV −8.4 mm (Paxinos and Watson, 1986).

2.2. Rotational behavior

4 h after intrastriatal or intrasubthalamic nucleus injection, rats were placed in a clear, hemispherical container and frequency of rotations ipsilateral and contralateral to the side of injection were recorded for a 5 min period. One rotation was defined as a 360° turn without a change of direction. Previous work from our laboratory (Kaatz and Albin, 1995) and others (Sacaan et al., 1991,1992) have determined this to be a reliable measure of rotational behavior, as contralateral rotations plateau at 3–4 h after injection and remain constant for several hours.

2.3. Drugs

1*S*,3*R*-ACPD (Tocris Cookson, Bristol, UK) was dissolved in 10 μl 4 N NaOH and diluted to volume with 0.1 M phosphate buffer. Theophylline (Sigma, St. Louis, MO, USA) was dissolved in a drop of 4 N HCl and diluted to volume with 0.1 M phosphate buffer. 8-(3-Chlorostyryl)caffeine (CSC) (RBI, Natick, MA, USA) and 8-cyclopentyl-1,3-dipropylxanthine (DPCPX) (RBI, Natick, MA, USA) were dissolved in 40% DMSO and diluted to volume with 0.1 M phosphate buffer. 2-*p*-(2-Carboxyethyl)phenethylamino-5′-*N*-ethylcarboxamido adenosine hydrochloride (CGS 21680) (RBI, Natick, MA, USA) and N^6-cyclopentyladenosine (CPA) (RBI, Natick, MA, USA) were dissolved in 0.1 M phosphate buffer.

Theophylline, CSC, DPCPX, CGS 21680, and CPA were administered i.p. 15 min prior to intrastriatal or intrasubthalamic nucleus injection of 1*S*,3*R*-ACPD. In separate experiments, theophylline was coinjected with 1*S*,3*R*-APCD into the striatum or subthalamic nucleus in a total volume of 2 μl. The experimental groups are summarized in Table 1.

2.4. Histology

Following measurement of rotational behavior, animals were deeply anesthetized and perfused transcar-

Table 1
Summary of treatment groups

mGluR agonist	Adenosine agonist or antagonist	References
i.s. 1*S*,3*R*-ACPD (1 μmol)	i.p. theophylline (25 mg/kg)	Jiang et al. (1993)
i.s. 1*S*,3*R*-ACPD (1 μmol)	i.s. theophylline (5 mM)	Ferré et al. (1993)
i.s. 1*S*,3*R*-ACPD (1 μmol)	i.p. CSC (3 mg/kg)	Jacobson et al. (1993)
i.s. 1*S*,3*R*-ACPD (1 μmol)	i.p. DPCPX (5 mg/kg)	Jacobson et al. (1993)
i.s. 1*S*,3*R*-ACPD (0.5 μmol)	i.p. CGS 21680 (0.1 μmol/kg)	Ferré et al. (1994)
i.s. 1*S*,3*R*-ACPD (0.5 μmol)	i.p. CPA (0.3 μmol/kg)	Ferré et al. (1994)
i.stn. 1*S*,3*R*-ACPD (1 μmol)	i.stn. theophylline (5 mM)	Ferré et al. (1993)
i.stn. 1*S*,3*R*-ACPD (1 μmol)	i.p. CSC (3 mg/kg)	Jacobson et al. (1993)
i.stn. 1*S*,3*R*-ACPD (1 μmol)	i.p. DPCPX (5 mg/kg)	Jacobson et al. (1993)

i.s. = intrastriatal; i.stn. = intrasubthalamic nucleus; i.p. = intraperitoneal. Appropriate vehicles were administered as controls.

