LOCOMOTOR ACTIVITY EFFECT OF MK-801 IN MORPHINE-TOLERATED AND NON-TOLERATED MICE

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ABSTRACT

N-methyl-D-aspartate (NMDA) receptors involve in different neurological systems and MK-801 as a noncompetitive NMDA antagonist would stimulate locomotors activity. In this study, the effect of MK-801 has been investigated on tolerant and non-tolerant mice to morphine induced locomotor activity. Three days subcutaneous administration of morphine (50mg/kg) daily caused tolerance in mice. Injection of different doses of MK-801 (0.015, 0.03 and 0.3) in tolerant mice, 30 min after subcutaneous injection of morphine (20 mg/kg) increased locomotion and indicated significant results in highest dose (0.3 mg/kg). In progress daily administration of different doses of MK-801 in first and second day, 15 min before morphine dose (50mg/kg), decreased the locomotors activity of the test dose of morphine (20 mg/kg) in 4th day; although that was significant even in lowest dose. It seems that NMDA receptors play noticeable roles in expression and development of tolerance to morphine-antinociception and morphine-locomotion effects.
INTRODUCTION:
Locomotor activity pertains to the movement from one to another location. In rodents, locomotion is one of the remarkable components of exploration, a noticeable activity of the animal’s ability of spontaneous movement. Furthermore, many physiological and behavioral functions refer to locomotor activity and exploration which affects by such external and internal factors. External ones instance light, noise, temperature and other environmental condition and also novelty of the experiments. And internal factors are age, strain, circadian rhythm, prior handling by the researcher, food- or drink-deprivation, gender, and many other agents (1).
Glutamate is the most abundant excitatory neurotransmitter in the central nervous system (2). There are three major types of inotropic glutamate receptors, as names N-methyl-D-aspartate (NMDA), a-amino3-hydroxy-5-methylisoxasole-4-propionic acid (AMPA) and kainite. Among these receptors, NMDA is unique because it is highly permeable to calcium and on the other hand it involves in learning memory and cognitive function (2, 3). In particular NMDA antagonists such as dextromethorphan, Phencyclidine (PCP) and Dizocilpine (MK-801) are being evaluated to clarify the mechanism(s) involved different type of behavior such as seizures, analgesia and psychomimetic states (4, 5). MK-801, a non-competitive NMDA antagonist induces a complex behavioral syndrome in the rodents, including ataxia, stereotype and hyper locomotion. These behaviors have been proposed as animal models for psychotic studies. The present study aims to determine the different effect of morphine-induced tolerance on locomotion induced by MK-801 and further to evaluate the changes of NMDA mechanism(s) during tolerance to morphine effects (6).

Materials & Methods:

Animals:
Male albino mice (20-25 g) were prepared for this experiments. 7 mice were located in each cage at environmental condition (temperature of 22-24 °C and a 12 hours light-dark cycle). Food and water were freely in access for animals, except during the experiments. Each animal was used once only and euthanized immediately after the experiments.

Drugs:
Morphine sulfate (Temad Company, Iran) and MK-801 (Research Biochemical Ins) were utilized in this study.

Locomotor activity measurement:
Locomotion was measured by an activity meter, Animex, Type S (LKB Farad). Each animal was placed in a plastic cage for 15 min to acclimatize to the environment. Immediately after drug
injection, animals were returned to the cage for measuring the locomotion. The locomotor activity expressed in terms of total counts in 1 hour every 10 minutes for each animal.

**Development of tolerance by morphine**

Tolerance to morphine-induced locomotor activity was achieved by daily subcutaneously administration of morphine sulfate (50 mg/kg) for 3 days. To assess the tolerance, locomotor activity induced by a test dose of morphine (20 mg/kg, IP) was measured on the 4th day after injection different doses of morphine (20, 30 and 45mg/kg).

Regards to the responses, the dose of 20mg/kg of morphine has been selected as test dose for further experiments.

**Statistical analysis:**

Comparison between groups was performed doing analysis of variance following by Tukey test. In this evaluation P< 0.05 was considered as significant value for result differentiation.

**RESULTS:**

The effect of subcutaneous (S.C.) injection of different doses of MK-801 (0.015, 0.03 and 0.3 mg/kg) on non-tolerant mice was illustrated in figure 1. Administration of MK-801, 30 min after morphine injection increased the locomotors activity in the highest doses (0.3mg/kg).

![Figure 1](image-url)  
*Figure 1:* Effect of different doses of MK-801 on locomotors activity on non-tolerant mice p<0.001.
The effect of subcutaneous (S.C.) injection of different dose of MK-801 (0.015, 0.03 and 0.3 mg/kg) on tolerant mice was depicted in figure 2. Injection of MK-801 30 min after subcutaneous injection of morphine increased locomotion in tolerant animals, but it was only significant at high dose (0.3 mg/kg).

**Figure 2**: Effect of different doses of MK-801 on locomotors activity of tolerant mice p<0.001.

The effect of different dose of MK-801 (0.015, 0.03 and 0.3 mg/kg) on locomotion of development animals. Animals received daily injection of different doses of MK-801 for 2 days after daily dose of morphine (50mg/kg). In the 4th day, the test dose of morphine (20mg/kg) decreased the locomotors activity of animals, although it was significant in lower dose.

**Figure 3**: Evaluation of effect MK-801 on development of morphine tolerated animals p<0.001.
DISCUSSION:
Outcome of sensitization tolerance and to the locomotor effects of morphine are more complicated and controversial; however, some evidences have claimed that NMDA receptor antagonists may inhibit these phenomena in an identical manner (7).

MK-801 was conventionally utilized in researches of NMDA receptor pharmacology since it is a highly potent and selective NMDA receptor antagonist. This molecule easily penetrates the blood-brain barrier hence it has potent central actions following peripheral administration. Furthermore it is comparatively inexpensive and effortlessly reachable in market (8). However, MK-801 and other drugs that have high affinity for the non-competitive site of the NMDA receptors would cause side effects on other psychological behaviors particularly, at moderate doses of MK-801 (0.15–0.3 mg/kg IP), an increase in locomotion was observed but in higher doses (0.3–1.0 mg/kg IP), acceleration in locomotion is accompanied by stereotypy, incoordination and ataxia. In the highest administered doses (above 1.0 mg/kg IP), animals become limp and appear to be incapable of voluntary motor activity (9).

The locomotors effects of original opiates are more complex than the analgesic effects. Morphine and other mu opioids, acutely administration to rats, produce a biphasic effect on locomotion, with an initial decrease in locomotion during the first hour of testing, following by a delayed increase over the next 2–3 h (10, 11).

In this study, the lowest dose of morphine (20mg/kg) decreased the locomotion in mice, but in higher doses increased locomotor activity. In tolerant mice, morphine dose dependently increased locomotors activity of animals. The similar results which have been reported indicate that opioid receptors are involved in locomotors activity (12-14). The non-competitive NMDA receptor antagonists, MK-801, in different doses caused hyperactivity in animals. The involvement of NMDA receptor in locomotor activity in mice, as a model of psychotic behavior has been investigated (3, 15). In morphine-tolerant animals, Mk-801 increased locomotor activity of morphine in compare with non-tolerant mice, but it was not significant. It probably indicates that administration of different doses of morphine during tolerance induction could not make notable effect on MK-801 locomotion response.

Daily administration of MK-801 with morphine (50mg/kg) decreased the responsiveness of animal to MK-801 effect. So we can suggest that MK-801 have remarkable effect on locomotion.
REFERENCES:
