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MK-801 (Dizocilpine): Synergist and Conditioned Stimulus in Bromocriptine-Induced Psychomotor Sensitization

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ABSTRACT Intraperitoneal injections of the D_2/D_3 dopamine agonist bromocriptine (5.0 mg/kg, IP) induced locomotion that became progressively stronger on successive days of testing. The sensitized response developed twice as rapidly when the non-competitive NMDA antagonist MK-801 (0.25 mg/kg, IP) was given 30 min after bromocriptine (so that the peak effects of the two drugs overlapped). In a second group of animals, MK-801 was given 30 min prior to bromocriptine (the pretreatment regimen typical of studies where MK-801 is reported to block cocaine, amphetamine or morphine sensitization) and locomotion was monitored during the pretreatment period; in this case sensitization to the locomotor-stimulating effects of MK-801 alone (in the pretreatment period) as well as sensitization to the locomotor-stimulating effects of the drug combination (following the second injection) were observed. No sensitization to the effects of MK-801 alone (pretreatment) were seen in animals that received saline rather than bromocriptine as their second injection in this experiment. Thus MK-801 does not block but rather enhances bromocriptine sensitization; it appears to do so by a synergism with the locomotor effects of bromocriptine and by becoming a conditioned stimulus for the sensitized response. These findings confirm the earlier report that NMDA receptor activation is not critical to bromocriptine-induced sensitization, and they illustrate the importance of controls for conditioning and state-dependency phenomena in studies of drug interactions in psychomotor sensitization.

INTRODUCTION

MK-801 (dizocilpine: a drug that stimulates locomotor activity in its own right) has been argued to block the progressive sensitization or "reverse-tolerance" to the psychomotor stimulant properties of amphetamine (Karler et al., 1989, 1990; Stewart and Druhan, 1993; Wolf and Jeziorski, 1993, but see Segal, 1975), cocaine (Karler et al., 1989; Pudiak and Bozarth, 1993; Wolf and Jeziorski, 1993), morphine (Jeziorski et al., 1994; Wolf and Jeziorski, 1993), and apomorphine (Druhan et al., 1993). The evidence for such blockade comes from challenge tests in which the stimulant alone is given to animals that have had previous daily treatments with either the stimulant alone or the stimulant in combination with MK-801. In such challenge tests, animals accustomed to the combination of stimulant plus MK-801 show locomotion that is typical of animals that are naive to the stimulant, whereas animals accustomed to the stimulant alone show a sensitized locomotor response.

However, in a study of the effects of MK-801 pretreatment on bromocriptine sensitization—where we also failed to see evidence of a sensitized response on "challenge" day—we (Carlezon et al., 1995) found that MK-801 did not block the day-to-day increases in bromocriptine-induced locomotion during the ten treatment days in which the animals received the combination of the two drugs. Similar observations have been reported for amphetamine (Segal et al., 1995). Not only were there progressive daily increases in bromocriptine-induced locomotion of MK-801-pretreated animals; the rate of sensitization in animals receiving the drug combination was identical to that in animals receiving bromocriptine alone. In agreement with what was seen by others with other stimulants, the sensitized response was not apparent when the animals accustomed to the drug combination were tested in the absence of MK-801 (with bro-

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mocriptine alone). There was also no evidence of a sensitized response when animals previously sensitized to bromocriptine alone were tested in the presence of MK-801. This raised the possibility that the presence or absence of MK-801 during testing was important only insomuch as it was a component of the same drug stimulus as was present during the sensitizing experience (the importance of drug-associated stimuli for sensitization to the locomotor-stimulating action of bromocriptine is well documented: Hoffman and Wise, 1992).

One concern about our study with the combination of MK-801 and bromocriptine arises from the fact that the locomotor-stimulating effects of bromocriptine outlast those of MK-801. This raises the possibility that bromocriptine sensitization survived MK-801 challenge in our study simply because the blockade of NMDA channels by MK-801 did not last the full duration of bromocriptine's locomotor-stimulating effect. To explore this possibility we reversed the order of treatment in the present study, administering the longer-acting bromocriptine 30 min prior to MK-801; if the effects of MK-801 were antagonistic to the development of bromocriptine sensitization, the antagonism should have been more evident when the peak effects of the drugs coincided under this treatment regimen. Instead, we found that MK-801 clearly augmented bromocriptine sensitization in this case. This caused us to examine more closely the case where MK-801 is administered first, giving the drug 30 min prior to bromocriptine and measuring locomotion prior to as well as after the bromocriptine injection. This comparison revealed that MK-801 alone can induce a conditioned sensitization; it did so when it regularly preceded bromocriptine treatment but not when it regularly preceded saline treatment.

