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Lack of NMDA Receptor Involvement in Caffeine-Induced Locomotor Stimulation and Tolerance in Rats

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POWELL, K. R. AND S. G. HOLTZMAN. *Lack of NMDA receptor involvement in caffeine-induced locomotor stimulation and tolerance in rats.* PHARMACOL BIOCHEM BEHAV **59**(2) 433–438, 1998.—The involvement of NMDA-type glutamate receptors in caffeine's locomotor stimulant effects and the development of tolerance to these effects was examined in rats. Caffeine and the noncompetitive NMDA receptor antagonists, MK-801 and phencyclidine (PCP), were examined alone and in combination. Caffeine produced a biphasic dose–effect curve. Both MK-801 and PCP increased locomotor activity at the highest doses tested. MK-801 and PCP shifted the caffeine curve upward, but only with the highest doses that increased locomotor activity when given alone. For the tolerance experiment, osmotic pumps containing either MK-801 or nothing at all and were implanted in rats that were given either caffeinated or drug-free tap water to drink. All rats drinking caffeine showed tolerance to its locomotor stimulant effects, whereas rats drinking drug-free tap water did not. Chronic infusion of MK-801 (0.1 and 0.3 mg/kg/day) failed to block the development of tolerance to caffeine. The 0.3 mg/kg/day infusion of MK-801 appeared to slightly delay the development of tolerance to caffeine, but this effect was probably due to the locomotor stimulant effects of this infused dose of MK-801 alone. These data provide no evidence that NMDA-type glutamate receptors play a crucial role in mediating caffeine's locomotor stimulant effects or tolerance to these effects. © 1998 Elsevier Science Inc.

Caffeine NMDA MK-801 Phencyclidine Rats Locomotor activity Tolerance

CAFFEINE is the most widely consumed of all psychoactive drugs worldwide. It is recognized as a stimulant, and human subjective reports indicate that caffeine is mildly reinforcing. Although caffeine is typically consumed on a daily basis, little is known about the effects of chronic caffeine administration in humans [see (17)]. In rodents, acute administration of caffeine and other methylxanthines produces reliable and concentration-dependent locomotor stimulation. Chronic administration of caffeine results in tolerance to its locomotor stimulant effect, as well as some degree of physical dependence, reflected by a disruption in locomotor behavior often observed following cessation of drug treatment (1,12,20,21).

Caffeine is a competitive antagonist at adenosine receptors (4,36). Adenosine receptor antagonism appears to be a primary mechanism of action underlying caffeine's locomotor stimulant effects: the relative affinities of caffeine and other methylxanthines for adenosine receptors correlate with their relative potencies for stimulating locomotor activity in rodents (4,37). Caffeine's ability to increase locomotor activity, however, occurs within a limited dose range. Specifically, high doses of caffeine (>60 mg/kg) actually decrease locomotor activity despite the ability of these doses to antagonize adenosine receptors (24). Therefore, it would be reasonable to speculate that other mechanisms may come into play, especially at the higher doses.

Recent studies indicate that the dopamine system plays a substantial role in caffeine's locomotor stimulant effects and in tolerance to these effects, perhaps secondary to blockade of adenosine A2A receptors (6,7). For example, dopamine depletion with reserpine or alpha-methyl-para-tyrosine (13) and antagonism of D_1 or D_2 dopamine receptors (14) attenuate or block completely caffeine-induced stimulation of locomotor activity in rats. In addition, caffeine and other adenosine receptor antagonists potentiate, whereas adenosine receptor

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agonists attenuate locomotor activity induced by various dopamine receptor agonists (6,9). Although caffeine has no direct interactions with dopamine receptors (5,40), it does alter central dopamine levels (27,29). Furthermore, there is evidence for both pre- and postsynaptic adenosine/dopamine receptor interactions where adenosine acts to inhibit dopaminergic activity (8–11). Therefore, caffeine may stimulate motor activity by blocking adenosine receptors and removing this inhibition on dopamine neurotransmission.

