Increase in Adenosine Sensitivity in the Nucleus Accumbens Following Chronic Morphine Treatment

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INTRODUCTION

Drug addiction is a disease characterized by neurochemical changes in the brain that contribute to acute tolerance and withdrawal, as well as to the long-term craving that often leads to relapse of drug taking behavior (Leshner 1997). The adenosinergic system has received considerable attention as one of the neurochemical systems involved in morphine tolerance and withdrawal. The idea that adenosine is involved in opioid effects originated from the demonstration that methylxanthines exacerbate opioid withdrawal symptoms (Collier et al. 1976). Although this was thought to be due to the ability of these agents to block phosphodiesterase and elevate cAMP levels, it is now clear that the adenosine receptor blocking properties of methylxanthines also contributed to these effects (Collier and Tucker 1983; Tucker et al. 1984). Subsequent research has demonstrated that adenosine agonists can reduce opioid withdrawal symptoms and that drugs acting on adenosine signaling pathways may have clinical utility for treating drug addiction (Ahlijianian and Takemori 1986; Kaplan and Coyle 1998; Kaplan and Sears 1996; Tucker et al. 1984).

A number of brain regions have been implicated in the development of drug tolerance and withdrawal. Foremost among these are regions of the brain stem involved in noradrenergic signaling such as the locus ceruleus and periaqueductal gray, and the mesolimbic dopaminergic system, including the ventral striatal and nucleus accumbens (NAcc) (Christie et al. 1997; Nestler and Aghajanian 1997). Several neurochemical changes have been demonstrated in the NAcc after chronic drug treatment, including changes in adenyl cyclase and protein kinase A activity (Chien and Williams 1998; Self et al. 1995; Tornvall et al. 1991; Valverde et al. 1996), dopamine levels (Acquas and Di Chiara 1992; Diana et al. 1999), acetylcholine levels (Fiserova et al. 1999; Rada et al. 1996), and NMDA receptors (Martin et al. 1999a,b). Despite the important role of the NAcc in mediating addictive behaviors, relatively few studies have examined the physiological consequences of altered adenosine signaling in the NAcc after chronic drug consumption.

The purpose of the present study was to determine the effects of chronic morphine treatment on adenosine-mediated modulation of excitatory synapses in the NAcc. Chronic morphine treatment did not significantly alter tonic inhibition by adenosine. However, chronic morphine treatment increased the sensitivity of excitatory synapses to exogenously applied adenosine, an effect that was prevented by blocking adenosine transport. It is concluded that chronic morphine treatment increases adenosine uptake in the NAcc.

METHODS

Chronic morphine treatment and preparation of NAcc slices

Young male Wistar rats (140–160 g) were anesthetized with a ketamine/suxamethonium mixture (50/21 mg/kg) and subcutaneously implanted with 75-mg morphine pellets. One pellet was implanted on day 1, and two were implanted on days 3 and 5. On days 7–9 the rats were anesthetized as above, killed, and their brains rapidly removed and cut with a vibratome into 250-μm horizontal...
slices at 4°C. Tissue surrounding the NAcc was removed and the slices were stored in physiological saline at room temperature. Slices were incubated for at least 1 h prior to use in the absence of morphine. Recordings were thus made under morphine-free conditions, i.e., acute morphine withdrawal. The saline used in all experiments contained the following (in mM): 126 NaCl, 2.5 KCl, 1.2 MgCl2, 2.4 CaCl2, 1.2 NaH2PO4, 11 glucose, 21.4 NaHCO3, oxygenated with 95% O2-5% CO2. Slices were incubated in the presence of the N-methyl-D-aspartate (NMDA) receptor antagonist (RS)-3-(2-carboxypiperazin-4-yl)-propyl-1-phosphonic acid (CPP; 10 μM). After 1–4 h, slices were transferred to a recording chamber and superfused with physiological saline at 2 ml/min. All experiments were performed in the presence of CPP (10 μM) and the γ-aminobutyric acid-A (GABA A ) antagonist picrotoxin (100 μM) to isolate α-amino-3-hydroxy-5-methyl-4-isoxazolopropionic acid (AMPA) receptor responses. The phosphodiesterase inhibitor R020-1724 (200 μM) was also included during the construction of all dose-response curves to inhibit the release of endogenous adenosine (Manzoni et al. 1998).