MATERIALS AND METHODS

Animals

Sixty-four male Long-Evans rats (Charles River, St. Constant, Quebec, Canada) were used; the animals weighted 300–325 g at the beginning of testing. They were individually housed in hanging wire mesh cages and were maintained on a 12-h light (0800–2000 h), 12-h dark cycle, with free access to food and water except during activity testing.

Apparatus

Locomotion was quantified in 20 × 40 × 24 cm activity chambers. Each chamber was constructed of wood (rear and two side walls), and had a wire screen ceiling, a floor with stainless steel rods spaced 1 cm apart, and a hinged clear plastic front door. Red light beams and photocells divided the length of the box into three sections; the number of photobeam interruptions made by each animal was recorded at 1 min intervals. White noise (75 dB) masked extraneous sounds during testing.

Drugs and solutions

Bromocriptine mesylate (a gift of Sandoz, Dorval, Quebec, Canada) was suspended in a vehicle of 6% Mulgofen EL-719 (Rhone-Poulenc, Mississauga, Ontario, Canada), 12% ethanol (95%), and 82% physiological (0.9%) saline. MK-801 (Research Biochemicals, Inc., Natick, MA) was dissolved in physiological saline. Drug doses are expressed in terms of the salts.

Procedure

The animals were tested in the light phase of their day-night cycle. Two experiments were carried out; in the first bromocriptine was given prior to MK-801; in the second MK-801 was given prior to bromocriptine. In each experiment, testing occurred in two phases: a sensitization phase in which repeated treatment was given daily (5 days per week) for 2 weeks, and a testing phase in which the treatment conditions were altered. In Experiment 1, the primary group of animals received bromocriptine followed by MK-801. Testing began only after both drugs had been administered. In Experiment 2, the primary group of animals received MK-801 followed by bromocriptine; in this case locomotor testing began immediately after administration of the first drug and continued after administration of the second. In each experiment there were several comparison groups.

Experiment 1 involved 32 animals, divided into four groups of 8, that were transported daily (5 days per week), to a test room where drug injections were given and locomotor testing was conducted. Two groups were first given bromocriptine (5.0 mg/kg IP), and two were first given the bromocriptine vehicle; 30 min later, one of the bromocriptine pretreated groups and one of the vehicle pretreated groups was administered MK-801 (0.25 mg/kg, IP), while each of the remaining groups was given IP injections of the MK-801 vehicle (physiological saline). Following the second injection, each animal was placed in an activity chamber where locomotion was measured in darkness for the next 180 min. This procedure was repeated daily, 5 days a week, for a total of 10 treatment days.

Three days after the last treatment injection, on Test Day 1, all animals were tested under the bromocriptine-saline treatment. On this day, each animal was transported to the locomotor testing room and given bromocriptine (5.0 mg/kg, IP) followed 30 min later by saline; locomotion was then quantified in darkness for 180 min. The following day, Test Day 2, all animals were tested under the vehicle-MK-801 condition; each animal received pretreatment with the bromocriptine vehicle followed 30 min later by MK-801 (0.25 mg/kg, IP), and was then tested in the activity chambers in darkness for 180 min.

Experiment 2 involved another 32 animals, also divided into four groups of 8, that were transported daily (5 days per week) to the test room where drug injections

were given and locomotor testing was conducted. These animals were tested for locomotor activity in the 30 min period between the first and second injections as well as for 180 min following the second injection. Immediately before the first (30 min) test, two groups were given MK-801 (0.25 mg/kg IP) and two groups were given saline; all animals were then tested in the activity chambers for 30 min. Then, one of the MK-801 pretreated groups and one of the vehicle pretreated groups were administered bromocriptine (5.0 mg/kg, IP), while each of the remaining groups was given IP injections of the bromocriptine vehicle. Each animal was then replaced in its activity chamber, and locomotion was measured for 180 min in darkness. This procedure was repeated daily, 5 days a week, for a total of 10 treatment days.

