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Effects of an Adenosine A_{2A} Receptor Blockade in the Nucleus Accumbens on Locomotion, Feeding, and Prepulse Inhibition in Rats

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ABSTRACT The nucleus accumbens (NAc) subserves behaviors governed by natural rewards, i.e., feeding or exploration, and has been implicated in control of prepulse inhibition (PPI), a measure of sensorimotor gating. The present study sought to determine whether a tonic stimulation of adenosine A_{2A} receptors in the rat NAc is involved in control of spontaneous locomotor activity, feeding behavior, and PPI. To this end, bilateral microinfusions of a prodrug (MSX-3) (3 μg and 5 μg in 1 μl per side) of the selective A_{2A} receptor antagonist MSX-2 or vehicle (1 μl per side) were administered into the NAc. Results show that blockade of intra-NAc adenosine A_{2A} receptors by a high (5 μg), but not by a low (3 μg), dose of MSX-3 increased locomotor activity in an open field, reduced food intake, and delayed intake onset in food-deprived rats examined in a test cage with standard laboratory chow. Furthermore, PPI was significantly disrupted after intra-NAc infusion of 5 μg, but not 3 μg, MSX-3. These findings suggest that locomotor activity as well as intact PPI and feeding behavior rely on tonic activation of intra-NAc A_{2A} receptors. The data add further support to the view that adenosine is a tonically active modulator of striatal function through actions on A_{2A} receptors. **Synapse 49: 279–286, 2003.**

INTRODUCTION

The nucleus accumbens (NAc), a subregion of the ventral striatum, is thought to play a critical role in the selection and execution of adaptive behaviors (Swanson et al., 1997; Kelley, 1999). In particular, the NAc is thought to subserve behaviors governed by natural rewards, i.e., feeding, drinking, sexual behavior, exploration, and instrumental learning (Robbins and Everitt, 1996). Furthermore, the NAc has been implicated in control of prepulse inhibition (PPI), an index of sensorimotor gating measured by the reduction in startle reflex that occurs when a startling stimulus is preceded by a weak prepulse (Koch, 1999). There is consistent evidence that meso-accumbal dopamine is involved in control of locomotion (Phillips et al., 1995; Turgeon et al., 1996; Swanson et al., 1997; Gong et al., 1999; Parkinson et al., 1999), feeding (Evans and Vaccarino, 1986; Bakshi and Kelley, 1991; Sills et al., 1993; Swanson et al., 1997), and PPI (Swerdlow et al., 1990a,b; Wan and Swerdlow, 1993). In addition, a considerable amount of data shows that the neuromodulator adenosine plays a role opposite to dopamine in the NAc in the control of behavior. Accordingly, dopamine antagonists and adenosine agonists produce similar effects in a number of behavioral tests (Ferre, 1997), e.g., on spontaneous motor activity (Hauber and Munkle, 1997). Adenosine acts on distinct cell-surface receptors coupled to G-proteins, which are termed A_1, A_{2A}, A_{2B}, and A_3 receptors (Fredholm et al., 1994). In the NAc, A_{2A} receptors are expressed with a high density (Ongini and Fredholm, 1996; Rosin et al., 1998) and play a critical role in behavioral control (Ferre, 1997).

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Most information on behavioral effects mediated by A_{2A} receptors in the NAc rely on studies with intracranial infusion of selective agonists. Thus, stimulation of A_{2A} receptors in the NAc inhibits locomotor activity (Barraco et al., 1994; Turgeon et al., 1996; Hauber and Munkle, 1997) and reversed the reduced PPI induced by systemic apomorphine (Hauber and Koch, 1997). The role of intra-NAc A_{2A} receptors in feeding behavior has not been investigated thus far.