Electrophysiological recording

Whole-cell recordings were made from medium spiny neurons (MSNs) using an Axopatch 1D patch-clamp amplifier. Recording electrodes were pulled from borosilicate glass (OD, 1.5 μm, ID, 1.2 mm, with filament; World Precision Instruments) on a Narishige micropipette puller and had tip resistances of 2–4 MΩ when filled with a solution containing the following (in mM): 125 Cs-glucuronate, 11 KCl, 10 HEPES, 0.1 CaCl2, 1 K-EGTA, 2 Mg-ATP, 0.3 Tris-GTP, pH adjusted to 7.3 with KOH, osmolarity adjusted to 288 mOsm. Cells were visualized with a 40× water immersion lens using Nomarski optics and infrared illumination. MSNs were selected within 200 μm of the medial boundary of the NAcc roughly midway between the rostral and caudal extremes of the NAcc and are considered to have come exclusively from the shell (Paxinos and Watson 1998). MSNs were identified based on their small size (10–15 μm diameter), negative resting membrane potential (approximately −75 to −80 mV), lack of spontaneous action potentials, and the presence of a fast inwardly rectifying potassium current but the absence of a slow Ih current at negative membrane potentials (Uchimura et al. 1989). MSNs were voltage clamped at −75 mV, and synaptic currents were evoked every 20 s with a tungsten bipolar stimulating electrode (Frederick Haer) placed on the surface of the slice rostral to the recording electrode. The resulting inward excitatory postsynaptic currents (EPSCs) were completely blocked by application of the AMPA receptor antagonist 6-nitro-7-sulfamoylbenzo[f]quinoxaline-2,3-dione (NBQX; 5 μM). Access resistance was determined with a bridge circuit in current clamp mode at the beginning and end of each experiment and was below 20 MΩ at all times. Series resistance was compensated by 80%, and voltages reported are corrected for a −15 mV liquid-liquid junction potential as determined using JPCalc software. All drugs were applied by dissolving them directly into the superfusion solution.

Statistical comparison

All statistical comparisons were made using Prism version 3 software (GraphPad). The Mann-Whitney test was used to compare normalized responses between different cells from different rats. A two-way analysis of variance (ANOVA) was used to compare dose-response relationships by both concentration and treatment condition. The criterion for statistical significance was P < 0.05.

Chemicals

Morphine base pellets (75 mg) were obtained from the National Institute on Drug Abuse. Adenosine, N6-cyclopentyladenosine (N6-CPA), and dipyridamole were obtained from Sigma Chemical. Picropylxanthine, 8-cyclopentyl-1,3-dipropylxanthine (DPCPX), and nitrobenzylthioinosine (NBTI) were from Research Biochemicals International. CPP and NBQX were obtained from Tocris Cookson.

RESULTS

Adenosine inhibits EPSCs in medium spiny neurons

The effects of adenosine were determined on AMPA receptor-mediated EPSCs recorded from MSNs in the shell of the NAcc. As shown in Fig. 1 and consistent with previous results (Harvey and Lacey 1997; Manzoni et al. 1998; Uchimura and North 1991), adenosine reduced the EPSC amplitude in a dose-dependent manner. This inhibition was completely reversed in all cases by application of the selective A1 adenosine receptor antagonist DPCPX (100–200 nM), indicating that the inhibition was mediated entirely by A1 adenosine receptors.

Chronic morphine treatment increases adenosine-mediated inhibition

To determine whether chronic morphine treatment altered the low, tonic level of adenosine normally present in a slice preparation (Dunwiddie and Diao 1994; Dunwiddie and Hoffer 1980), NAcc slices were superfused with 100 nM DPCPX to block the action of endogenous adenosine at A1 receptors. As shown in Fig. 2A, DPCPX produced a small increase in the EPSC amplitude that was not significantly different between untreated and chronic morphine-treated rats (untreated: 9 ± 7% increase, n = 6; morphine: 24 ± 12% increase, n = 10; P = 0.37 Mann-Whitney test). This indicates that chronic morphine treatment did not significantly alter the tonic level of endogenous adenosine at excitatory synapses in the NAcc.