It is unclear what role adenosine receptor antagonism plays in the development of tolerance to caffeine's behavioral effects. Specifically, chronic caffeine administration produces an upregulation of adenosine receptors and a decrease in the potency of caffeine (18,23); however, chronic administration of a competitive antagonist should not produce a loss of antagonist potency. In fact, caffeine maintains its potency as an antagonist of adenosine agonists in rats made tolerant to caffeine's locomotor stimulant effects (22). Finally, tolerance to caffeine is insurmountable (12,22). Theoretically, if tolerance to caffeine is due to upregulation of adenosine receptors, then tolerance should be surmountable. Together, these results suggest that caffeine's locomotor stimulant effects and tolerance to these effects involve mechanisms in addition to or downstream from adenosine receptor antagonism.

In looking for other receptor mechanisms that might underlie caffeine tolerance, we focused on NMDA glutamate receptors. Several studies have shown that NMDA-type glutamate receptors interact with dopamine neurotransmission and play an important role in modulating locomotor activity in rodents (30–34). In addition, NMDA receptors appear to mediate some types of drug-induced synaptic plasticity. For example, NMDA receptor antagonists block the development of sensitization to the locomotor stimulant effects of both cocaine and d-amphetamine (25,26,34) and tolerance to the analgesic effects of morphine (38,39).

Few studies have examined the role of NMDA receptors in mediating caffeine's locomotor stimulant effects. The NMDA receptor antagonist, dizocilpine (MK-801), administered into the nucleus accumbens, does not alter caffeine-induced locomotor stimulation in rats (34), although systemically administered caffeine enhances the locomotor stimulant effects produced by MK-801 in mice (28). In addition, stimulation of NMDA receptors blocks the locomotor stimulant effects of another methylxanthine, theophylline (16). Furthermore, the locomotor stimulant effects of caffeine and of the NMDA antagonists, MK-801 and phencyclidine (PCP), are all blocked by D_1 and D_2 receptor antagonists (3,14,19,30). Together, these reports suggest that NMDA receptors could play a role in mediating the locomotor stimulant effects of caffeine and, perhaps, the development of tolerance to these effects. Therefore, the purpose of this study was to examine the ability of systemically administered NMDA antagonists to alter the acute effects of caffeine on locomotor activity in rats and the development or expression of tolerance to caffeine's locomotor stimulant effects.

METHOD

Subjects

Male Sprague–Dawley rats (Charles River, Raleigh, NC) weighing 300–350 g at the beginning of the experiment were housed individually and maintained under a 12 L:12 D cycle in a climate controlled cabinet. Ten rats were used for the acute phase of the experiment and 48 rats were used for the chronic phase of the experiment (approx. 12 days). During the acute phase of the experiment, food and water were freely available in the home cages. During the chronic phase of the experiment, food was freely available and water or a caffeinated drinking solution was available for 10 min every 6 h for 7 days (12).

Apparatus

Locomotor activity was measured using two-channel Electronic Activity Monitors (Stoelting Co., Chicago, IL). Each rat was placed in a polycarbonate cage ($51 \times 41 \times 22$ cm) that was centered on a sensor platform inside a ventilated, sound-attentuating chamber that was illuminated with fluorescent light. Locomotor movements were measured as changes in capacitance across the surface of the sensor platform that were transformed into counts via a Locomotor Activity Counter (Stoelting Co.). Locomotor activity counts reflected gross body movements as well as finer movements such as grooming and sniffing.

Experimental Procedures

Initially, rats were habituated to the locomotor test chambers for 30 min each day for 4 days. Following habituation, locomotor testing was conducted twice weekly with at least 3 days separating each test to allow sufficient time for recovery from residual drug effects. On 2 separate days rats were given five injections of saline, 35 min apart, and locomotor activity was measured during the final 20 min of each interinjection interval to obtain baseline data under a cumulative dosing timeline. Then, on 2 separate days locomotor activity was measured following cumulative dosing with caffeine (3.0–100 mg/kg, IP) over five components. The first component followed saline administration and served as a baseline measure of locomotor activity for that day. Finally, a moderate dose of caffeine (30 mg/kg) was evaluated for its onset of action and peak effect to determine whether a 15-min pretreatment period was adequate for the cumulative caffeine dosing regimen. As described above, injections were given 35 min apart and locomotor activity was measured during the final 20 min. Immediately following each 20-min measuring period, rats were injected with the next dose of caffeine that, when added to the previous dose(s), equaled a dose one-half log unit higher than the previous cumulated dose. For example, 3.0 mg/kg followed by 7.0 mg/kg equals a cumulative dose of 10 mg/kg. Rats remained in the locomotor test chambers at all times except when removed briefly for injections.