The present study sought to characterize the role of intra-NAc A_{2A} receptors on locomotor activity, PPI, and feeding behavior in more detail. In particular, we wondered whether a tonic stimulation of A_{2A} receptors in the NAc is involved in control of these behaviors. This question has not been addressed in detail because water-soluble and selective A_{2A} receptor antagonists with low affinity to A_{2B} receptors have not been available. Using the novel compound MSX-3, a prodrug of the A_{2A} receptor antagonist MSX-2 (Müller et al., 1998), suitable for intracranial microinfusion (Hauber et al., 1998, 2001), we tested the effects of an intra-NAc blockade of A_{2A} receptors on spontaneous locomotion, feeding behavior, and PPI. MSX-3 is hydrolyzed by phosphatases to MSX-2, which shows a 100-fold higher affinity to A_{2A} receptors than for A_1 receptors and is almost inactive at A_{2B} and A_3 receptors (Müller et al., 1998). The initial study described here addressed the role of A_{2A} receptors in the entire NAc and was not intended to discriminate their role in the core and shell subregion of the NAc (Heimer et al., 1991). Therefore, microinfusions were given into the central NAc.

MATERIALS AND METHODS

All animal experiments were conducted according to the current version of the German Law on the Protection of Animals and approved by the proper authorities in Stuttgart, Germany.

Subjects

Male Sprague-Dawley rats (220–280 g; Charles-River, Sulzfeld, Germany, n = 63) were housed in a temperature (20 ± 2°C) and humidity (50 ± 10%) controlled animal unit. A 12-h light/dark cycle was maintained with lights on at 06:00. Rats used in Experiments 1 (n = 15) and 2 (n = 32) were housed in standard Macrolon® type IV cages (55 × 35 × 10 cm; Ebeco, Castrup-Rauxel, Germany) in groups of up to five. Standard maintenance chow (Altromin, Lage, Germany) was restricted to 15 g per animal per day. Rats used in Experiment 3 (n = 20) were housed until surgery in standard Macrolon® type IV cages (55 × 35 × 10 cm; Ebeco) in groups of up to five. After stereotaxic surgery they were individually housed in Macrolon® type III cages (37 × 21 × 30 cm, Ebeco). Standard maintenance chow (Altromin) was available ad libitum. All animals had free access to water.

Surgery

Rats were anesthetized with sodium pentobarbital (50 mg/kg i.p.) (Sigma, Deisenhofen, Germany) 15 min after pretreatment with atropine sulfate (0.5 mg/kg i.p.) (Research Biochemicals, Natick, MA). Stainless steel guide cannulae (outer diameter: 0.8 mm) aiming at the NAc (AP +3.4 mm, L ± 1.5 mm relative to bregma and 6.5 mm below dura) were bilaterally implanted according to the atlas of Pellegrino et al. (1981). Each animal had at least 5 days for postoperative recovery.

Drugs and infusion

The phosphate prodrug MSX-3 (disodium salt) of the selective A_{2A} adenosine receptor antagonist MSX-2 (3-(3-hydroxypropyl)-7-methyl-8-(m-methoxystyryl)-1-propargylxanthine (Sauer et al., 2000) was dissolved in 0.9% saline. MSX-3 at a dose of 3 μg or 5 μg in 1 μl per side was administered bilaterally into the NAc. Doses were selected according to previous (Hauber et al., 1998, 2001) and pilot studies showing optimal efficacy of MSX-3 with 5 μg in 1 μl and low efficacy with 3 μg in 1 μl after intrastriatal infusion. Infusion cannulae (outer diameter: 0.45 mm) connected via polyethylene tubing to 1 μl syringes (SGE, Victoria, Australia) were lowered to the final site of infusion. The infusions were made at a rate of 0.5 μl/min. Infusion cannulae were left in position for an additional minute to allow diffusion of the drug. Thereafter the infusion cannulae were removed and the animal was placed immediately into the testing apparatus. Controls received bilateral vehicle infusion (1 μl saline per side) into the NAc.

Experimental procedures

Three experiments were performed with separate groups of rats. Each animal received only one microinfusion.

Experiment 1

Effects of intra-NAc infusion of the adenosine A_{2A} receptor antagonist MSX-3, 0 μg (saline) (n = 9), 3 μg (n = 11), and 5 μg (n = 8), on locomotor activity was tested in an open field (69 × 69 cm) divided by lines into nine squares. The testing area was illuminated by red light and surrounded by a cubicle providing optical and acoustical isolation. Locomotor activity was monitored by a video recording system and analyzed off-line. The day before testing each animal was placed individually into the open field for habituation (10 min). On the test day, the number of line-crossings in a 30-min session was analyzed. Analysis started 6 min after an animal was introduced into the open field. The video

records were evaluated by an observer blind to the treatment.

