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RAPID COMMUNICATION

The NMDA Receptor Antagonist MK-801 Increases Morphine Catalepsy and Lethality

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TRUJILLO, K. A. AND H. AKIL. *The NMDA receptor antagonist MK-801 increases morphine catalepsy and lethality.* PHARMACOL BIOCHEM BEHAV **38**(3) 673–675, 1991.—Interactions between excitatory amino acids and opioids were examined by studying the ability of the noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist MK-801 to affect morphine catalepsy and lethality. MK-801 (0.3 mg/kg) reduced the ED_{50} for morphine-induced catalepsy from approximately 30 mg/kg to less than 10 mg/kg, and reduced the LD_{50} for morphine from approximately 100 mg/kg to approximately 10 mg/kg. Lower doses of MK-801 did not affect morphine catalepsy or lethality. MK-801, in the absence of morphine, produced no catalepsy or lethality at doses up to 3.0 mg/kg; at 0.3 mg/kg MK-801 caused weaving, body rolling and ataxia, as previously described, while at 3.0 mg/kg animals appeared to lose muscle tone, becoming limp. These results demonstrate that blockade of NMDA receptors can dramatically potentiate morphine catalepsy and lethality, and suggest a potential dangerous interaction with opioids in the clinical use of NMDA receptor antagonists.

N-Methyl-D-aspartate MK-801 Dizocilpine Morphine Opiate Opioid Catalepsy Lethality ED_{50} LD_{50}

EXCITATORY amino acids and their receptors are widespread throughout the central nervous system, and have been the subject of considerable recent attention. Studies using excitatory amino acid antagonists have found these neurotransmitters to be important in a variety of behavioral and neurological phenomena, ranging from learning and memory to brain damage (4,16). As a result of their many effects, excitatory amino acid antagonists have been suggested to be of potential use in several clinical situations including brain damage (4,16), seizure disorders (4,16), anxiety (4,16), migraine (16) and Parkinson's disease (8,13). The broad distribution of excitatory amino acid systems, and the broad range of effects of their antagonists, suggest the possibility that these drugs may produce harmful effects in addition to their beneficial effects, either by acting alone, or by interacting with other substances. Such actions could limit the clinical usefulness of excitatory amino acid antagonists.

Opiate compounds are clinically very important. These agents are the drugs of choice for treating severe or intractable pain resulting from trauma or disease. At moderate doses, opiates decrease pain responsiveness without affecting consciousness or movement. However, at high doses, these drugs produce muscular rigidity in humans and catalepsy in rats, and eventually produce death by respiratory depression. In the course of examining interactions between the prototypical opiate morphine and the excitatory amino acid antagonist MK-801 we have found that MK-801 dramatically increases morphine catalepsy and lethality.

METHOD

Subjects were 160 adult male Sprague-Dawley rats (n = 3 to 24 per group). Animals were administered saline or (+)-MK-801 maleate (0.03, 0.1, 0.3 or 3.0 mg/kg IP) followed 30 minutes later by saline or morphine sulfate (1.0, 3.0, 10.0, 30.0 or 100 mg/kg SC). MK-801 was purchased from Research Biochemicals Incorporated and morphine from the University of Michigan Hospital Pharmacy. Following injection animals were placed in plastic boxes and observed for gross behavioral effects. Catalepsy was determined as follows: 60 minutes following the morphine injection the rat was grasped gently around the back by the experimenter, lifted from the box, and gently inverted so that the legs were pointed toward the ceiling. A rat was considered cataleptic if it maintained a completely rigid posture, and did not attempt to right. Results are presented as percent of animals cataleptic at 60 minutes after morphine injection (catalepsy), and the percent of animals found dead within 12 hours following injections (lethality).

RESULTS

In saline-pretreated rats, no catalepsy was observed at doses of morphine up to 10 mg/kg. At 30 mg/kg 3 of 6 animals (50%) were cataleptic, while at 100 mg/kg 6/6 (100%) were cataleptic; the ED_{50} for morphine-induced catalepsy thus was approximately 30 mg/kg (Fig. 1). Animals treated with MK-801 (0.03 to 3.0

