Actions of Adenosine A2A Receptors on Synaptic Connections of Spiny Projection Neurons in the Neostriatal Inhibitory Network

Tomomi Shindou, Gordon W. Arbuthnott, and Jeffery R. Wickens

Department of Anatomy and Structural Biology, University of Otago, Dunedin, New Zealand; and Neurobiology Research Unit, Okinawa Institute of Science and Technology, Okinawa, Japan

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Shindou T, Arbuthnott GW, Wickens JR. Actions of adenosine A2A receptors on synaptic connections of spiny projection neurons in the neostriatal inhibitory network, J Neurophysiol 99: 1884–1889, 2008. First published February 13, 2008; doi:10.1152/jn.01259.2007. There is growing evidence that adenosine plays a crucial role in basal ganglia function, particularly in the modulation of voluntary movement. An adenosine-based treatment for Parkinson’s disease shows promise in recent clinical studies. Adenosine A2A receptors, the receptors involved in this treatment, are highly expressed in the neostriatum. Previous studies have suggested opposing actions of these receptors on synaptic transmission at striatal and pallidal terminals of the same spiny projection neurons, but the cells of origin of the intrastriatal terminals mediating these actions have not been identified.

We used dual whole cell recordings to measure the effects of intrastriatal terminals mediating these actions have not been identified. We used dual whole cell recordings to record simultaneously from intrastriatal terminals mediating these actions have not been identified. We used dual whole cell recordings to record simultaneously from pairs of striatal cells; this enabled definitive identification of the presynaptic and postsynaptic cells mediating the effects of A2A receptors. We found that A2A receptors facilitate GABAergic synaptic transmission by intrastriatal collaterals of the spiny projection neurons, consistent with their previously reported actions on synaptic transmission at pallidal terminals. This neuromodulatory action on lateral inhibition in the striatum may underlie, in part, the therapeutic efficacy of adenosine-based treatments for Parkinson’s disease.

INTRODUCTION

The neostriatum is a central component of the basal ganglia and is crucial for control of voluntary movement and intentional behavior. Dysfunction of the striatum underlies the symptoms of Parkinson’s disease, Huntington’s disease, and several other movement disorders. The principal neuron of the neostriatum is a spiny projection neuron (Somogyi et al. 1981; Wilson and Groves 1980), which accounts for the great majority of neurons in the rat neostriatum (Oorschot 1996). The spiny projection neurons produce local axon collaterals that make GABAergic synapses (Fujiyama et al. 2000) with other spiny projection neurons to form an interconnected network in which several classes of interneuron also participate (Tepper and Bolam 2004). The operation of this microcircuitry is crucial for normal movement and behavior.

The electrophysiological operation of the neostriatal network has only begun to be elucidated. Recent reports show that spiny projection neurons provide functional synaptic input to one another via their local axon collaterals (Czubayko and Plenz 2002; Koos et al. 2004; Tunstall et al. 2002; Venance et al. 2004). Spiny projection neurons also receive inputs from several types of GABAergic interneuron, including a fast-spiking (FS) interneuron that has been shown to exert strong inhibitory control over neostriatal output (Koos and Tepper 1999). This GABAergic circuitry, comprising feedback inhibition by spiny projection neurons and feedforward inhibition by FS interneurons, plays a critical role in integrating cortical inputs and regulating basal ganglia output activity (Kita 1993; Koos and Tepper 1999; Plenz 2003).

There is growing evidence that adenosine plays an important role in basal ganglia function (Richardson et al. 1997; Svensson et al. 1999). Adenosine is an endogenous purine released (or generated) intracellularly and extracellularly. It is present at low levels (20–300 nM) in the extracellular space and interacts with specific receptors. Adenosine has four G-protein-coupled, membrane-bound receptor subtypes designated A1, A2A, A2B, and A3. Of these subtypes, the adenosine A2A receptor is highly expressed in the striatum, particularly in striatopallidal projection neurons (Dixon et al. 1996). Recently, antagonists of adenosine A2A receptors have emerged as an important new class of effective anti-parkinsonian agents (Hauser and Schwarzschild 2005; Jenner 2005).