Experiment 2

The effects of intra-NAc infusion of the A_{2A} receptor antagonist MSX-3, 0 μg (saline) (n = 9), 3 μg (n = 5), and 5 μg (n = 6) on feeding behavior were investigated. At the beginning of experimental testing animals were food-deprived for 19 h (Bakshi and Kelley, 1991). Tests were performed in Macrolon® type III cages prepared with a grid floor above a sheet of paper to collect spilled food. The day before the experiment each animal was placed individually for a 2-h habituation session into the test cage. On the test day the test cage was supplied with a defined amount (9 g) of standard lab chow (Altromin) in a food well. The amount of food ingested in 30 min was measured and corrected for spilled food. Each test was videotaped to measure the latency to the first chow contact of the animal's snout as well as latency to the first food intake, i.e., the animal takes a first bite of the food.

Experiment 3

The effects of intra-NAc administration of MSX-3, 0 μg (saline) (n = 6), 3 μg (n = 4), and 5 μg (n = 5) on PPI of the acoustic startle response (ASR) were investigated. The ASR was measured after placing the rat in a wire mesh cage (20 × 10 × 12 cm) mounted on a piezoelectric accelerometer inside a sound-attenuated chamber. The voltage output of the accelerometer caused by the rat's motion was amplified and transmitted via an A/D converter to a computer for further analysis. Acoustic stimuli were computer-generated using a function synthesizer (Hortmann, Neckarenzlingen, Germany) and delivered through a loudspeaker mounted at a distance of 40 cm from the test cage. All intensity measurements were done with a 0.5 inch condenser microphone and a measuring amplifier (Brüel & Kjaer, Copenhagen, Denmark) after bandpass filtering (frequency range: 0.25–80 kHz). The whole body ASR amplitude was calculated from the difference between the maximum voltage output of the accelerometer for 80 ms after and 80 ms before the onset of the acoustic startle stimulus. The test session included an initial startle stimulus followed by four different trials given in a pseudo-random order: 1) pulse alone (100 dB SPL broad band noise bursts, 20 ms duration); 2) prepulse (75 dB SPL 10 kHz tone pulse, 20 ms duration including 0.4 ms rise/fall times) followed by a pulse 100 ms after prepulse onset; 3) prepulse alone; and 4) no stimulus. Background noise intensity was 55 dB SPL. A total of five presentations of each trial type was given with an interstimulus interval of 30 sec. PPI was calculated as the difference between the pulse-alone trials and the prepulse trials and expressed as percent PPI [100× (mean ASR amplitude on pulse alone trials–mean ASR amplitude on prepulse trials/mean ASR amplitude on pulse alone trials)]. The responses to the single pulse at the beginning of the test session were discarded.

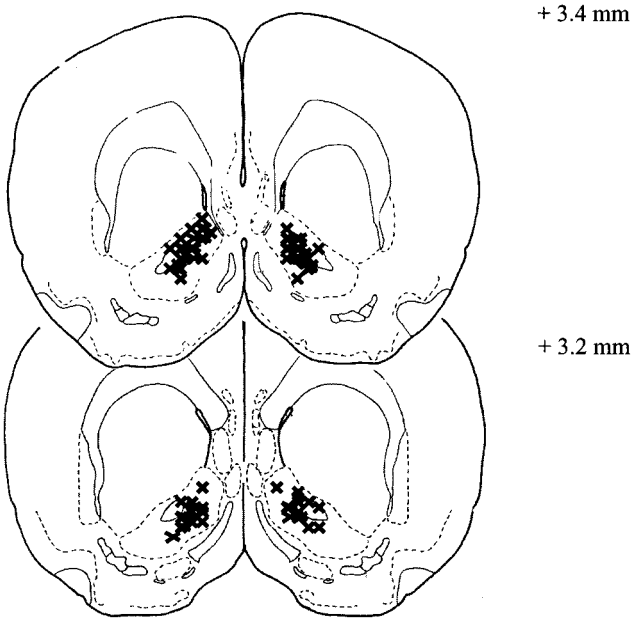

Fig. 1. Location of injection sites in the NAc. The schematics depict the location of injection cannulae tips in the NAc for all rats used for data analysis. Plates are adaptations from the atlas of Pellegrino et al. (1981). Numbers beside each plate correspond to millimeters anterior to bregma.