Three days after the last day of the sensitization phase, on Test Day 1, all of the animals were tested in the saline-bromocriptine condition. On this day, each animal was transported to the locomotor testing room, given saline, placed in an activity chamber, and tested for 30 min. Then each animal received bromocriptine (5.0 mg/kg, IP) and was replaced in its activity chamber and tested in darkness for an additional 180 min. On the next day, Test Day 2, all of the animals were tested in the MK-801-vehicle condition. Each animal was transported to the locomotor testing room, given pretreatment with MK-801 and tested for 30 min; then each animal received an injection of the bromocriptine vehicle and was tested for an additional 180 min in darkness.

Statistical analysis

For Experiment 1, differences in locomotor activity among the first 10 days of the experiment were evaluated using a 2 × 2 × 10 (Pretreatment × Treatment × Days) analysis of variance (ANOVA) with repeated measures. Within-session differences in activity on Test Day 1 and on Test Day 2 were evaluated using separate 2 × 2 ×18 [Prior Pretreatment × Prior Treatment × Time (10 min bins)] ANOVAs with repeated measures.

For Experiment 2, differences in locomotor activity across the first 10 days of the experiment were evaluated for the first (30 min) test session using a 2 × 2 × 3 [Pretreatment × Impending Treatment × Time (10 min bins)] analysis of variance (ANOVA) with repeated measures; likewise, differences within the second (180 min) test session were evaluated using a 2 × 2 × 18 [Pretreatment × Treatment × Time (10 min bins)] analysis of variance (ANOVA) with repeated measures. Within-session differences in activity on Test Day 1 and on Test Day 2 were evaluated using separate 2 × 2 × 21 [Prior Pretreatment × Prior Treatment × Time (10 min bins)] ANOVAs with repeated measures.

When an ANOVA revealed significant interactions, post hoc comparisons were made using Tukey's t-tests.

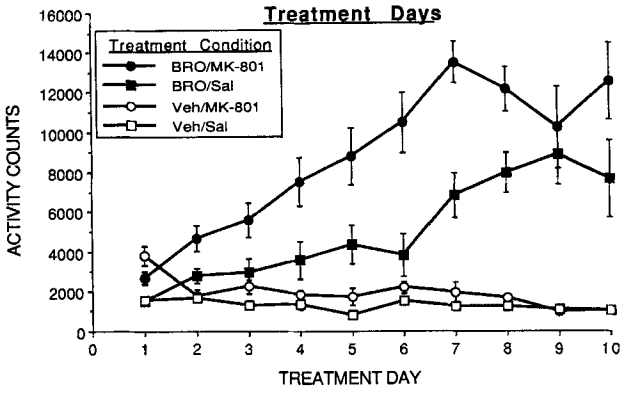

Fig. 1. Mean daily activity counts (±S.E.M.) for the treatment period of Experiment 1. Repeated treatment of bromocriptine followed by vehicle caused locomotion that became progressively stronger over days. This effect was enhanced when bromocriptine was followed by MK-801 (Pretreatment × Treatment × Days interaction: $F_{9,252} = 1.95$, $P < 0.05$). For animals that received bromocriptine followed by saline, activity was elevated (relative to respective day 1 scores) on days 5–6 ($P < 0.05$) and on days 7–10 ($P < 0.01$); likewise, for animals that received bromocriptine followed by MK-801, activity scores were elevated (relative to those of day 1) from day 3 onward ($P < 0.05$ day 3, $P < 0.01$ days 4–10). Treatment with MK-801 significantly enhanced bromocriptine locomotion on all days except days 1, 2, and 9 (day 3: $P < 0.05$; days 4–8, 10: $P < 0.01$). Activity scores of animals given vehicle plus MK-801 diminished with repeated testing (locomotion on days 9–10 was lower than on day 1: $P < 0.05$). The activity scores of animals given vehicle plus saline did not change significantly with repeated testing.

RESULTS

In the first experiment, repeated treatment with bromocriptine led to progressively increasing daily activity scores regardless of whether bromocriptine was followed by saline or by MK-801 (Fig. 1; statistical details in figure legend). However, least-squares regression lines fit to the data points for the rising portions (the first 7 days) of Figure 1 have slopes of 694 and 1686, respectively, indicating that sensitization occurred more than twice as rapidly when bromocriptine was followed by MK-801. MK-801 alone (MK-801 following the bromocriptine vehicle) caused significantly more locomotion than was seen in animals treated with saline (following bromocriptine vehicle), but the degree of elevation in the MK-801 (following vehicle) condition decreased from the first day to the tenth. The activity scores of animals repeatedly treated with vehicle (following saline) did not change significantly from the first day to the tenth day (Fig. 1).