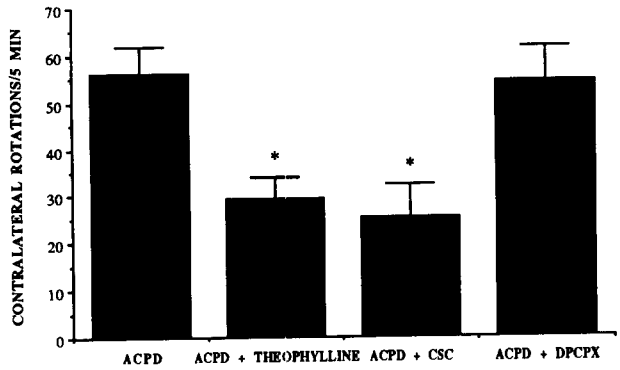

Fig. 1. Effect of the adenosine receptor antagonists theophylline (A_1/A_2), CSC (A_2) and DPCPX (A_1) on contralateral rotation induced by unilateral striatal mGlu receptor activation. Theophylline (25 mg/kg, i.p., $n=11$), CSC (3 mg/kg, i.p., $n=5$), DPCPX (5 mg/kg, i.p., $n=5$) or vehicle ($n=18$) was administered 20 min prior to unilateral, intrastriatal 1*S*,3*R*-ACPD (1 μmol in 2 μl). 4 h after 1*S*,3*R*-ACPD injection, rotations ipsilateral and contralateral to the side of injection were measured for a 5 min period. $^*P < 0.005$ (ANOVA, Fisher's PLSD). Data are means ± S.E.M.

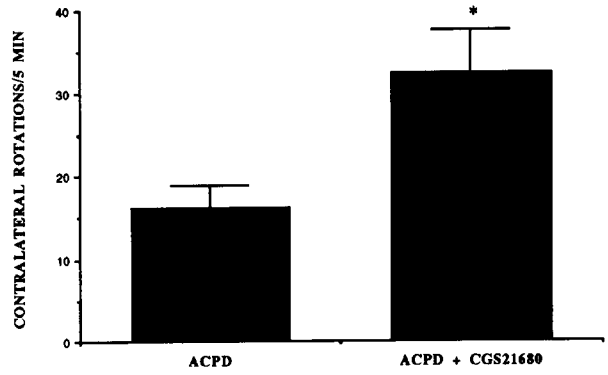

Fig. 3. Effect of the adenosine A_2 receptor agonist CGS 21680 on contralateral rotation induced by unilateral striatal mGlu receptor activation. CGS 21680 (0.1 μmol/kg, i.p., $n=6$) or vehicle ($n=5$) was administered 20 min prior to unilateral intrastriatal 1*S*,3*R*-ACPD (0.5 μmol in 2 μl). 4 h after intrastriatal injection, rotations ipsilateral and contralateral to the side of injection were measured for a 5 min period. $^*P < 0.005$ (ANOVA, Fisher's PLSD). Data are means ± S.E.M.

dially with 0.1 M phosphate buffer and 4% paraformaldehyde. Brains were postfixed overnight and then placed in 20% sucrose until ready for slicing. Brains were sliced in 40 μm sections, mounted on gelatin-coated slides, and stained with 0.5% cresyl violet to confirm injection sites.

2.5. Statistics

The number of contralateral rotations was compared between groups with Student's *t*-tests or ANOVA with Fisher's protected least significant difference (PLSD).

3. Results

Pretreatment with the adenosine receptor antagonist theophylline (25 mg/kg, i.p.) significantly reduced contralateral rotations induced by unilateral intrastriatal 1*S*,3*R*-ACPD (1 μmol) (Fig. 1). Intrastriatal coinjection of theophylline (5 mM) and 1*S*,3*R*-ACPD (1 μmol) also significantly reduced 1*S*,3*R*-ACPD-induced contralateral rotation, suggesting that mGlu receptors and adenosine receptors are interacting locally (Fig. 2). These effects appear to be mediated by adenosine A_2 receptors, as pretreatment with the selective adenosine A_2 receptor antagonist CSC (3 mg/kg, i.p.) significantly reduced contralateral rotation induced by intrastriatal 1*S*,3*R*-ACPD, whereas pretreatment with the selective adenosine A_1 receptor antagonist DPCPX (5