Histological analysis

After completion of testing animals were killed by an overdose of pentobarbital (150 mg/kg). The brains were removed and placed in 10% formalin for 2.5 h and immersed in 30% (w/v) sucrose for at least 2 days. Brains were frozen and cryosections through the injection site were done with a cryostat (Reichert and Jung, Heidelberg, Germany). The location of the infusion side was verified in frontal sections (60 μm) stained by cresyl violet (Fig. 1).

Data analysis

Results are expressed as means ± standard error of the mean (SEM). Data were tested for normality using the Kolmogorov-Smirnov test with Lilliefors' correction. Normally distributed data were analyzed using a parametric one-way analysis of variance (ANOVA) followed by a multiple comparison procedure (Tukey-Test). Data not normally distributed were analyzed using a Kruskal-Wallis ANOVA on ranks followed by a multiple comparison procedure after Dunn's method for unequal sample sizes, if appropriate. The alpha level of statistical significance was set at $P < 0.05$. Statistical analyses were carried out using the Sigma-

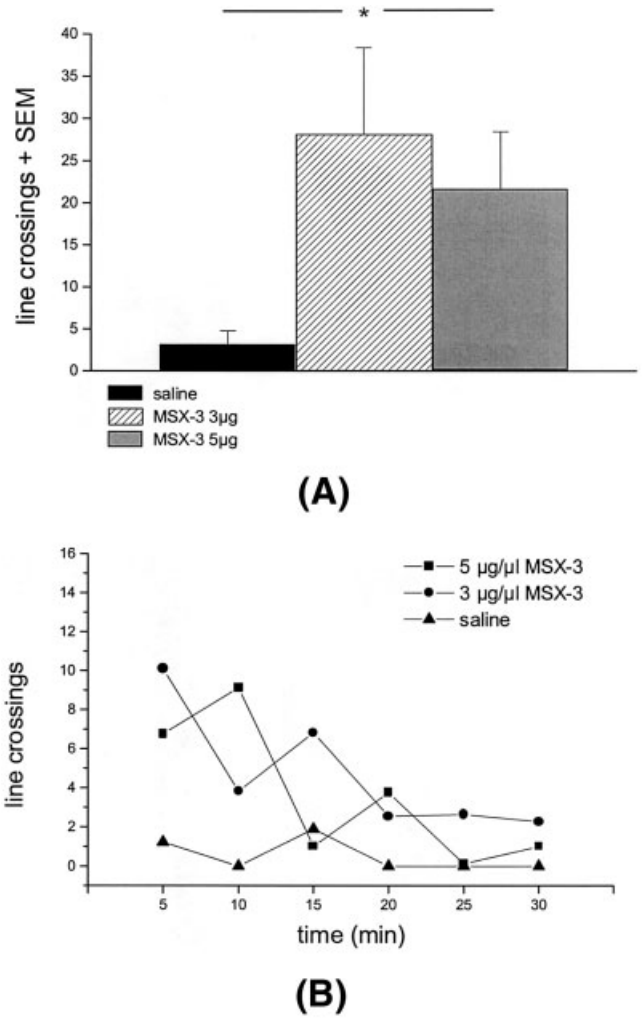

Fig. 2. Effects of intra-NAc administration of 0 (saline) (n = 9), 3 (n = 11), or 5 µg (n = 8) MSX-3 on locomotion in an open-field determined by the number of line-crossings in 30-min test session. **A:** Number of line crossings within 30 min. Values are means ± SEM, $*P < 0.05$, significant difference from vehicle (Kruskal-Wallis ANOVA followed by Dunn's post-hoc test). **B:** Number of line crossings in 5-min intervals. Values are means of treatment groups.