During the acute phase of the experiment, the effects of caffeine and the NMDA receptor antagonists, MK-801 and PCP, were examined on locomotor activity using the cumulative dosing procedure, whereby up to four doses of a drug were tested in a single session. In addition, time-course evaluations were conducted with a dose each of MK-801 and PCP that stimulated locomotor activity to determine whether the duration of action of these drugs was adequate for the entire cumulative dosing regimen. When testing drug combinations, the cumulative dose–effect curve for caffeine was determined as described above; however, prior to the first component rats were injected with a single dose of either MK-801 or PCP instead of saline.

During the chronic phase of the experiment, rats were initially water deprived for 24 h to motivate them to drink the caffeinated solution. Approximately 4 h prior to reintroducing the drinking solutions, osmotic pumps were surgically implanted in the rats. Access to drinking solutions was then reinstated on a schedule of 10-min access every 6 h. Locomotor

activity was then measured in two components every other day for 12 days, the first component following saline administration and the second following a single challenge dose of caffeine (30 mg/kg). This test schedule allowed for assessment of the development of tolerance to caffeine in rats drinking the caffeinated solution without producing tolerance in control animals. On day 7, the caffeinated drinking solution was replaced with drug-free tap water and osmotic pumps were surgically removed. Water bottles were weighed daily during the chronic regimen to determine the amount of caffeine or water consumed.

Surgical Procedure

At the beginning of the chronic experiment, approximately 4 h prior to the first access to the drinking solutions, rats were lightly anesthetized with halothane and osmotic pumps (Model 2ML1, Alzet Co., Palo Alto, CA) were implanted subcutaneously through a small incision in the upper midregion of the back. Two groups of rats received empty pumps (sham pumps), two groups of rats received pumps that delivered 0.1 mg/kg/day of MK-801 for 7 days and two groups received pumps that delivered 0.3 mg/kg/day of MK-801 for 7 days (n = 8/group). On day 7, rats were lightly anaesthetized and the osmotic pumps were removed through the original incision.

Data Analysis

Locomotor activity was recorded and analyzed as total activity counts. From the acute experiment, dose–effect curves were compared for caffeine alone and caffeine/NMDA antagonist combinations using a two-factor analysis of variance (ANOVA). When a significant main effect was obtained, post hoc comparisons were made using Tukey's Multiple Comparison test. From the chronic experiment, the effects of the challenge dose of caffeine (30 mg/kg) were averaged across days 2, 4, and 6 and compared to the effects of this dose prior to the chronic caffeine regimen and on day 12 (5 days after pump removal) following the chronic caffeine regimen using the same statitstical tests described above.

Drugs

Caffeine sodium benzoate (Sigma Chemical Co., St. Louis, MO) and phencyclidine hydrochloride (National Institutes on Drug Abuse, Rockville, MD) were dissolved in 0.9% saline. MK-801 maleate (Research Biochemicals Inc., Natick, MA) was dissolved in distilled water. All drugs were administered IP in a volume of 1 ml/kg body weight and doses are expressed as the free base. The caffeinated drinking solution was made with anhydrous caffeine (Sigma Chemical Co.) dissolved in tap water in a concentration of 1 mg/ml.