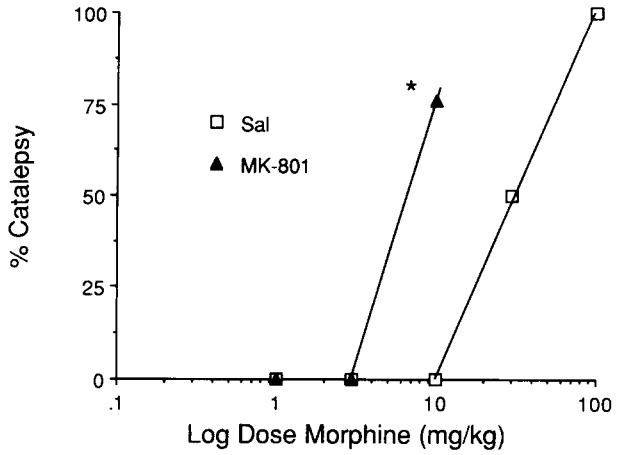

FIG. 1. Potentiation of morphine-induced catalepsy by MK-801. Animals were treated with saline (open squares) or MK-801 (0.3 mg/kg IP; closed triangles), followed 30 minutes later by morphine (1.0–100 mg/kg SC). Effects are represented as the percent of animals cataleptic 60 minutes following morphine treatment. The dose of morphine is shown on a logarithmic scale on the abscissa. *All 6 animals treated with 0.3 mg/kg MK-801 and 30 mg/kg morphine, and 3 of 24 animals treated with 0.3 mg/kg MK-801 and 10 mg/kg morphine died before the test for catalepsy. Since these animals were not tested, their data is not shown; however, it is assumed that these animals did become cataleptic, since this was uniformly observed for other animals treated with either saline and morphine or MK-801 and morphine prior to death.

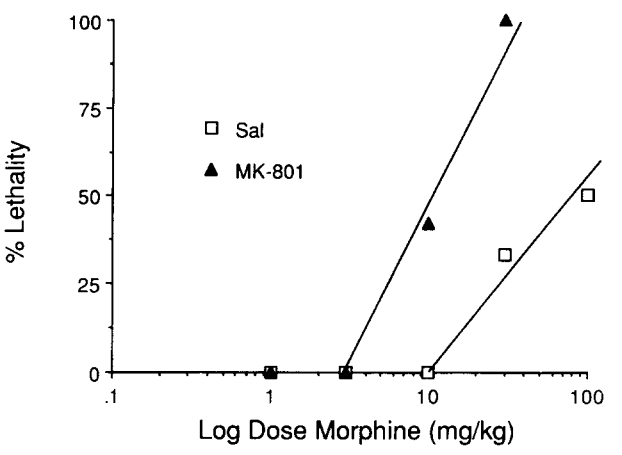

FIG. 2. Potentiation of morphine lethality by MK-801. Animals were treated with saline (open squares) or MK-801 (0.3 mg/kg IP; closed triangles), followed 30 minutes later by morphine (1.0–100 mg/kg SC). Effects are represented as the percent of animals found dead within 12 hours following injections. The dose of morphine is shown on a logarithmic scale on the abscissa.

mg/kg), followed by saline, showed no catalepsy. At 0.3 mg/kg MK-801 produced head weaving, body rolling and ataxia as previously described (6,14), and at 3.0 mg/kg, rather than rigid, animals appeared to have a lack of muscle tone, becoming quite limp. Potent interactions occurred when MK-801 was administered prior to morphine treatment. At a dose of 0.3 mg/kg, MK-801 caused a shift to the left in the cataleptic actions of morphine, decreasing the ED_{50} from approximately 30 mg/kg to less than 10 mg/kg (Fig. 1). Lower doses of MK-801 did not affect morphine catalepsy. The catalepsy seen in rats treated with MK-801 and morphine was very similar to that seen in rats treated with high doses of morphine. The animals showed a high degree of muscular rigidity with the tail extended stiffly, and showed little or no movement.

MK-801 also increased the lethal effects of morphine. Morphine, following saline pretreatment, produced no deaths at doses up to 10 mg/kg. At 30 mg/kg 2 of 6 animals (33%) died, while at 100 mg/kg 3 of 6 (50%) died (Fig. 2). No deaths were observed in any animals treated with MK-801, followed by saline, at doses up to 3.0 mg/kg, the highest dose examined. When MK-801 (0.3 mg/kg) was administered prior to morphine treatment, a dramatic shift in the lethality for morphine occurred (Fig. 2); 11/24 animals (46%) died following 10 mg/kg morphine, and 6/6 (100%) died following 30 mg/kg morphine. Although precise LD_{50}'s were not determined, the present data suggest a nearly 10-fold shift in the LD_{50} for morphine in the presence of 0.3 mg/kg of MK-801, from approximately 100 mg/kg to approximately 10 mg/kg. Lower doses of MK-801 did not affect morphine lethality. Catalepsy and lethality produced in animals treated with the combination of morphine and MK-801 was prevented by naloxone (2.0 mg/kg SC; data not shown).