On Test Day 1, when all animals in Experiment 1 were tested in the bromocriptine-saline condition, only the animals with a history of bromocriptine-saline testing showed significantly elevated levels of locomotion; the activity scores of animals in the other three groups were not reliably different from each other (Fig. 2). On Test Day 2, when all animals were tested in the vehicle-MK-801 condition, animals with a history of bromocriptine plus MK-801 were substantially more active than

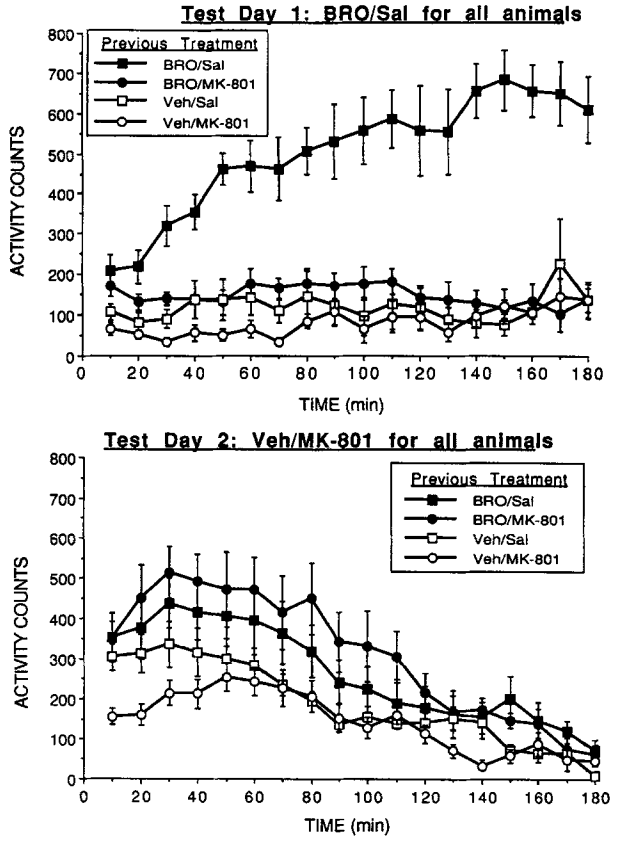

Fig. 2. Time-course of mean activity on the two test days of Experiment 1. On Test Day 1 (upper graph) all animals received bromocriptine followed by saline; on Test Day 2 (lower graph) all animals received vehicle followed by MK-801. On Test Day 1, only animals previously treated with the bromocriptine-vehicle sequence (the same testing conditions as Test Day 1) appeared sensitized [Prior Pretreatment × Prior Treatment × Time (10 min bins): $F_{17,476} = 5.40$, $P < 0.0001$]; animals previously treated with bromocriptine followed by MK-801 showed no evidence of sensitization and showed the same response as animals that were receiving bromocriptine for the first time (animals in the vehicle plus saline treatment condition). Animals accustomed to repeated MK-801 did not show a cross-sensitized response to bromocriptine; rather, they were significantly less active, at several time points within the first 70 min of testing, than animals receiving bromocriptine alone for the first time. On Test Day 2, animals accustomed to receiving bromocriptine followed by MK-801 were most active; however, statistically significant effects were not attributable to experience with MK-801 (Main effect of Treatment with MK-801: 0.0, $P = .99$, n.s.; Prior Pretreatment × Prior Treatment × Time interaction: $F_{17,476} = 1.46$, n.s.), but rather were only attributable to bromocriptine experience (Main Effect of Prior Pretreatment: $F_{1,28} = 10.9$, $P < 0.01$; Prior Treatment × Time interaction: $F_{17,476} = 2.64$, $P < 0.001$).

animals that had prior treatment with vehicle and MK-801 or than animals that were receiving MK-801 for the first time; however, a significant component of this effect was attributable to a main effect of bromocriptine, inasmuch as i) there was no statistically significant effect of treatment (MK-801), and ii) animals accustomed to receiving only bromocriptine were also more active than animals accustomed to receiving treatment with saline (thus receiving MK-801 for the first time). Animals accustomed to repeated treatment with MK-801 alone were the least active in response to MK-801 alone on Test Day 2.