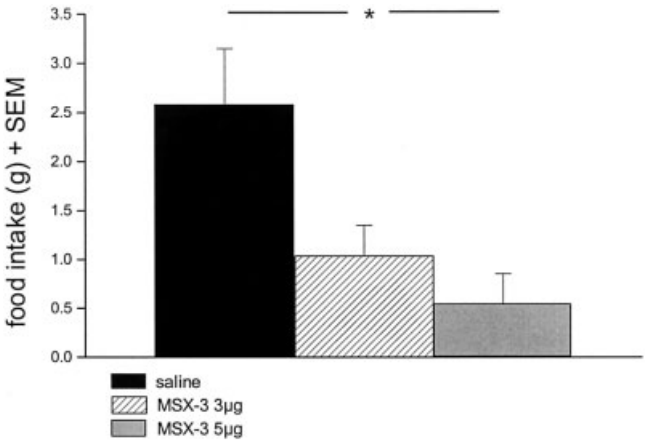

Fig. 3. Effects of intra-NAc administration infusion of 0 (saline) (n = 9), 3 (n = 5), or 5 µg (n = 6) MSX-3 on the amount of ingested food. Values are means ± SEM, $*P < 0.05$ (one-way ANOVA followed by Tukey's post-hoc test).

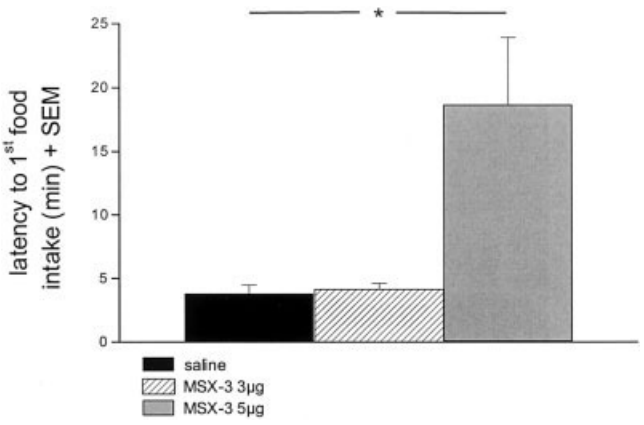

Fig. 4. Effects of intra-NAc administration of infusion of 0 (saline) (n = 9), 3 (n = 5), or 5 µg (n = 6) MSX-3 on the latency until the first intake of food by the animals. Values are means ± SEM, $*P < 0.05$, significant difference from vehicle (Kruskal-Wallis ANOVA followed by Dunn's post-hoc test).

Stat software package (v. 2.0, Jandel, Erkrath, Germany).

RESULTS

Experiment 1: Effect of intra-NAc A_{2A} receptor blockade on locomotion

Infusions of MSX-3 into the NAc resulted in an increase in locomotion (Kruskal-Wallis ANOVA: H = 7.008; d.f. = 2; N = 28; $P < 0.05$) (Fig. 2A) induced within 30 min. This effect was significant with 5 µg MSX-3 (multiple comparisons MSX-3 vs. saline; Dunn's method: difference of ranks = 9.229, Q = 2.406, $P < 0.05$), but not with 3 µg MSX-3 (difference of ranks = 7.712, Q = 2.174, $P > 0.05$). The time course of locomotor activity of all treatment groups is depicted in Figure 2B.

Experiment 2: Effects of intra-NAc A_{2A} receptor blockade on feeding behavior

Infusions of MSX-3 into the NAc significantly decreased food intake (ANOVA; $F_{(2,17)} = 4.946$; $P < 0.05$) (Fig. 3). Post-hoc analysis revealed that the amount of food consumed was significantly reduced after 5 µg MSX-3 (multiple pair-wise comparisons; Tukey test: MSX-3 vs. saline: difference of means = 2.035; q = 4.20; $P < 0.05$), but not after 3 µg MSX-3 (Tukey test: MSX-3 vs. saline: difference of means = 1.510; q = 2.944; $P > 0.05$).