DISCUSSION

The present studies demonstrate that the noncompetitive NMDA receptor antagonist MK-801 dramatically potentiates morphine-induced catalepsy and lethality. The observed potentiation was quite striking; a dose of 0.3 mg/kg of MK-801 shifted the ED_{50} for morphine-induced catalepsy by over 3-fold, and the LD_{50} for morphine by approximately 10-fold. Lower doses of MK-801 did not increase morphine-induced catalepsy or lethality. This interaction thus appears to occur at relatively high doses of MK-801 and morphine. While MK-801 potentiates morphine-induced catalepsy and lethality, this drug antagonizes morphine tolerance and dependence, and has no effect on morphine analgesia (15). The effects of MK-801 on the actions of morphine are, therefore, behaviorally quite specific. NMDA receptor antagonists have previously been reported to interact with several drugs broadly classified as CNS depressants. For example, MK-801, phencyclidine and ketamine have been observed to increase the effects of general anesthetics (5,17); phencyclidine and ketamine have been observed to interact with morphine (1,10); and phencyclidine has been observed to potentiate the effects of ethanol (2,17). It thus appears that noncompetitive NMDA receptor antagonists have the ability to increase the CNS depressant actions, including the toxicity, of several different drugs.

The present findings may help to resolve an important conflict in the literature regarding the behavioral effects of MK-801. While some studies have reported cataleptic actions of this drug (9, 11, 18), others have reported no such effects (6,14). Importantly, each of the studies finding cataleptic actions of MK-801 in rodents injected the drug in animals pretreated with a general anesthetic, suggesting that the catalepsy resulted from an interaction between the MK-801 and the anesthetic, rather than from the MK-801 by itself. We observed no cataleptic actions of MK-801 in the absence of morphine at doses up to 3.0 mg/kg. Doses up to 50 mg/kg have been injected in mice without producing catalepsy (5). The potentiation of morphine-induced catalepsy seen in the present studies with MK-801 is in stark contrast to the antagonism of haloperidol-induced catalepsy reported by others (13). It, therefore, appears that MK-801 may either potentiate or antagonize catalepsy, depending on the experimental procedure producing the catalepsy. This distinction may have important implications regarding the mechanisms involved in morphine- and haloperidol-induced catalepsy. Previous studies have emphasized the differences between the states produced by these drugs, characterizing the morphine-induced state as "catatonia" and the

haloperidol-induced state as "catalepsy" (12).

The mechanisms responsible for the effects of MK-801 on morphine-induced catalepsy and lethality are presently unclear. Evidence suggests that the periaqueductal gray (PAG) region is the primary locus for the cataleptic actions of opioid compounds (12). However, recent studies have reported that striatal injections of the NMDA receptor antagonist AP7 potentiate opioid-induced catalepsy (3). MK-801 may, therefore, act in either the PAG or the caudate-putamen (or both) to potentiate the cataleptic effects of opioid compounds. In regards to lethality, it is well established that the cause of death from morphine overdose is respiratory arrest from actions at brainstem breathing control nuclei (7). Animals in the present experiments that died from combinations of morphine and MK-801 appeared very similar to those that died from high doses of morphine, becoming cataleptic and rigid, and showing signs of respiratory distress shortly prior to death. MK-801 may, therefore, act at the level of the brainstem to potentiate the respiratory depressant effects of morphine, producing deaths at doses of morphine that are not normally fatal. Although the above evidence suggests that different brain structures may be responsible for the cataleptic and lethal interactions between these drugs, a common site (or sites) cannot be ruled out.

The widespread neural and behavioral effects of NMDA receptor antagonists have led to suggestions that these drugs may be useful in a variety of clinical disorders. The present results, together with previous findings, suggests that potent interactions may occur when these drugs are administered in the presence of CNS depressants. Therefore, appropriate caution should be used when MK-801 or other NMDA receptor antagonists are used in combination with opioids or other CNS depressants. More insidiously, these findings suggest a potential danger for the coabuse of NMDA antagonists, such phencyclidine, and opiates, such as morphine, two classes of drug that are commonly abused.

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