In the second experiment MK-801 elevated locomotion in the 30-min period before the second injection, both in animals expecting bromocriptine and in animals expecting saline (Fig. 3). However, the animals that received vehicle as their second daily injection became progressively less responsive to the MK-801 injections, habituating to the level of the saline-vehicle animals by the tenth day of testing. Meanwhile, the animals that received MK-801 followed by bromocriptine as their second injection showed no such habituation, maintaining their elevated locomotor response to MK-801 throughout the 10-day period of testing. Each of the groups pretreated with vehicle before the initial 30 min test period showed progressively less locomotion—in this 30 min period—across days.

Progressive increases in locomotion were seen across days in the second (180 min) test period when the second injection was bromocriptine. Least-squares regression lines fit to the data points of Figure 3 have slopes of 540 and 1,024, respectively, indicating that sensitization occurred almost twice as rapidly when bromocriptine was preceded by MK-801 as when bromocriptine was preceded by saline. The activity scores of animals that received vehicle after having been pretreated 30 min earlier with MK-801 diminished with repeated testing, whereas the activity scores of animals given vehicle after having been pretreated 30 min earlier with saline were low throughout this second test period.

On Test Day 1, when all animals were tested with saline followed by bromocriptine, there were no significant differences among groups during the first 30 min test period (Fig. 4). Within the second (180 min) test period, only the animals with a history of bromocriptine following saline showed significantly elevated levels of locomotion. On Test Day 2, when all animals received MK-801 followed 30 min later by vehicle, animals with a history of bromocriptine treatment were most active, regardless of whether their usual pretreatment was MK-801 or vehicle (Fig. 4).

DISCUSSION

Sensitization of the locomotor response to drug treatment was seen in each case where MK-801 and bromocriptine were given in combination but in neither case where MK-801 was given alone. In the first experiment, where bromocriptine was given 30 min prior to MK-801, progressive sensitization of the locomotor response developed twice as rapidly as that seen with bromocriptine alone or when MK-801 was given 30 min prior to bromocriptine, as in Experiment 2 or in our previous work (Carlezon et al., 1995). Since the locomotor stimulating effects of bromocriptine typically have at least a 30 min latency, this represents a synergism of the locomotor-stimulating effects of MK-801 with those of