To determine whether chronic morphine treatment altered the sensitivity of NAcc synapses to adenosine, adenosine dose-response curves were constructed (Fig. 2B). In untreated rats, adenosine dose-dependently inhibited EPSCs to a maximum of

![Graph showing EPSC amplitudes](http://jn.physiology.org/)

FIG. 1. Adenosine dose-dependently inhibited excitatory postsynaptic currents (EPSCs) in nucleus accumbens (NAcc) medium spiny neurons. The graph shows the time course of EPSC amplitudes in a representative neuron. Adenosine was applied at the times and concentrations indicated at the bottom of the graph. The A1 adenosine receptor antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX) was applied at 100 nM. Each point on the graph represents the average of 3 EPSCs taken at 20-s intervals. Each example sweep shown at the top was taken from the drug application period directly below it and is the average of 10 individual responses from the last 3 min of the corresponding drug application period.
84 ± 9% inhibition with a Hill slope of 0.95 ± 0.20 and an EC₅₀ of 9.6 ± 2.8 μM (n = 4–7 for all points). Chronic morphine treatment increased the sensitivity of these synapses to adenosine and shifted the dose-response curve to the left without altering the maximum inhibition. In chronic morphine-treated animals adenosine produced a maximum of 88 ± 6% inhibition with a Hill slope of 1.00 ± 0.18 and an EC₅₀ of 5.1 ± 1.0 μM (n = 4–7). A two-way ANOVA showed a highly significant effect of treatment condition on the responses (P < 0.0001, F value for treatment = 17.78), indicating that the two dose-response curves were significantly different from each other.

To rule out the possibility that the changes observed were due to an artifact of the pellet implantation procedure, a group of rats were implanted with morphine-free placebo pellets under identical conditions as the morphine pellet-implanted rats. The effects of adenosine were determined on these animals at two concentrations: 10 and 30 μM. As shown in Fig. 2C, animals implanted with placebo pellets showed a nearly identical response to adenosine as the untreated animals (at 10 μM: untreated, 40 ± 3% ; placebo: 42 ± 5%, n = 7; morphine: 58 ± 4% inhibition, n = 7; at 30 μM: untreated, 66 ± 4%, n = 4; placebo: 62 ± 4%, n = 6; morphine: 78 ± 2% inhibition, n = 6). There was no significant difference between the untreated animals and the placebo-treated animals at either concentration (10 μM: P = 0.88; 30 μM: P = 0.48; Mann-Whitney test). There was a significant difference between the morphine-treated animals and the placebo-treated animals (10 μM: P = 0.03; 30 μM: P = 0.03; Mann-Whitney test), as well as between the morphine-treated animals and the untreated animals (10 μM: P = 0.01; 30 μM: P = 0.01; Mann-Whitney test). Hence, the pellet implantation procedure had no effect on adenosine sensitivity, and the changes observed after chronic morphine treatment were entirely due to morphine exposure.

Chronic morphine treatment does not alter A₁ receptors

One possible explanation for the increased sensitivity of NAcc synapses to adenosine after chronic morphine treatment is that the number, affinity, or effector coupling of A₁ adenosine receptors has been increased. To test this possibility, dose-response curves were constructed for the selective A₁ adenosine receptor agonist N6-CPA, which is not a substrate for uptake or metabolism. As shown in Fig. 3, the dose-response curve for N6-CPA in chronic morphine-treated rats was nearly identical to the dose-response curve in untreated rats (untreated: max inhibition = 74 ± 6%, EC₅₀ = 47 ± 14 nM, n = 5–8; morphine: max inhibition = 84 ± 10%, EC₅₀ = 55 ± 27 nM, n = 4–8). A two-way ANOVA found no significant difference of treatment condition between these groups (P = 0.21, F value for treatment = 1.606). These data indicate that chronic morphine treatment did not alter the adenosine receptors at these synapses and that some other adaptation must be responsible for the increased sensitivity of these synapses to adenosine.
The increased sensitivity to adenosine requires adenosine transport