Previous brain slice electrophysiological studies have shown that A2A receptors facilitate GABAergic transmission in the globus pallidus, a major projection area of the neostriatal spiny projection neurons (Shindou et al. 2003). Paradoxically, it has been reported that A2A receptors decrease GABAergic transmission in the neostriatum (Mori et al. 1996), suggesting opposite effects of A2A receptors on the pallidal and striatal terminals of the same spiny neurons. However, because field stimulation was used to evoke IPSCs in the neostriatum (Mori et al. 1996), both FS interneurons and spiny projection neurons may have been activated. Thus it is important to determine the effects of A2A receptors on GABAergic transmission in the neostriatum that are mediated by spiny projection neurons.

We used dual whole cell recording to measure the effects of adenosine A2A agonists on GABAergic synaptic transmission in the striatum. We investigated postsynaptic responses to single action potentials evoked in the presynaptic neuron before and after exposure to an adenosine A2A agonist drug. By intracellular labeling of the recorded cells, we were able to identify the presynaptic neurons definitively, allowing us to determine the adenosine A2A receptor actions that are mediated specifically by spiny projection neurons.

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METHODS

Animals were handled in accordance with protocols approved by the University of Otago Animal Ethics Committee. The experiments were performed on male Wistar rats (age: 21–28 days). Animals were deeply anesthetized with pentobarbital sodium (SIGMA). They were perfused transcardially for 2 min with cold modified-artificial cerebrospinal fluid (ACSF) containing the following (in mM): 126.0 NaCl, 2.5 KCl, 2.4 CaCl₂, 1.2 MgCl₂, 26.0 NaHCO₃, 1.0 NaHPO₄, and 11.0 glucose and saturated with 95% O₂-5% CO₂. Slices containing the striatum were cut on a VT1000S microtome (Leica) at a thickness of 300 μm in an oblique plane, ~45° rostral-up to the horizontal (Tunstall et al. 2002). Slices were then incubated in oxygenated standard ACSF maintained at a temperature of 32–33°C for 1 h. The standard ACSF had the following composition (mM): 126.0 NaCl, 2.5 KCl, 2.4 CaCl₂, 1.2 MgCl₂, 26.0 NaHCO₃, 1.0 NaHPO₄, and 11.0 glucose. After incubation, a single slice was transferred to a recording chamber placed on the stage of an upright microscope, and was continuously perfused (3–4 ml/min) with oxygenated ACSF at room temperature.

Whole cell recordings were obtained from neostriatal neurons with patch pipettes (2–4 MΩ) filled with internal solution containing the following (in mM): 64.0 K-glucurate, 60.0 KCl, 8.0 NaCl, 10.0 HEPES, 0.5 EGTA, 4.0 ATP, 0.3 GTP, and 0.5% biocytin; pH 7.2–7.4. The series resistance was not compensated but was monitored following (in mM): 64.0 K-gluconate, 60.0 KCl, 8.0 NaCl, 10.0 NaCl, 2.5 KCl, 2.4 CaCl₂, 1.2 MgCl₂, 26.0 NaHCO₃, 1.0 NaHPO₄, and 11.0 glucose. After incubation, a single slice was transferred to a recording chamber placed on the stage of an upright microscope, and was continuously perfused (3–4 ml/min) with oxygenated ACSF at 30°C. The remaining slices were kept in a holding chamber containing oxygenated ACSF at room temperature.

Recordings were made in a solution containing blockers of excitatory transmission, namelyD-2-amino-5-phosphonovaleric acid (APV, 50 μM), and 6-cyano-7-nitroquionexanline-2,3-dione (CNQX, 10 μM). Unitary IPSCs were elicited at 0.066 – 0.2 Hz by single action potentials generated in the presynaptic cells by depolarizing somatic currents. The neuron exhibited the characteristic electrophysiological properties of a spiny projection neuron. Whole cell recordings were obtained from the presynaptic neuron of the same pair, showing response to hyperpolarizing and depolarizing current pulses. The neuron exhibited the characteristic electrophysiological properties of a spiny projection neuron. Whole cell recordings were obtained from the presynaptic neuron of the same pair, showing response to hyperpolarizing and depolarizing current pulses.