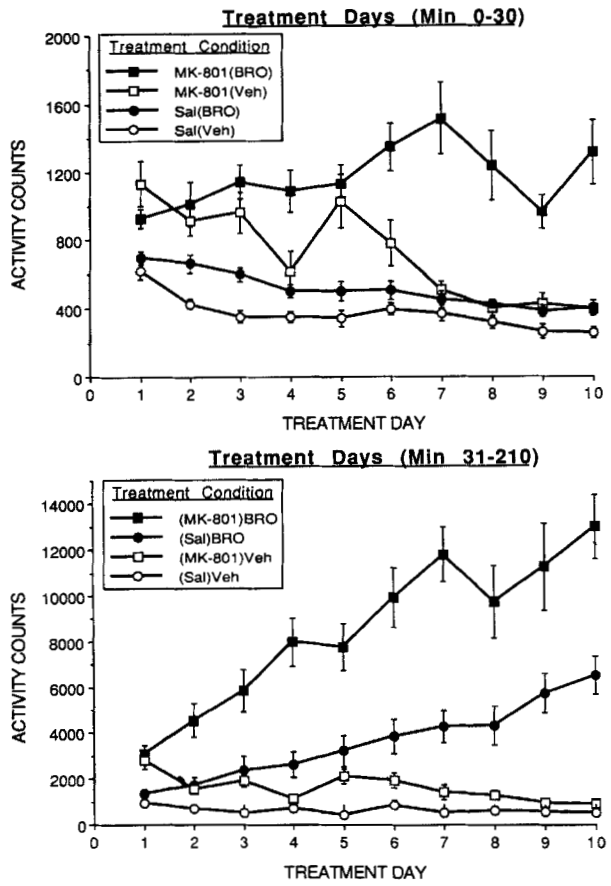

Fig. 3. Mean daily activity counts (±S.E.M.) during the treatment phase of Experiment 2. Upper graph shows locomotion during the 30 min following the first injection (MK-801 or saline); impending second injections are indicated in parentheses. The locomotor response to MK-801 during this period depended entirely upon the drug condition that normally followed the period of testing (Pretreatment × Impending Treatment × Days interaction: $F_{9,252} = 7.37$, $P < 0.0001$); habituation to the locomotor-stimulating effects of MK-801 occurred in animals accustomed to receiving saline 30 min after MK-801 (day 2, $P < 0.05$; days 4, 6–10, $P < 0.01$, relative to day 1), whereas animals accustomed to receiving bromocriptine 30 min after MK-801 (days 6–8, and 10: $P < 0.01$, relative to day 1) showed sensitization reflected in failure to habituate. Habituation to exploratory locomotion occurred in each group of animals given saline before the initial 30 min test period, although it occurred more quickly in animals accustomed to receiving vehicle (days 3–7, $P < 0.05$; days 8–10, $P < 0.01$, relative to day 1) rather than bromocriptine (days 7–8, $P < 0.05$; days 9–10, $P < 0.01$, relative to day 1) as their second injection. Lower graph shows locomotion during the 180 min following the second injection; pretreatment injections are indicated in parentheses. Repeated daily treatment with bromocriptine caused locomotion that increased progressively over days, and this effect was strongly enhanced when bromocriptine was preceded 30 min earlier by MK-801 (Pretreatment × Treatment × Days interaction: $F_{9,252} = 5.36$, $P < 0.0001$). For animals that received bromocriptine preceded by saline, activity was elevated (relative to Day 1) from Day 5 onward ($P < 0.01$), whereas for animals that received bromocriptine preceded by MK-801, the activity scores were elevated from Day 2 onward ($P < 0.05$, day 2; $P < 0.01$, days 3–10). Pretreatment with MK-801 significantly enhanced bromocriptine-induced locomotion on all days ($P < 0.01$). Activity scores of animals given vehicle preceded by MK-801 diminished with repeated testing (days 4, 7–8, $P < 0.05$; days 9–10, $P < 0.01$), whereas the activity scores of animals given vehicle plus saline did not change significantly with repeated testing.