The latency to the first food ingestion significantly increased after infusion of 5 µg MSX-3 (Kruskal-Wallis ANOVA; H = 7,680; d.f. = 2; $P < 0.05$) (Fig. 4) (multiple pair-wise comparisons; Dunn's method: MSX-3 vs. saline: difference of ranks = 8.444; Q = 2.712; $P < 0.05$), but not of 3 µg (Dunn's method MSX-3 vs. saline:

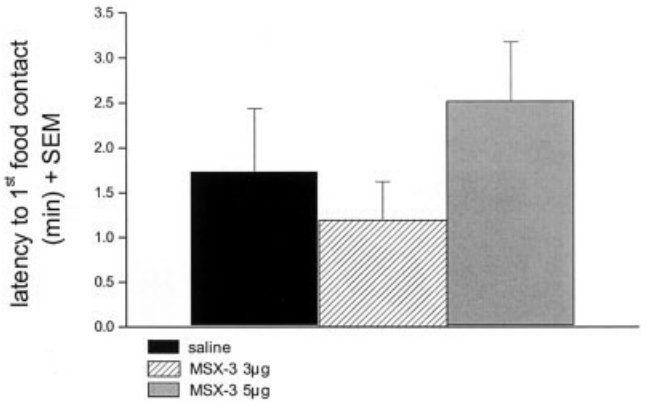

Fig. 5. Effects of intra-NAc administration of infusion of 0 (saline) (n = 9), 3 (n = 5), or 5 μg (n = 6) MSX-3 on the latency until the first snout contact to the presented food pellets. Values are means ± SEM.

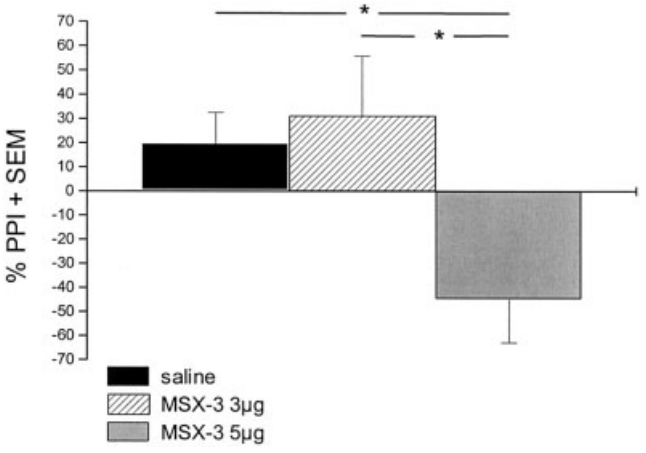

Fig. 6. Effects of intra-NAc administration of infusion of 0 (saline) (n = 6), 3 (n = 4), or 5 μg (n = 5) MSX-3 on PPI of the ASR. Values are means ± SEM, *$P < 0.05$, significant difference from vehicle and 3 μg MSX-3 (one-way ANOVA followed by Tukey's post-hoc test).

difference of ranks = 1.644; Q = 0.499; $P > 0.05$). In contrast, the latency to the first snout contact with food was not altered by infusion of MSX-3 into the NAc (ANOVA; $F_{(2,17)} = 0.817$; $P > 0.05$) (Fig. 5).

Experiment 3: Effects of intra-NAc A_{2A} receptor blockade on PPI

As shown in Figure 6, MSX-3 infusion into the NAc affected the PPI (ANOVA; $F_{(2,12)} = 5.294$; $P < 0.05$). Post-hoc analysis (Tukey test; multiple pair-wise comparisons) revealed that PPI was significantly reduced after 5 μg MSX-3 (MSX-3 vs. saline: difference of means = 64.737; q = 3.844 $P < 0.05$; MSX-3 5 μg vs. MSX-3 3μg: difference of means = 76.401; q = 4.095; $P < 0.05$), while 3 μg MSX-3 had no effect (MSX-3 vs. saline: difference of means = 11.664; q = 0.650; $P > 0.05$). The mean ASR amplitude was not significantly altered by MSX-3 in either dose (Table I).