RESULTS

Time-course evaluations revealed that the onset of caffeine's locomotor stimulant effects occurs within 15 min, suggesting that this pretreatment period is adequate for these evaluations (Fig. 1a). The dose of 0.3 mg/kg of MK-801 produced significant stimulation of locomotor activity by 15 min and lasted for up to 200 min for horizontal activity and 160 min for vertical activity, long enough to evaluate interactions between MK-801 and caffeine under our cumulative dosing regimen (Fig. 1b). The dose of 3.0 mg/kg of PCP, on the other-hand, had a shorter duration of action (<80 min) (Fig. 1c). The peak effect of PCP at the 20–40-min time point was significantly greater than effects during baseline and following caffeine, but only about one-third the effect of MK-801. The effects of PCP at other time points were not significantly different from baseline levels.

Caffeine (3.0–100 mg/kg) dose dependently increased locomotor activity with stimulant effects peaking at 30 mg/kg and the highest dose of caffeine (100 mg/kg) decreasing locomotor activity to baseline levels (Fig. 2a and b). The biphasic characteristic of the caffeine dose–effect curve is consistent with previous reports (12,15). When administered alone, both

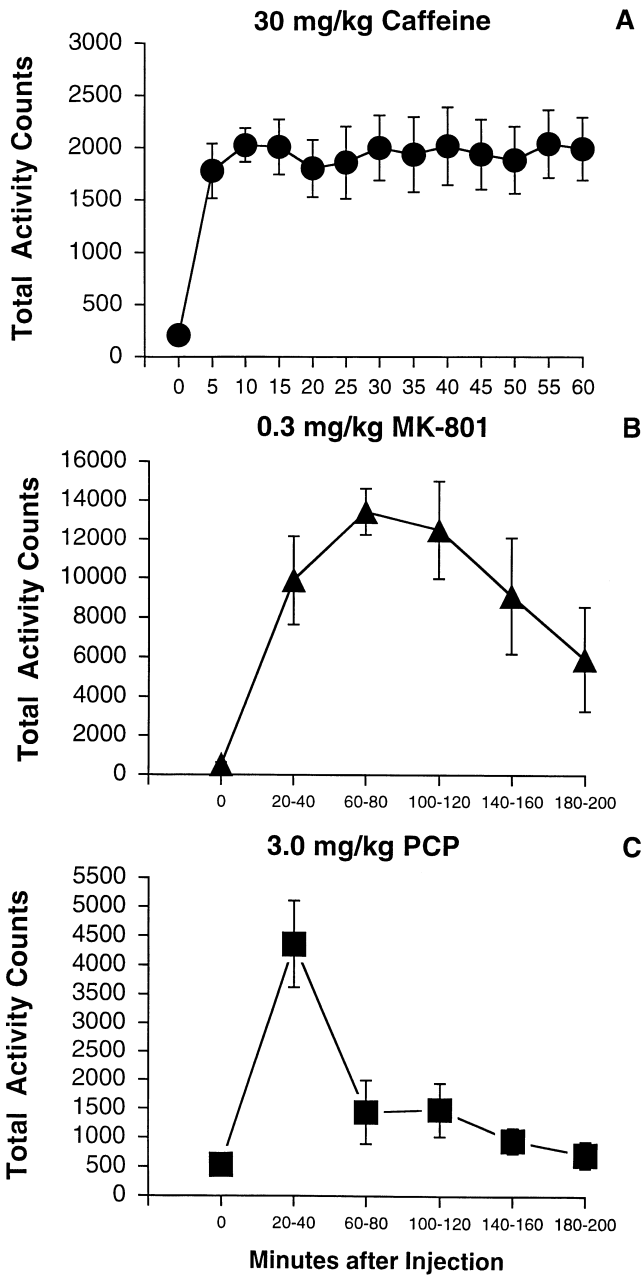

FIG. 1. (a–c) Time-course evaluations with 30 mg/kg of caffeine (a), 0.3 mg/kg of MK-801 (b), and 3.0 mg/kg of PCP (c). Ordinate: mean total activity counts + 1 SE (n = 8). Abscissa: Time in min.

noncompetitive NMDA antagonists increased significantly ($p < 0.05$) locomotor activity at the highest doses tested (0.3 mg/kg of MK-801 and 3.0 mg/kg of PCP. When combined with caffeine, the highest doses of MK-801 and PCP shifted the caffeine dose–effect curve upward compared to caffeine alone ($p < 0.05$). The interactions between caffeine and these doses of MK-801 and PCP are consistent with simple additivity of drug effects. Although PCP seemed to reverse the decrease in locomotor activity produced by 100 mg/kg of caffeine, this effect was significant only with the highest dose of PCP ($p < 0.05$), which also significantly increased locomotor activity when administered alone. Interestingly, these results were observed despite the fact that the effects of PCP were most likely dissipated by the end of the testing period (175 min).