For morphological identification of recorded cells, 0.5% biocytin was included in the pipette solution and cells were filled by diffusion. After a recording was completed, slices containing biocytin-loaded cells were fixed by immersion in 4% paraformaldehyde in 0.1 M phosphate buffer (PB) overnight at 4°C. They were rinsed in PB for 20 min and incubated in PB containing 0.5% H₂O₂ for 30 min. They were then incubated in 4% paraformaldehyde in 0.1 M phosphate buffer (PB) overnight at 4°C. They were rinsed in PB for 30 min and incubated in PB containing 0.5% H₂O₂ for 30 min. They were then incubated in 15 and 30% sucrose for 30 min and 1 h, respectively. The slices were then washed with Tris-buffered saline (TBS) containing 0.5% Triton X and streptavidin-Alexa fluor 488 (1:1000, Mol Probe) for 2 h at room temperature. To determine the localization of A₂A receptors in spiny projection neurons, we incubated the slices in TBS containing 0.5% Triton X, 10% normal donkey serum (NDS), and a mouse anti-adenosine A₂A receptor antibody (1:1000, Mol Probe) for 2 h at room temperature. To determine the localization of A₂A receptors in spiny projection neurons, we incubated the slices in TBS containing 0.5% Triton X, 10% normal donkey serum (NDS), and a mouse anti-adenosine A₂A receptor antibody (1:1000, Mol Probe) for 2 h at room temperature.

Data analysis was performed using custom software written in AxoGraph. All data are given as means ± SE unless stated otherwise. Responses to agonists are expressed as a percentage of the control obtained before the addition of the agonists. Paired t-tests were performed to compare the control period with the responses in the presence of agonists and wash period on the same cell. For analysis of individual cells, the nonparametric Mann-Whitney U test was applied between the control (15–20 consecutive IPSCs, over 4–5 min, stimulation every 15 s) and treatment period (15–20 consecutive IPSCs from last 1–2 min of drug application until 2–3 min after application) and between control and washout periods.

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antibody (1:1,000, Upstate, Lake Placid, NY) for 4 days at 4°C. We
then incubated the slices overnight at 4°C in 0.3% Triton X, 10% NDS,
and anti-mouse conjugated Alexa Fluor 543 (1:200, Chemicon).
After washing with TBS, the slices were mounted on a glass slide and
were observed under a confocal laser scanning microscope (LSM 410,
Zeiss) with a confocal laser depth of ~0.5 μm.

Drugs (APV and CNQX) were bath-applied in the solution super-
fusing the slice. For experiments with CGS21680, the solution super-
fusing the slice was replaced with one containing a set concentration
of active drug. APV and CNQX were obtained from Tocris Cookson
(Bristol, UK); CGS21680 was from Research Biochemicals Interna-
tional (Natick, MA).

RESULTS

Recordings were obtained from 194 pairs of spiny projection
neurons in which direct connections were tested for by induc-
ing action potentials in one neuron while simultaneously re-
cording the response in the other. The recorded spiny projection
neurons were identified by their characteristic electrophys-
iological properties and also by staining of intracellularly
 injected biocytin. Spiny projection neurons exhibited charac-
teristic delay in action potential firing and onset of firing at low
rates in response to depolarizing current pulses, heavily spine-
encrusted distal dendrites, and a local plexus of axon collaterals.
The electrophysiological characteristics, unitary synaptic re-
sponses and morphology of a typical connected spiny projec-
tion neuron pair are shown in Fig. 1 (A–C).

GABAergic synaptic connections were detected in 29% of
spiny projection neuron pairs tested (56/194, Fig. 1D). In these
pairs, inward-going postsynaptic currents were measured in
response to a single action potential evoked in the presynaptic
spiny projection neuron. These inward currents were com-
pletely suppressed by the GABA_A antagonist bicuculline
(10 μM, data not shown), therefore the evoked synaptic cur-
rrents were GABA_A-receptor mediated IPSCs. Reciprocal con-
nnections were rare, occurring in only 7% of connected pairs (4
of 56 pairs). The amplitude, 10–90% rise time, width at
half-amplitude, and latency of the IPSCs were 22 ± 4 pA,
1.1 ± 0.1 ms, 8.1 ± 0.6 ms, and 0.9 ± 0.1 ms, respectively
(n = 41). The distances between the somata of the connected
spiny projection neuron pairs that were reconstructed ranged
from 46 to 140 μm (89 ± 4 μm, n = 35). The probability of
a connection existing between spiny projection neurons was
estimated from this data to be 0.15 (60 of 388 chances).