The data showing that adenosine receptors are not altered by chronic morphine treatment suggest that there may be a change in the ability of the NAcc to remove or metabolize adenosine present in the extracellular space. To test this possibility, slices were superfused with the nucleoside transporter blockers (NBTI; 100 nM) and dipyridamole (5 μM), concentrations sufficient to completely block adenosine transport in slices (Dunwiddie and Diao 1994; Shank and Baldy 1990). The combination of NBTI and dipyridamole inhibited EPSCs by 19 ± 3% in untreated rats (n = 7) and by 18 ± 5% in morphine-treated rats (n = 5), and this inhibition was reversed by the A₁ adenosine receptor antagonist DPCPX (200 nM) in all cases (data not shown). Hence, blocking adenosine transport caused a small increase in the steady-state concentration of endogenous adenosine in the slice (Fig. 4A), even in the presence of the phosphodiesterase inhibitor RO20-1724, which was included in all dose-response curve experiments to reduce endogenous adenosine formation (Manzoni et al. 1998). The inhibition caused by the transport blockers was nearly identical in untreated and morphine-treated rats (P = 0.64, Mann-Whitney test), providing further evidence that the production and release of endogenous adenosine under baseline conditions is not altered by chronic morphine treatment. To determine if the transport blockers changed the sensitivity of the slices to exogenously applied adenosine, adenosine dose-response curves were constructed in the presence of NBTI and dipyridamole (Fig. 4B). NBTI and dipyridamole substantially increased the sensitivity of the slices to adenosine, which inhibited EPSCs with an EC₅₀ of 2.9 ± 0.8 μM (n = 3–5) in untreated rats and 2.6 ± 0.6 μM (n = 3–4) in morphine-treated rats. A two-way ANOVA found no significant difference between these two groups (P = 0.37, F value for treatment = 0.8372), indicating that the transport blockers eliminated the shift in the dose-response curve caused by chronic morphine treatment. Hence, the increase in adenosine sensitivity observed after chronic morphine treatment depended on adenosine transport and was likely caused by a change in the net rate of adenosine transport during exogenous adenosine application.

**DISCUSSION**

The overall goal of this study was to determine whether chronic morphine exposure altered the ability of adenosine to modulate synaptic activity in the nucleus accumbens. The major observation was that chronic morphine increased the sensitivity of excitatory synapses in the NAcc to exogenously applied adenosine. The results demonstrate that the increased sensitivity to adenosine was a specific effect of chronic exposure to morphine, in that implantation of placebo pellets under identical anesthesia conditions did not alter adenosine sensitivity. This effect was not due to a change in the number or affinity of adenosine receptors, or any downstream components of the adenosine signaling pathway, because sensitivity to the adenosine agonist N6-CPA, which is not a substrate for uptake and metabolism, was unchanged. Finally, the shift in adenosine sensitivity was eliminated when nucleoside transporters were...
blocked with NBTI and dipyridamole. This suggests that the shift in sensitivity was due to a decrease in the rate of adenosine transport.

**Effects of chronic morphine on adenosine transport**

The effects of changes in adenosine transport on the adenosine dose-response curve are somewhat complex. To reach the synapses, exogenously applied adenosine must diffuse deep into the slice through tissue rich in nucleoside transporters. Most of the applied adenosine was probably transported into cells and metabolized, with only a small fraction (in the high nM range) making it to the receptors (Brundege et al. 1997; Dunwiddie and Diao 1994). Hence, exogenous adenosine is only active at concentrations high enough to saturate the nucleoside transporters, and the position (though not the slope or maximal inhibition) of the adenosine dose-response curve is largely determined by the saturation point of the transporters (Dunwiddie and Diao 1994). The parallel shift in the adenosine dose-response curve observed would be expected from a decrease in the maximal rate at which cells take up adenosine. This could be due to a change in the transporters themselves, a decrease in the number of transporters, or a decrease in the maximal rate of intracellular adenosine metabolism. A decrease in the affinity of adenosine for the nucleoside transporters is a less probable explanation, as this would be expected to increase sensitivity at low concentrations of adenosine, but would have relatively little impact at higher concentrations when the transporters in much of the slice are at saturating levels.