TABLE I. Effects of MSX-3 on startle amplitude

	Mean ASR amplitude ± SEM	
Treatment	Pulse alone	Prepulse plus pulse
MSX-3 0 μg (vehicle)	161.27 ± 37.03	146.1 ± 103.64
MSX-3 3μg	89.5 ± 18.67	50.95 ± 12.35
MSX-3 5μg	127.12 ± 20.20	189 ± 48.64

DISCUSSION

Using infusions of the water-soluble phosphate prodrug MSX-3 of the selective A_{2A} adenosine receptor antagonist MSX-2, the present study provides evidence that locomotor activity as well as intact sensorimotor gating and feeding behavior relies on tonic activation of intra-NAc A_{2A} receptors.

Locomotor activity

Previous studies consistently demonstrated locomotor stimulation after systemic blockade of A_{2A} receptors in rats (Svenningsson et al., 1997b; Popoli et al., 1998; Halldner et al., 2000) and mice (Ferre et al., 2001). In addition, intra-NAc stimulation of A_{2A} receptors inhibited locomotor activity (Barraco et al., 1994; Turgeon et al., 1996; Hauber and Munkle, 1997). While these investigations strongly implicate an involvement of A_{2A} receptors in locomotor control, evidence for a role of tonic stimulation of intra-NAc A_{2A} receptors in locomotor control was lacking since selective antagonists suitable for intracerebral infusion were not available. The present data reveal that intra-NAc blockade of A_{2A} receptors by the higher dose of MSX-2 enhanced locomotion in an open field. The locomotor effects induced by the lower dose were not significant, probably due to considerable interindividual variability. Inspection of the magnitude and time course of locomotor effects revealed that MSX-2 did not elicit a massive and persistent stimulation as elicited by intra-NAc amphetamine (van den Boss et al., 1988; Essman et al., 1993). Rather, there was a moderate MSX-2-induced increase of locomotor activity which declined due to habituation and/or decreasing efficacy of the drug. In contrast, vehicle controls displayed low levels of locomotor activity during the complete observation period, probably due to pretest habituation. Moderate behavioral effects were also observed after blockade of A_{2A} receptors in the caudate-putamen of rats: infusion of higher doses of MSX-3 (9 μg) as used here did not induce stereotyped sniffing, as seen after intrastriatal infusion of dopamine agonists (Kelley and Delfs, 1994), but a modest, albeit significant, enhancement of sniffing activity (Hauber et al., 1998). Extracellular concentrations of adenosine in the NAc are presumably high enough (Nagel and Hauber, 2002) to stimulate a significant proportion of A_{2A} receptors (Daly and Fredholm, 1998). Hence, the moderate locomotor effects might be explained by a partial A_{2A} receptor blockade produced by MSX-2. Alternatively, blockade of intra-NAc A_{2A} recep-

tors might be complete, but failed to induce pronounced hyperlocomotion. In line with this latter notion, massive locomotor stimulation was observed only after a simultaneous blockade of A_{2A} and A_1 receptors (Jacobson et al., 1993). By virtue of its connectivity and histochemical profile, the NAc has been subdivided into at least two major subcomponents, core and shell (Heimer et al., 1991), which might subserve distinct behavioral functions (Kelley, 1999). Both subregions have been implicated in locomotor control as excitotoxic lesions of core or shell both produced changes in locomotor activity and open field behavior (Maldonado-Irizarry and Kelley, 1995). It is difficult to delineate whether locomotor effects measured here were brought about by the NAc core or shell (or both) as infusions were directed into the more central part of the NAc.