Figure 3 illustrates the effect of the challenge dose of caffeine (30 mg/kg) during the chronic phase of the experiment in rats with sham pumps or receiving an infusion of 0.1 mg/kg/day of MK-801. Caffeine-drinking rats with sham pumps showed rapid tolerance to the locomotor stimulant effects of the challenge dose of caffeine compared to rats receiving tap water to drink. Caffeine-drinking rats infused with 0.1 mg/kg/day MK-801 did not show any disruption in the development of tolerance to caffeine. Furthermore, compared to the sham pumps, infusions of 0.1 mg/kg of MK-801 failed to alter locomotor activity in rats drinking drug-free tap water. All rats drinking drug-free tap water appeared to show a slightly heightened locomotor activity response to the challenge dose of caffeine during the chronic phase of the experiment compared to the prechronic response; however, this effect was not statistically significant.

Water-drinking rats infused with the higher dose of MK-801 (0.3 mg/kg/day) showed significantly greater stimulation of locomotor activity during the chronic phase of the experiment than did water-drinking rats with sham pumps (Fig. 4). This most likely accounts for the apparent delay in the devel-

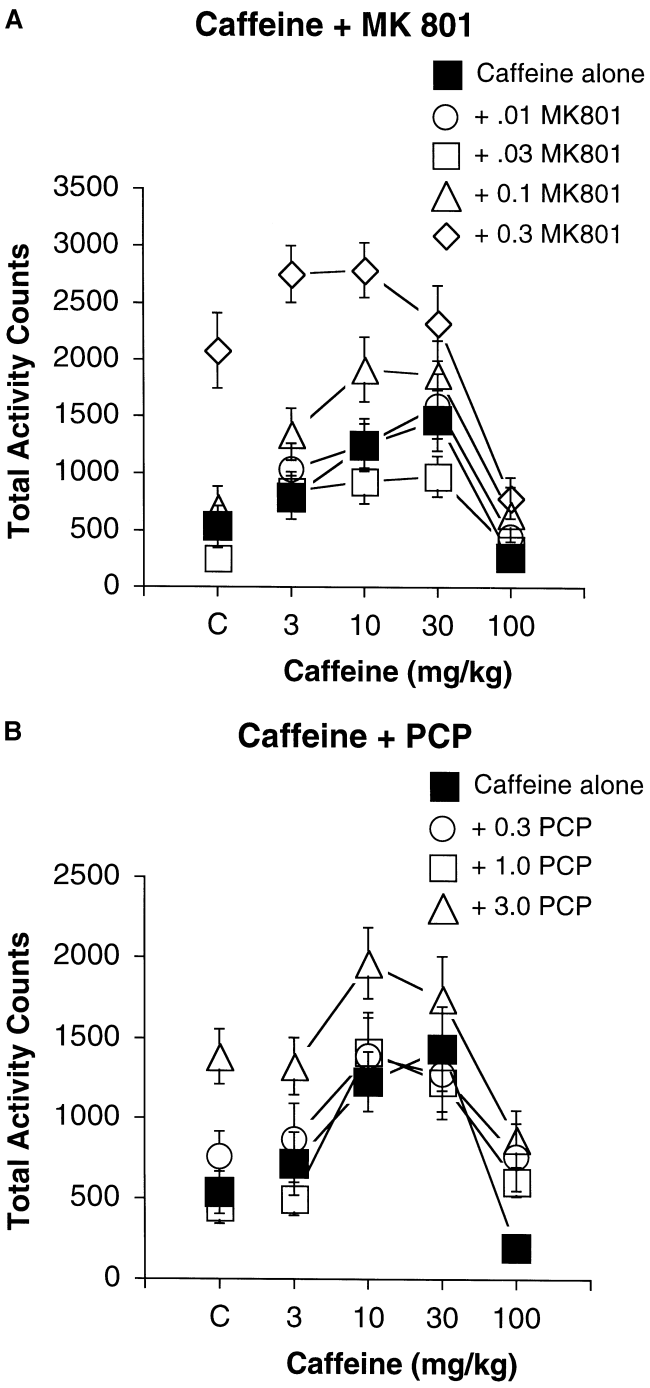

FIG. 2. (a,b) The acute locomotor stimulant effects of caffeine alone and combined with various doses of the noncompetitve NMDA antagonists, MK-801 (a) and PCP (b). Ordinate: mean total activity counts + 1 SE ($n = 8$). Abscissa: dose of caffeine in mg/kg. The points above C represent the effects on locomotor activity of administration of saline or various doses of MK-801 or PCP alone.

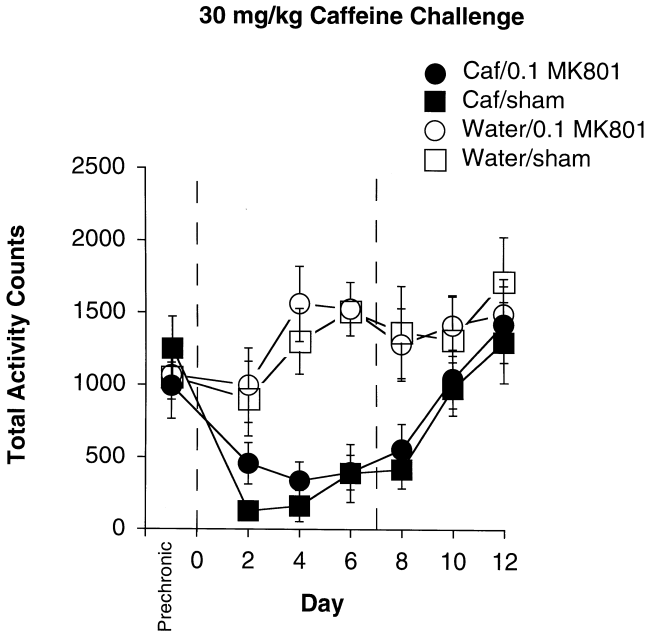

FIG. 3. The effects of the challenge dose of caffeine (30 mg/kg) before the chronic phase of the experiment and following every other day administration during and after the chronic phase of the experiment in rats receiving either caffeine or drug-free tap water to drink and implanted with either sham or 0.1 mg/kg/day MK-801 osmotic pumps. Ordinate: mean total activity counts + 1 SE ($n = 8$/group). Abscissa: day number from the start of the chronic phase of the study. The broken lines represent the start and end of the chronic phase of the study.