In addition to a change in nucleoside transporter activity or number, the present results can also be explained by a change in the intracellular metabolism of adenosine. This is because adenosine transport and adenosine metabolism are closely related and interdependent on one another. Adenosine uptake occurs through facilitated diffusion nucleoside transporters that can only move adenosine down its concentration gradient (Bender et al. 1980, 1981; Gu et al. 1995). Intracellular metabolism of adenosine, primarily through the actions of adenosine kinase (Zimmermann et al. 1979), keeps the intracellular concentration low and maintains the concentration gradient necessary for continued uptake. Any interruption in intracellular metabolism could potentially decrease the transport rate and thus appear identical to a direct change in transporter activity. Hence both of these possibilities increase adenosine sensitivity through a net change in adenosine transport.

One of the most intriguing and perplexing aspects of these findings is their contrast to the results of Manzoni et al. (1998) and Kaplan and Leite-Morris (1997). Manzoni et al. examined the effects of chronic cocaine administration on excitatory synaptic transmission in NAcc slices and found that adenosine sensitivity was decreased. The decrease in sensitivity was due to an increase in nucleoside transporter activity, the opposite effect as observed in the present study. It is possible that this difference can be explained by the different drugs used in these two studies (cocaine vs. morphine). If so, it suggests that changes in the NAcc adenosine system are not associated with drug withdrawal in general, but may contribute to the unique symptoms associated with withdrawal from a particular class of drug.

The results of Kaplan and Leite-Morris (1997) also suggest an increase in adenosine transport. They measured NBTI binding to nucleoside transporters in mice and found that chronic morphine treatment increased the total number of transporter binding sites in the striatum and hypothalamus. However, an increase in NBTI binding was found in only two of six brain regions, and the NAcc was not examined. It is also important to note that NBTI binding only detects one subtype of nucleoside transporter. The NBTI insensitive nucleoside transporters are blocked by dipyridamole, and this was the rationale for using a combination of NBTI and dipyridamole in the present study (Hammond and Clanachan 1985; Shank and Baldy 1990). It is therefore possible that chronic morphine treatment produced a decrease in dipyridamole-sensitive transport that would not have been detected in the Kaplan and Leite-Morris study. The NBTI binding study would also not have detected a change in intracellular adenosine metabolism.

**Effects of chronic morphine on endogenous adenosine**

Most areas of the brain have a low, tonic level of extracellular adenosine present under normal conditions (Clark and Dar 1988; Dunwiddie and Diao 1994; Dunwiddie and Hoffer 1980; Snyder et al. 1981; Wojcik and Neff 1982). This adenosine may come from a variety of sources, but it is likely that the actual concentration of extracellular adenosine is determined by a balance between the rate of release/production and the rate of uptake (Brundege and Dunwiddie 1997). Two results in the present study suggest that the production and release of endogenous adenosine were not altered after chronic morphine treatment. First, there was no change in the excitation produced by the A1 adenosine receptor antagonist DPCPX, suggesting that the basal concentration of adenosine in the extracellular space was unchanged after morphine treatment. Second, the inhibition produced by the adenosine transport blockers NBTI and dipyridamole was similar in both groups of animals. Since this inhibition was due to the buildup of endogenous adenosine, it is unlikely that an identical level of inhibition would result if the production rates of adenosine were different between the two groups of animals. However, it is important to note that these experiments did not evaluate the possibility of a change in the production of adenosine from the extracellular metabolism of cAMP. Because this source of adenosine formation was blocked by the phosphodiesterase inhibitor RO20-1724 during the application of nucleoside transporter blockers, a morphine-induced change in the production of adenosine from cAMP would not have been detected. If such a change did occur, it would have to be relatively small or counterbalanced by the change in adenosine uptake to not have been detected by the application of DPCPX alone, which was applied in the absence of RO20-1724.

One of the more counterintuitive aspects of the present results is the observation that adenosine transport was decreased, but endogenous adenosine levels did not increase. However, this would be expected if chronic morphine decreased the maximal rate of adenosine transport. Under basal conditions adenosine levels are low and the transporters are far from saturated. The steady-state concentration of adenosine may simply reflect the time it takes for adenosine to diffuse from the sites of production/release to the transporters. A small change in transport activity would therefore have little or no effect on endogenous adenosine levels because the transporters...
have an excess capacity to take up adenosine as fast as it reaches them. As mentioned above, exogenous adenosine is not active until transporter-saturating concentrations are reached, so dose-response curves, unlike the low tonic concentration of adenosine present at the synapse, are a sensitive measure of the concentration of adenosine needed to saturate the transporters. A decrease in the maximal transport rate should cause a parallel shift in the dose-response curve while having no effect on the small (nM) level of endogenous adenosine.