Feeding behavior

Blockade of intra-NAc A_{2A} receptors had dose-dependent and prominent effects on feeding behavior, i.e., food intake was decreased and onset of feeding was delayed. It is unlikely that these effects are simply due to motor inhibition, because the latency to the first food contact was unchanged after intra-NAc MSX-2 and results from experiment 1 showed that locomotor activity was enhanced by MSX-2. The shell subregion of the NAc has been suggested to be a central integrator of feeding (Kelley, 1999) as inhibition of striatal GABAergic projection neurons by muscimol or DNQX in the shell activated feeding involving disinhibition of neurons in the lateral hypothalamus (Stratford et al., 1997, 1999). Thus, one possibility is that MSX-2 might inhibit feeding behavior per se by drug actions within the shell. Alternatively, MSX-2-induced inhibition of feeding behavior might be due to other behavioral effects induced by its intra-NAc actions. Among these, an increased switching as observed after intra-NAc amphetamine is unlikely to account for the pattern of behavioral changes induced by MSX-2. In a detailed analysis of the effects of intra-NAc amphetamine on feeding, food intake was decreased but feeding onset time was unchanged (Bakshi and Kelley, 1991) and not reduced as observed here. Yet the observation that the latency to the first food contact was unchanged suggests that intra-NAc A_{2A} receptor blockade left food approach behavior intact. However, feeding onset time in Experiment 2 corresponds with the time locomotor activity started markedly to decline in Experiment 1. This tentatively suggests that by blocking the actions of adenosine on intra-NAc A_{2A} receptors, MSX-2 might stimulate locomotor activity and inhibit consummatory behavior, i.e., feeding behavior. Thus, the decrease in food intake most probably reflects behavioral competition, i.e., as long as MSX-2 induced locomotor stimulation, animals were less capable of focusing on stationary feeding behavior. Indirect support for this notion is provided by studies showing that systemic and intra-NAc administration of the selective A_{2A} receptor agonist CGS21680 inhibited locomotor activity (Barraco et al., 1994; Turgeon et al., 1996; Hauber and Munkle, 1997), while systemic administration of CGS21680 enhanced feeding (Coupar and Tran, 2002).

Prepulse inhibition

Previous studies suggest an involvement of intra-NAc A_{2A} receptors in control of PPI because infusion of the selective agonist CGS21680 counteracted reduced PPI after systemic treatment with apomorphine (Hauber and Koch, 1997). In keeping with these data, Experiment 3 demonstrates that intra-NAc blockade of A_{2A} receptors by a high, not low, dose of MSX-3 abolished PPI. The effects of MSX-2 might be brought about by actions within the core and/or shell of the NAc, as both subregions have been implicated in regulation of PPI (Kodsi and Swerdlow, 1997). The interpretation of PPI data is limited, first because, for unknown reasons, PPI in controls was low compared to other studies. However, baseline levels of PPI show strain differences and within-strain differences, depending on the animal supplier (Kinney et al., 1999; Swerdlow et al., 2000). Furthermore, Swerdlow et al. (2000) demonstrated that PPI-disruptive effects of apomorphine occurred regardless of the level of the baseline. Thus, PPI, although having low basal levels in our study, are likely to be sensitive to the effects of MSX-2. Second, the high dose of MSX-2 produced strong reduction of PPI, resulting in a negative PPI percent value. Thus, the inhibition of pulse-induced startle responding mediated by the prepulse was completely abolished and the prepulse even facilitated pulse-induced startle responding. Facilitative effects of the prepulse on pulse-induced startle responding have been observed occasionally, e.g., after NMDA infusion into the hippocampus (Klarner et al., 1998). However, the mechanism underlying this phenomenon is unknown at present. A prominent increase of vigilance known to be induced by unselective adenosine receptor antagonists such as caffeine (Nehlig et al., 1992) is one potential effect of MSX-2 which could in part explain facilitative effects of the prepulse on pulse-induced startle responding. Regardless of these limitations, the present data indicate a role of intra-NAc A_{2A} receptor in control of PPI.

Implications for the role of intra-NAc A_{2A} receptors in control of behavior

A_{2A} receptors have been detected in the NAc shell and core by recombinant monoclonal antibodies with a similar intensity of labeling in both subregions (Rosin et al., 1998). Furthermore, studies with systemic administration of A_{2A} receptor selective ligands and intra-NAc infusion of A_{2A} receptor agonists suggest that A_{2A} receptors in the NAc are involved in behavioral

control (Hauber and Koch, 1997; Svenningsson et al., 1997a; Koch and Hauber, 1998; Rimondini et al., 1998). Using a water-soluble and selective A_{2A} receptor antagonist, the present data provide evidence that locomotor activity as well as intact PPI and feeding behavior rely on tonic activation of intra-NAc A_{2A} receptors on core and/or shell neurons in the NAc. The data add further support to the general notion that adenosine is a tonically active modulator of striatal function through actions on A_{2A} receptors (Sveningsson et al., 1999).

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