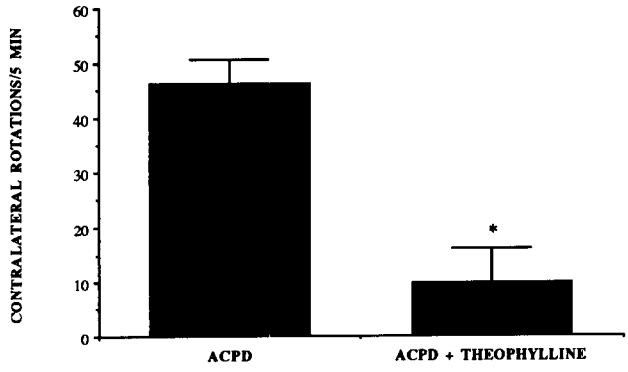

Fig. 2. Effect of intrastriatal administration of the adenosine receptor antagonist theophylline on contralateral rotation induced by unilateral striatal mGlu receptor activation. 1*S*,3*R*-ACPD (1 μmol) and theophylline (5 mM, $n=6$) or vehicle ($n=5$) were coinjected unilaterally into the striatum (total volume, 2 μl). 4 h after intrastriatal injection, rotations ipsilateral and contralateral to the side of injection were measured for a 5 min period. $^*P < 0.005$ (Student's *t*-test). Data are means ± S.E.M.

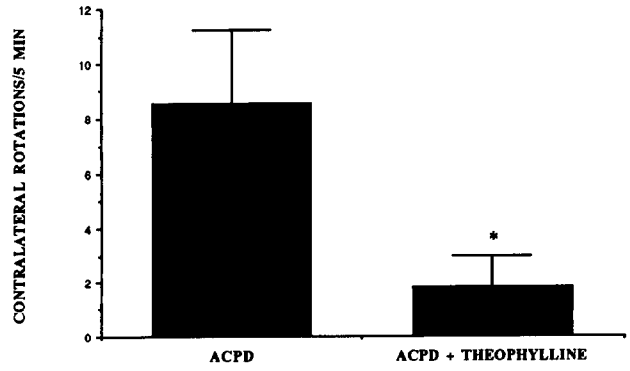

Fig. 4. Effect of intrasubthalamic nucleus theophylline on contralateral rotation induced by unilateral subthalamic mGlu receptor activation. 1*S*,3*R*-ACPD (1 μmol) and theophylline (5 mM) were coinjected unilaterally into the subthalamic nucleus (total volume, 2 μl). 4 h after intrasubthalamic nucleus injection, rotations ipsilateral and contralateral to the side of injection were measured for a 5 min period. $^*P < 0.005$ (Student's *t*-test). Data are means ± S.E.M.

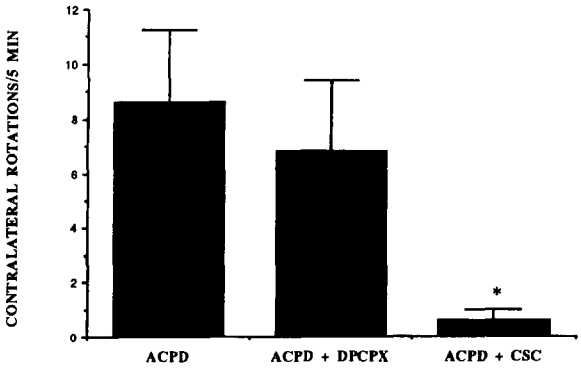

Fig. 5. Effects of the adenosine A_1 receptor antagonist DPCPX and the adenosine A_2 receptor antagonist CSC on contralateral rotation induced by unilateral subthalamic nucleus mGlu receptor activation. DPCPX (5 mg/kg, i.p., $n = 5$), CSC (3 mg/kg, i.p., $n = 6$), or vehicle ($n = 5$) was administered 20 min prior to unilateral, intrastriatal 1*S*,3*R*-ACPD (1 μmol in 2 μl). 4 h after intrasubthalamic injection, rotations ipsilateral and contralateral to the side of injection was measured for a 5 min period. $^*P < 0.01$ (ANOVA, Fisher's PLSD). Data are means ± S.E.M.

mg/kg, i.p.) had no effect (Fig. 1). Pretreatment with the selective adenosine A_2 receptor agonist CGS 21680 (0.1 μmol/kg, i.p.) significantly potentiated contralateral rotation induced by intrastriatal 1*S*,3*R*-ACPD (0.5 μmol) (Fig. 3), while pretreatment with the selective adenosine A_1 receptor agonist CPA (0.3 μmol/kg, i.p.) had no effect (data not shown).