The lack of an effect on endogenous adenosine levels is particularly interesting in light of previous evidence demonstrating an increase in endogenous adenosine levels after chronic morphine treatment. Under nearly identical animal treatment and slice preparation protocols, Chieng and Williams (1998) found that chronic morphine treatment significantly increased adenosine-mediated tonic inhibition at GABAergic synapses onto NAcc cholinergic interneurons (as opposed to the glutamatergic synapses onto medium spiny neurons assayed in the present study). This suggests that adenosine levels may vary independently at different synapses within the NAcc. Salem and Hope (1999) found that naloxone increased the concentration of adenosine metabolites in the NAcc in opiate withdrawn rats, as measured by microdialysis in vivo, suggesting a change in endogenous adenosine levels. However, this technique may have been sensitive to a withdrawal-induced change in adenosine transport, since microdialysis can elevate endogenous adenosine levels due to mechanical disruption of tissue (Dunwiddie and Diao 1994).

Blockade of phosphodiesterase

One of the difficulties of testing adenosine sensitivity in the presence of nucleoside transport blockers is that the blockade of adenosine uptake is usually associated with a buildup of endogenous adenosine that nearly saturates adenosine receptors (Dunwiddie and Diao 1994; Manzoni et al. 1998). In the NAcc, much of this endogenous adenosine comes from the extracellular metabolism of cAMP, and the formation of this adenosine can thus be blocked by the application of the phosphodiesterase inhibitor RO20-1724 (Manzoni et al. 1998). To avoid complications associated with the excessive buildup of endogenous adenosine, all of the dose-response curves described were conducted in the presence of RO20-1724 (200 μM). Hence, all of the differences in adenosine sensitivity between control and chronic morphine-treated animals were observed under conditions of reduced extracellular phosphodiesterase activity and reduced extracellular formation of endogenous adenosine from cAMP.

Effects of chronic morphine on other systems

The present study examined the effects of chronic morphine treatment on the ability of adenosine to inhibit AMPA receptor-mediated EPSCs. This particular synaptic response was chosen because of the following: 1) AMPA receptor-mediated EPSCs are one of the major determinants of when MSNs fire and thus help regulate the output of the NAcc, and 2) AMPA receptor-mediated EPSCs are very sensitive to the effects of adenosine and thus offered an excellent assay with which to look for changes in adenosine signaling. It should be noted that chronic morphine has been found to mediate a number of synaptic changes in the NAcc, including an increase in GABAergic transmission due to an increase in adenylyl cyclase activity (Chieng and Williams 1998), a decrease in NMDA receptor-mediated transmission (Martin et al. 1999a), and an increase in presynaptic inhibition of glutamate release by metabotropic glutamate receptors (Martin et al. 1999b). Thus numerous synaptic responses have been found to be altered by chronic morphine treatment when those responses were studied in isolation. The sum alterations in NAcc synaptic physiology depend on the complex interaction of all of these changes. Another complicating factor in these effects is the role of A2a adenosine receptors. These receptors are concentrated in the striatum and nucleus accumbens and may further regulate synaptic activity in these brain regions, including a strong interaction with dopamine signaling (Ribeiro 1999; Svenningsson et al. 1999). The change in adenosine transport observed in this study is likely to alter adenosine activity at A2a as well as A1 receptors, and this will undoubtedly influence information processing in the nucleus accumbens. It is clear that we are still at the stage of identifying isolated biochemical and physiological effects of drugs of abuse and that understanding how these effects summarize into higher level physiological and behavioral responses will require a far more detailed understanding of the workings of these brain areas.

Conclusion

In conclusion, the present study found that chronic morphine treatment increased the sensitivity of excitatory synapses on nucleus accumbens medium spiny neurons to the inhibitory effects of exogenous adenosine due to an apparent decrease in adenosine transport. This change in the adenosine system occurred in the absence of any change in endogenous adenosine levels or in A1 adenosine receptors. These findings further characterize the manner in which the adenosine system is altered by chronic drug use and may contribute to the development of new pharmacotherapies for drug addiction and withdrawal based on the adenosine signaling system.

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