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. PHARMA- 
MACOL 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 EDso for morphine-induced catalepsy from approximately 30 mg/kg to less than 10 

mg/kg, and reduced the LDso 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 poten-
tiate morphine catalepsy and lethality, and suggest a potential dangerous interaction with opioids in the clinical use of NMDA re-
ceptor antagonists.

N-Methyl-D-aspartate MK-801 Dizocilpine Morphine Opiate Opioid Catalepsy Lethality

EDso LDso

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 impor-
tant in a variety of behavioral and neurological phenomena, rang-
ing 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 in-
cluding brain damage (4,16), seizure disorders (4,16), anxiety 
(4,16), migraines (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 sub-
stances. Such actions could limit the clinical usefulness of exci-
tatory amino acid antagonists.

Opiate compounds are clinically very important. These agents 
are the drugs of choice for treating severe or intractable pain re-
sulting from trauma or disease. At moderate doses, opiates de-
crease pain responsiveness without affecting consciousness or 
movement. However, at high doses, these drugs produce muscu-
lar rigidity in humans and catalepsy in rats, and eventually pro-
duce death by respiratory depression. In the course of examining 
interactions between the prototypical opiate morphine and the ex-
citatory 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 Hos-
pital Pharmacy. Following injection animals were placed in plas-
tic 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 ex-
perimenter, lifted from the box, and gently inverted so that the 
legs were pointed toward the ceiling. A rat was considered cata-
leptic if it maintained a completely rigid posture, and did not at-
tempt to right. Results are presented as percent of animals cataleptic at 60 minutes after morphine injection (catalepsy), and the per-
cent 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 EDso for morphine-induced catalepsy thus was approximately 
30 mg/kg (Fig. 1). Animals treated with MK-801 (0.03 to 3.0
NMDA receptor antagonist MK-801 dramatically potentiates morphine and MK-801 was prevented by naloxone (2.0 mg/kg SC; data not shown). Lethality produced in animals treated with the combination of 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. 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 ED50 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 LD50’s were not determined, the present data suggest a nearly 10-fold shift in the LD50 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 ED50 for morphine-induced catalepsy by over 3-fold, and the LD50 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, suggest 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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