Next we examined the action of A2A receptors on spiny
projection neuron interactions. The effects of an adenosine A2A
receptor agonist CGS21680 on the IPSCs were tested in 17
connected spiny projection neuron pairs. An example pair is
shown in Fig. 2 (A and B). Bath application of CGS21680 0.1
μM had no significant effect on the IPSC amplitudes, but 0.3
and 1.0 μM of CGS21680 increased the amplitude of the
IPSCs. Group averages showed these effects were statistically
significant, with CGS21680 producing excitatory PSC (EPSC)
amplitudes 100 ± 3% (n = 7), 140 ± 11% (P < 0.05, n = 6),
and 150 ± 28% (P < 0.05, n = 4) of control at 0.1, 0.3 and 1.0
μM, respectively (Fig. 2C).

Analysis of individual spiny neuron pairs using non para-
metric statistics showed a nonuniform effect. At 1 μM
CGS21680 in three of four tested pairs, there were no signif-
ificant differences between before and during application
of CGS21680. One tested pair showed a significant difference
between before and during application (P = 0.007, Mann-
Whitney U test). At 0.3 μM CGS21680, two of six tested pairs
showed a significant difference (P < 0.05) between before and
during application. In the remaining four pairs, there were no
significant differences between before and during application
of CGS21680. Combining these results, three of nine pairs
tested individually showed a significant effect of CGS21680.
Although these proportions are not inconsistent with the exis-
tence of different subclasses of presynaptic spiny neurons, we
could not determine which of the presynaptic neurons was a
striatopallidal versus striatonigral neuron in these experiments.

The CGS21680 (0.3 μM)-induced enhancement of spiny
projection neuron IPSCs was accompanied by a reduction in
the paired-pulse ratio (PPR, Fig. 3A, 1 and 2). Synaptic
responses were elicited at 50-ms interresponse intervals. Before
application of CGS21680, the ratio of the amplitudes was
0.95 ± 0.07 (n = 6). Application of CGS21680 (0.3 μM) led
to an increase of the first IPSC, accompanied by a reduction in
the PPR to 0.74 ± 0.07 in the same neurons (n = 6, P < 0.05,
Fig. 3A2).
Application of CGS21680 also caused a decrease in the mean failure rate (Fig. 3A). The failure rate was 0.47 ± 0.11 prior to CGS21680 application and decreased to 0.27 ± 0.08 during application of CGS21680 (0.3 μM, P < 0.05, n = 6). To take account of this, the effects of CGS21680 on spiny-spiny IPSCs were analyzed with failures excluded. Both 1 μM (n = 4) and 0.3 μM CGS21680 (n = 6) caused statistically significant changes in IPSC amplitude when failures were excluded (P < 0.05, paired t-test).

The changes in failure rate and PPR indicate that A2A receptors act presynaptically at the terminals of spiny neurons to enhance the probability of GABA release. The effects of antagonists of A2A receptors were not examined, but the concentration (0.3 and 1 μM) of CGS21680 used in this study was confirmed to selectively activate A2A receptors for modulation of IPSCs in the striatum (Mori et al. 1996; Shindou et al. 2001, 2002) using rat brain slices.

To determine the localization of A2A receptors in axon collaterals of spiny projection neurons, we performed double-labeling with immunostaining of A2A receptor antibody and biocytin labeling of intracellularly filled spiny projection neurons (Fig. 3B). Double-labeling of A2A receptors (Fig. 3B1) and biocytin-filled spiny projection neurons (B2) was evident in axon terminals (B3, △) and also in some dendritic spines (B3, →). The presence of A2A receptors on dendritic spines suggests potential postsynaptic actions on the glutamatergic afferents to the striatum, which terminate on dendritic spines. The labeling of axon terminals of spiny projection neurons, which synapse with somata, dendrites, and spine shafts of other spiny projection neurons, is consistent with the presynaptic locus of action suggested by the actions of CGS21680 on PPRs and failure rates.

The action of CGS21680 on IPSC amplitude had a slow onset and was slow to reverse, as previously described (Mori et al. 1996; Shindou et al. 2003). The decrease in the PPR also had a slow onset and was slow to reverse. To demonstrate the time course of effect onset and its subsequent reversal, the data for all cases combined is shown in Fig. 4, A and B. In the figure, data for IPSCs from CGS21680 0.3 and 1.0 μM groups were pooled, there being no significant differences between them. Although washout was slow, the effects reversed, as evidenced by finding no significant differences between baseline and washout after CGS21680 0.3 μM (P = 0.4123, n = 6) or 1.0 μM (P = 0.1516, n = 4).
DISCUSSION

The main finding of the present study is that A2A receptors facilitate GABAergic synaptic transmission by intrastriatal collaterals of the spiny projection neurons. We believe this is the first direct evidence of A2A receptor-mediated facilitation of intrastriatal GABAergic synaptic transmission. The use of paired whole cell recording, moreover, enabled definitive identification of the spiny projection neurons mediating this effect.