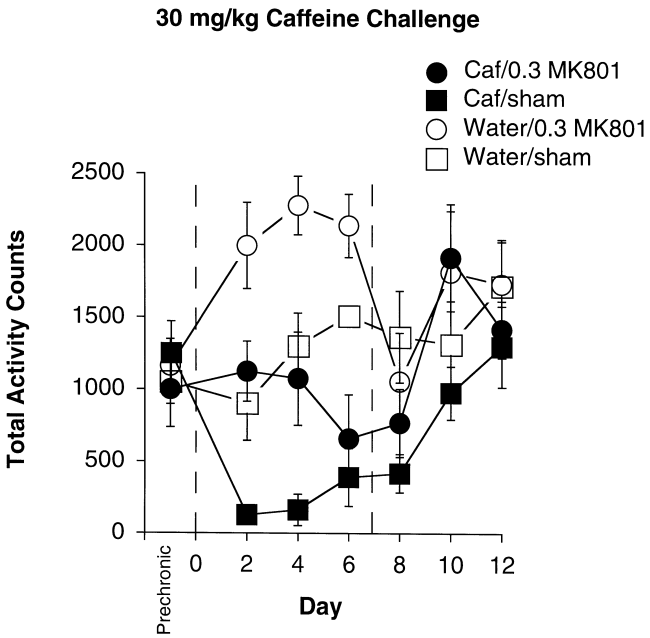

FIG. 4. The effects of the challenge dose of caffeine (30 mg/kg) before the chronic phase of the experiment and following every other day administration during and after the chronic phase of the experiment in rats receiving either caffeine or drug-free tap water to drink and implanted with either sham or 0.3 mg/kg/day MK-801 osmotic pumps. Ordinate: mean total activity counts + 1 SE (n = 8/group). Abscissa: day number from the start of the chronic phase of the study. The broken lines represent the start and end of the chronic phase of the study.

opment of tolerance in caffeine-drinking rats infused with 0.3 mg/kg/day of MK-801 compared to caffeine-drinking rats with sham pumps. Whereas caffeine-drinking rats with sham pumps began to show tolerance to caffeine by day 2, the caffeine-drinking rats receiving an infusion of 0.3 mg/kg/day of MK-801 did not show tolerance until day 6. Overall, the level of tolerance observed by day 6 did not differ between the two groups drinking caffeine.

DISCUSSION

The present results suggest that NMDA receptors probably do not play a crucial role in caffeine's locomotor stimulant effects or in the development of tolerance to these effects in rats. Neither MK-801 nor PCP altered the acute locomotor stimulant effects of caffeine. Continuous infusion of 0.3 mg/kg/day of MK-801 increased significantly locomotor activity in water-drinking rats, which probably accounts for the apparent delay in the development of tolerance to caffeine.

Under a cumulative dosing procedure, caffeine produced dose-dependent increases in locomotor activity except at the highest dose tested, which decreased locomotor activity to baseline levels or below. These results are consistent with previous reports of the effects of caffeine on locomotor activity under single dosing procedures (14,24).

As previously reported, both MK-801 and PCP increased locomotor activity at high doses (30,31). When caffeine was combined with either NMDA antagonist, the caffeine dose–effect curve was shifted upward only by the highest doses of MK-801 and PCP, indicating that the shift in the caffeine curve was probably due to the additive effects of caffeine plus MK-801 or PCP. This report is consistent with a previous study showing that MK-801 administered into the nucleus accumbens did not alter caffeine-induced locomotor stimulation in rats (34). Another report showed that the combined effect of intrastriatal dopamine and MK-801 on locomotor activity in rats was no greater than additive (2). In addition, the locomotor stimulant effects of both cocaine and methamphetamine are blocked only by doses of NMDA receptor antagonists that alter spontaneous locomotor activity when administered alone (41). Although the duration of action of PCP was shorter than the duration of the cumulative dosing regimen, nonetheless, the highest dose of PCP significantly reversed the decrease in locomotor activity produced by the highest dose of caffeine. Furthermore, the effects of PCP when combined with caffeine revealed a possible additive interaction over the entire duration of the cumulative testing period. Together, these results indicate that interactions between NMDA antagonists and dopamine agonists are due mainly to a functional additivity of drug effects rather than to an interaction with a neuronal substrate common to both drugs.

The rapid development of tolerance to caffeine is consistent with previous studies in rats made tolerant to caffeine (15,21). Doses of MK-801 that failed to alter the development of caffeine tolerance in this study are within the range of doses that prevent sensitization to other psychomotor stimulants (25,26,35,42) and tolerance to morphine (38,39). Although the largest dose of MK-801 appeared to slightly delay the development of tolerance to caffeine, the effects of this dose of MK-801 alone can account for this outcome. Furthermore, the degree of tolerance, once observed, was not different from that occurring in caffeine-drinking rats implanted with sham pumps.

In conclusion, the processes that underlie tolerance to caffeine-induced locomotor stimulation remain obscure; however, they are apparently unique from those that underlie changes in sensitivity to drugs of other pharmacological classes, notably nonxanthine psychomotor stimulants and morphine.

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