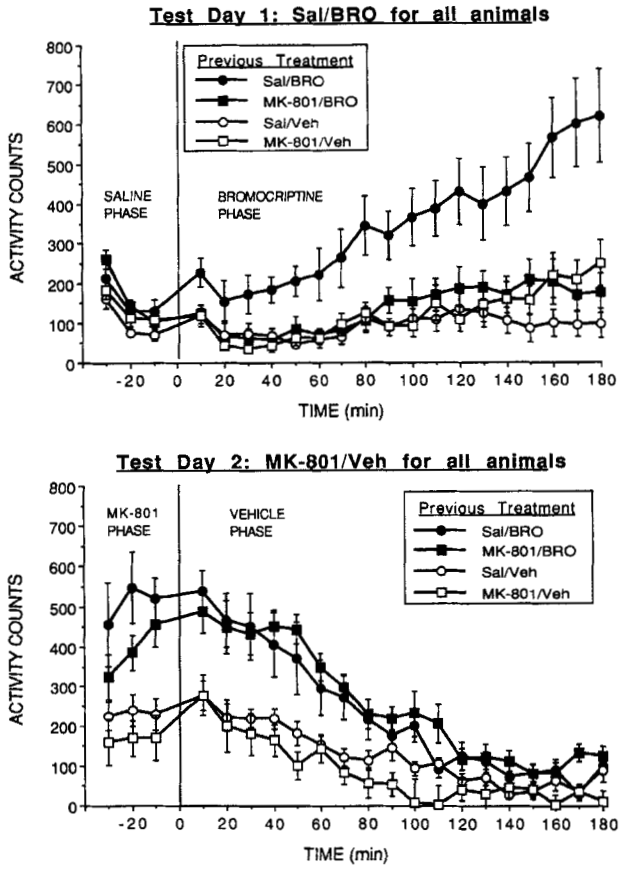

Fig. 4. Time-course of mean activity (±S.E.M.) on the two test days of Experiment 2. On Test Day 1 all animal received bromocriptine preceded by saline; on Test Day 2 all animals received vehicle preceded by MK-801. On Test Day 1 (upper graph), only animals used to the Veh/BRO condition (the same testing conditions as Test Day 1) showed evidence of a sensitized response to bromocriptine [Prior Pretreatment × Prior Treatment × Time (10 min bins): $F_{20,560} = 5.40$, $P < 0.0001$]; evidence of sensitization was not apparent during the first 30 min after saline pretreatment (during possible anticipation of bromocriptine), but only within the second phase of testing, after actual injection of bromocriptine. Animals accustomed to treatment with bromocriptine following saline were more active than animals in each of the other three groups at all time periods except from 11–20 min ($P < 0.05$, 0.01). No differences in activity scores were apparent among the three groups of animals that were receiving bromocriptine alone for the first time except in the final 20 min of testing (when the activity of the saline-vehicle animals dropped below that of the two groups accustomed to receiving MK-801). On Test Day 2 (lower graph), statistically significant differences among groups were attributable only to previous experience with bromocriptine (Main effect of Treatment: $F_{1,28} = 36.4$, $P < 0.0001$; Treatment × Time interaction: $F_{20,560} = 7.32$, $P < 0.001$); there was no significant effect of prior pretreatment with MK-801 (Main effect of Prior Pretreatment: 0.62, n.s.; Prior Pretreatment × Prior Treatment × Time interaction: $F_{20,560} = 1.36$, n.s.).

bromocriptine. This synergism was somewhat surprising, since the sensitization in response to the combination of MK-801 and bromocriptine in our earlier experiment was not merely a summation of independent sensitizations to each of the two drugs; there was no sensitization to the locomotor-stimulating effects of

MK-801 alone in our earlier study (Carlezon et al., 1995).

In Experiment 2, sensitization was found to the locomotor-stimulating effects of MK-801 alone. However, such sensitization was seen in animals regularly given bromocriptine 30 min following MK-801 injections but not in animals regularly given saline 30 min following MK-801 injections. MK-801 induced locomotion in animals receiving each treatment (bromocriptine and saline) but progressive increases were only seen from day-to-day in animals receiving the bromocriptine treatment. This sensitization would appear to be conditioned sensitization, resulting from the pairing of MK-801 intoxication with bromocriptine injections and occasioned, after the first few pairings of the two drugs, by the MK-801 drug cue in advance of the bromocriptine injection. In this perspective, MK-801 is seen as becoming a conditioned stimulus for an augmented locomotor response because of its pairing with the unconditioned psychomotor stimulant effects of bromocriptine.

These findings cast a new light on the role of NMDA receptors in sensitization phenomena, at least in the case of bromocriptine. NMDA receptor activation, almost certainly blocked with this dose of MK-801, does not appear to be necessary for robust and long lasting (Carlezon et al., 1995) neuronal changes that underlie progressive development of the sensitized locomotor response to bromocriptine. NMDA receptor blockade is necessary for the expression of bromocriptine sensitization, however, if the sensitization was established under NMDA receptor blockade. This should not be too surprising, since bromocriptine sensitization is almost entirely conditioned sensitization; prior experience under different environmental conditions does not sensitize animals to the locomotor-stimulating effects of bromocriptine (Hoffman and Wise, 1992). Moreover, MK-801 has well-known stimulus properties (Willetts and Balster, 1988) and produces a drug state in which other examples of state-dependent learning are known to occur (Jackson et al., 1992). In the case of bromocriptine sensitization it appears that the MK-801 cue (which is probably dependent upon NMDA receptor blockade) becomes associated with bromocriptine and becomes capable of eliciting the conditioned locomotion that is normally elicited by the bromocriptine-associated environment. When more than one cue predicts an event, the stronger stimulus frequently "overshadows" the weaker; in this sense MK-801 seems to be a dominant stimulus relevant to the environmental cues or injection ritual that produce weaker conditioned sensitization in experiments not involving MK-801 (Hoffman and Wise, 1992).