Previous work has shown that A2A receptors facilitate GABAergic transmission in the globus pallidus (Shindou et al. 2003) yet decrease GABAergic transmission in the neostriatum (Mori et al. 1996) in contrast to the present results. The present findings suggest a parsimonious explanation for these apparently opposite effects of A2A receptors on the pallidal and striatal terminals of the spiny projection neurons. We show that A2A receptors facilitate GABAergic transmission in the striatal terminals of the spiny projection neurons as previously shown for the pallidal terminals of the same cell type. In the present case, the presynaptic neurons could be definitively identified. In contrast, Mori et al. (1996) used intrastriatal field stimulation, which would preferentially activate the more excitable FS interneurons (Tecuapeta et al. 2005) rather than the strongly hyperpolarized spiny projection neurons. Furthermore, the A2A-mediated decrease in field IPSC reported by Mori et al. was measured at an early stage of development (p9–p12) at which stage lateral inhibition by projection neurons may not be detectable (Koos et al. 2004). This suggests that the effects of A2A receptors in juvenile rat slices may be largely mediated by FS interneurons. Previous studies (Koos and Tepper 1999, 2002; Koos et al. 2004) show that GABAergic interneurons have a high probability of being connected to nearby neostriatal cells and that the connection strength can be several times greater than the effects of projection neurons on each other. Therefore actions of A2A receptors on inhibition mediated by interneurons may be significant under some conditions.

Several pieces of evidence suggest a presynaptic locus of action by A2A receptors on spiny projection neuron terminals in the striatum. We found that the increase in GABAergic synaptic transmission by projection neurons was associated with a reduction in the PPRs and a decreased failure rate, consistent with a presynaptic action of A2A receptors. Also our immunohistochemical results showed that A2A receptors were expressed on presynaptic terminals of spiny projection neurons. Although we also observed postsynaptic A2A receptors on spiny dendrites, as previously reported (Hettinger et al. 2001), these postsynaptic receptors are unlikely to mediate the effects we observed. First Mori et al. (1996) found no effects of A2A agonists on postsynaptic responses of spiny neurons to exogenously applied GABA, as would be expected if A2A receptors acted postsynaptically to modulate GABAergic responses. Second, the localization of postsynaptic A2A receptors to dendritic spines is more suggestive of a modulatory effect on the glutamatergic, excitatory inputs to projection neurons (Ferre et al. 2002; Kachroo et al. 2005; Norenberg et al. 1997; Popoli et al. 1995; Wirkner et al. 2000), which synapse on dendritic spines, than inhibitory inputs, which commonly synapse on dendritic shafts. Collectively, these considerations argue for a presynaptic locus of action of the modulatory effect of A2A receptors on GABAergic transmission between spiny projection neurons in the striatum.

The data in the present study demonstrate that presynaptic A2A receptors enhance GABAergic transmission of spiny projection neurons via their local axon collaterals. This action of A2A receptors may play an important role in striatal function. In particular, A2A receptors may alter the ratio of feedback inhibition (mediated by lateral inhibition) to feedforward inhibition (mediated by interneurons), leading to a change in neurodynamics. Theoretical studies suggest that feedback inhibition leads to competitive neurodynamic modes in which the initially most active neurons can suppress activity in others (Fukai and Tanaka 1997). Although it has been argued that the sparse connectivity of spiny projection neurons is not consistent with “winner-take-all” dynamics (Koos et al. 2004; Tepper et al. 2004) realistic values of connectivity have been shown to be consistent with feedback regulation of activity and competitive modes of activity (Wickens et al. 2007). Modulating the efficacy of the spiny neuron connections may significantly alter striatal dynamics.

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GRANTS

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REFERENCES

Koos T, Tepper JM. Inhibitory control of neostriatal projection neurons by GABAergic interneurons. Nat Neurosci 2: 467–472, 1999.