Unilateral intrasubthalamic nucleus coinjection of theophylline (5 mM) and 1*S*,3*R*-ACPD (1 μmol) significantly reduced contralateral rotation induced by intrasubthalamic nucleus injection of 1*S*,3*R*-ACPD alone (Fig. 4). This appears to be an adenosine A_2 receptor effect as pretreatment with the selective adenosine A_2 receptor antagonist CSC (3 mg/kg, i.p.) also significantly reduced contralateral rotation induced by unilateral intrasubthalamic nucleus 1*S*,3*R*-ACPD (1 μmol), whereas pretreatment with the selective adenosine A_1 receptor antagonist DPCPX had no effect (Fig. 5).

Ipsilateral rotations were infrequent under all of the treatment conditions and there were no significant differences between groups.

4. Discussion

Pretreatment with the adenosine receptor antagonist theophylline significantly decreases 1*S*,3*R*-ACPD-induced contralateral rotation suggesting that the contralateral rotation may be due, in part, to modulation of adenosine effects. Additionally, intrastriatal coinjection of theophylline and 1*S*,3*R*-ACPD also reduces contralateral rotation, suggesting that mGlu receptors and adenosine receptors interact locally within the striatum. This effect appears to be mediated by adenosine A_2 receptors, as pretreatment with the selective adenosine A_2 receptor antagonist CSC reduces contralateral rotation induced by unilateral intrastriatal 1*S*,3*R*-ACPD, whereas pretreatment with the adenosine A_1 receptor antagonist DPCPX has no effect. In addition, pretreatment with the selective adenosine A_2 receptor agonist CGS 21680 potentiates the contralateral rotation induced by unilateral striatal mGlu receptor activation.

Taken together, these results suggest that striatal mGlu receptor activation may, in part, act to modulate adenosine tone in the striatum. Adenosine receptors are thought to tonically inhibit striatal dopaminergic actions (Green et al., 1982; Caporali et al., 1987; Popoli et al., 1989). In particular, stimulation of adenosine A_2 receptors is thought to decrease the affinity of dopamine D_2 receptors, as well as inhibit the effects produced by D_2 receptor stimulation (Ferré et al., 1991). Dopamine D_2 and adenosine A_2 receptors are colocalized on striatopallidal neurons (Gerfen et al., 1990; Schiffman et al., 1991).

Activation of mGlu receptors in hippocampal slices have been shown to increase cAMP accumulation in response to endogenous adenosine, presumably mediated by adenosine A_2 receptors positively coupled to adenylyl cyclase (Winder and Conn, 1993). Striatal mGlu receptor activation may, in part, potentiate cAMP accumulation in response to endogenous adenosine in striatopallidal neurons which contain adenosine A_2 receptors, and facilitate adenosine A_2 receptor-mediated decrease in dopamine D_2 affinity and inhibition of the effects of dopamine D_2 stimulation.

A possible mechanism to explain the effects of striatal mGlu receptor activation on adenosine A_2 receptors is presented in Fig. 6. Activation of striatal mGlu receptors may potentiate the effects of endogenous adenosine at adenosine A_2 receptors in striatopallidal neurons, decreasing dopamine D_2 receptor affinity and inhibiting the effects produced by dopamine D_2 receptor stimulation. This would lead to a decrease in the activity of the globus pallidus, which would disinhibit the subthalamic nucleus. Excessive activation of the subthalamic nucleus may, in turn, lead to increased release of dopamine by the substantia nigra pars compacta.

Another potential site for interaction of striatal mGlu receptors and adenosine A_2 receptors is striatal cholinergic interneurons. Striatal administration of 1*S*,3*R*-ACPD has been shown to lead to increases in acetylcholine (Sacaan et al., 1992). Additionally, administration of the muscarinic cholinergic antagonist scopolamine decreases contralateral rotation induced by unilateral striatal 1*S*,3*R*-ACPD (Feeley Kearney and Albin, unpublished observations). Activation of adenosine A_2 receptors has been shown to lead to increases in acetylcholine (Kirk and Richardson, 1994). Adenosine A_2 receptors and mGlu receptors may interact to modulate striatal levels of acetylcholine.