It is not clear whether the same will prove true of the effects of MK-801 on sensitization to the psychomotor effects of other drugs. It has been argued that NMDA receptor activation is a necessary condition for the development of sensitization to the psychomotor stimulant effects of amphetamine (Karler et al., 1990; Wolf and Jeziorski, 1993), cocaine (Wolf and Jeziorski, 1993), or morphine (Jeziorski et al., 1994; Wolf and Jeziorski, 1993), and such activation clearly seems necessary for the expression of sensitization to these agents when the sensitization occurs in the absence of NMDA antagonists. However, Jeziorski et al. (1994) show progressive increases in the locomotion induced by the combination of MK-801 plus morphine (their Fig. 10) and Segal et al. (1995) show progressive increases in the locomotion induced by the combination of MK-801 plus amphetamine that are consistent with our observations with bromocriptine. Other investigators have either tested doses of amphetamine or cocaine that produce locomotion bordering on stereotypy, which can mask the locomotor-stimulating effects of these drugs (Schiorring, 1971) and thus their locomotor-sensitizing effects (Segal, 1975), or have given the MK-801-stimulant combination in the home cage and have only quantified locomotion on "challenge" days when the stimulant was given in the absence of MK-801. Thus most studies of the interaction of MK-801 with amphetamine, cocaine, apomorphine, or morphine sensitization either lack the controls for state-dependent or conditioned MK-801 effects or lack the sensitivity to reveal such effects.

These data confirm that the blockade of NMDA receptors with a high dose of MK-801 does not block but rather can enhance the development of progressively stronger sensitivity to the psychomotor stimulant actions of bromocriptine. Moreover, MK-801 can itself serve as a conditioned stimulus for bromocriptine-dependent locomotion, producing anticipatory locomotion or supplemental locomotion depending on the timing of injections. The fact that the stimulus properties of MK-801 can interact with the stimulant properties of bromocriptine to produce state-dependent or conditioned psychomotor sensitization suggests the need for more elaborate controls than have traditionally been used in studies of the effects of MK-801 on psychomotor sensitization.

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REFERENCES

Carlezon, W.A., Jr., Mendrek, A., and Wise, R.A. (1995) MK-801 disrupts the expression but not the development of bromocriptine sensitization: A state-dependency interpretation. Synapse, 20:1–9.

Druhan, J.P., Jakob, A., and Stewart, J. (1993) The development of

behavioral sensitization to apomorphine is blocked by MK-801. Eur. J. Pharmacol., 243:73–77.

Hoffman, D.C., and Wise, R.A. (1992) The locomotor-activating effects of the D_2 agonist bromocriptine show environment-specific sensitization following repeated injections. Psychopharmacology, 107: 277–284.

Jackson, A., Koek, W., and Colpaert, F.C. (1992) NMDA antagonists make learning and recall state-dependent. Behav. Pharmacol., 3:415–421.

Jeziorski, M., White, F.J., and Wolf, M.E. (1994) MK-801 prevents the development of behavioral sensitization during repeated morphine administration. Synapse, 16:137–147.

Karler, R., Calder, L.D., Chaudhry, I.A., and Turkanis, S.A. (1989) Blockade of "reverse-tolerance" to cocaine and amphetamine by MK-801. Life Sci., 45:599–606.

Karler, R., Chaudry, I.A., Calder, L.D., and Turkanis, S.A. (1990) Amphetamine behavioral sensitization and the excitatory amino acids. Brain Res. 537:76–82.

Pudiak, C.M., and Bozarth, M.A. (1993) L-NAME and MK-801 attenuate sensitization to the locomotor-stimulating effect of cocaine. Life Sci., 53:1517–1524.

Schiorring, E. (1971) Amphetamine induced selective stimulation of certain behaviour items with concurrent inhibition of others in an open field test with rats. Behaviour, 39:1–17.

Segal, D.S. (1975) Behavioral and neurochemical correlates of repeated d-amphetamine administration. In: Neurobiological Mechanisms of Adaptation and Behavior. A.J. Mandell, ed. Raven Press, New York, pp. 247–261.

Segal, D.S., Kuczenski, R., and Florin, S.M. (1995) Does dizocilpine (MK-801) selectively block the enhanced responsiveness to repeated amphetamine administration? Behav. Neurosci., 109:532–546.

Stewart, J., and Druhan, J.P. (1993) Development of both conditioning and sensitization of the behavioral activating effects of amphetamine is blocked by the non-competitive NMDA receptor antagonist, MK-801. Psychopharmacology, 110:125–132.

Willetts, J., and Balster, R.L. (1988) Phencyclidine-like discriminative stimulus properties of MK-801 in rats. Eur. J. Pharmacol., 146:167–169.

Wolf, M.E., and Jeziorski, M. (1993) Coadministration of MK-801 with amphetamine, cocaine or morphine prevents rather than masks the development of behavioral sensitization. Brain Res., 613:291–294.