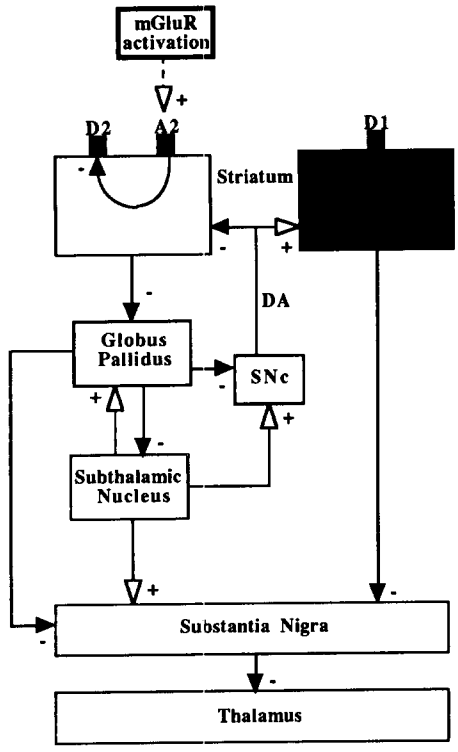

Fig. 6. Diagram of the striatal direct and indirect pathways showing a potential mechanism for mGlu receptor-mediated contralateral rotation (modified from Albin et al., 1989). The 'direct' pathway arises from striatal GABA/substance P/dynorphin neurons and contains dopamine D_1 receptors. The 'indirect' pathway arises from striatal GABA/enkephalin neurons and contains dopamine D_2 receptors. Unilateral striatal mGlu receptor activation may potentiate responses to endogenous adenosine at adenosine A_2 receptors in striatopallidal neurons which would lead to excessive activation of the subthalamic nucleus and a subsequent increase in dopamine release from the substantia nigra pars compacta (SNc).

Unilateral intrasubthalamic nucleus mGlu receptor activation also causes contralateral rotation which can be attenuated by adenosine receptor blockade. The magnitude of the rotation induced by intrasubthalamic injection of 1*S*,3*R*-ACPD is smaller compared to that induced by intrastriatal 1*S*,3*R*-ACPD, possibly due to some activation of the contralateral subthalamic nucleus due to diffusion from the injection site (Kaatz and Albin, 1995). This effect is not non-specific as 1*S*,3*R*-ACPD injections in other brain regions does not induce any rotation (Sacaan et al., 1991; Kaatz and Albin, unpublished observations). Intrasubthalamic nucleus coinjection of the adenosine receptor antagonist theophylline decreases 1*S*,3*R*-ACPD-induced contralateral rotation, which suggests that there is local interaction between mGlu receptors and adenosine receptors in the subthalamic nucleus. This effect also appears to be mediated by adenosine A_2 receptors, as the selective adenosine A_2 receptor antagonist CSC decreases 1*S*,3*R*-ACPD-induced contralateral rotation, whereas the selective adenosine A_1 receptor antagonist DPCPX has no effect. Although most studies of adenosine A_2 receptor localization have shown the highest density to be in the striatum, low levels of adenosine A_2 receptors have been shown to exist in other brain regions (Ferré et al., 1992). Activation of mGlu receptors in the subthalamic nucleus appears to lead directly to excessive subthalamic nucleus activity, presumably resulting in increased dopamine release by substantia nigra pars compacta neurons (Fig. 6) (Kaatz and Albin, 1995).

We report mGlu receptor-adenosine A_2 receptor interaction in two regions of the basal ganglia. Other investigators have reported mGlu receptor-adenosine interaction in hippocampal slices (Winder and Conn, 1993) and cultured hippocampal astrocytes (Ogata et al., 1994). This suggests that mGlu receptor-adenosine receptor interactions may be widespread in the brain. In addition, our results suggest that the mGlu receptor-adenosine receptor interaction is physiologically relevant in the control of extrapyramidal motor behavior.

Although 1*S*,3*R*-ACPD is active at both group I and group II mGlu receptors, it has 10 times greater affinity for group II (Pin and Duvosin, 1995). Group II mGlu receptors ($mGlu_2$, $mGlu_3$) are expressed in both the striatum and subthalamic nucleus. The subthalamic nucleus shows high levels of $mGlu_2$ receptor and low levels of $mGlu_3$ receptor mRNA expression, while the striatum shows high levels of $mGlu_3$ receptor mRNA expression and $mGlu_2$ receptor mRNA expression restricted to cholinergic interneurons (Testa et al., 1994). The potentiation of cAMP responses to other agonists by mGlu receptors in hippocampal slices is thought to be mediated by group II receptors (Winder and Conn, 1995). As selective agonists and antagonists become available, it will be interesting to determine the mGlu receptor subtypes involved in rotational behavior.

Acknowledgements

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