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Anticataleptic Effects of the N-Methyl-D-Aspartate Antagonist MK-801 in Rats

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SCHMIDT, W. J. AND M. BUBSER. *Anticataleptic effects of the N-methyl-D-aspartate antagonist MK-801 in rats.* PHARMACOL BIOCHEM BEHAV **32**(3) 621–623, 1989.—The N-methyl-D-aspartate (NMDA) antagonist MK-801 was administered to rats in three doses (0.08, 0.16, 0.33 mg/kg) in order to examine its effects on catalepsy that was induced by haloperidol (0.5 mg/kg). The degree of catalepsy was assessed 30 and 60 min after application of drugs by placing the rat on a horizontal bar, on a podium and on a vertical grid. Animals having received saline and haloperidol showed a higher degree of catalepsy than animals having received MK-801 and haloperidol (except for the lowest dose of MK-801). These findings may suggest a therapeutic potential of MK-801 and possibly of other NMDA antagonists in the treatment of Parkinson's disease.

NMDA MK-801 Haloperidol Catalepsy Dopamine Glutamate Rat

N-METHYL-D-ASPARTATE (NMDA) receptors play a major role in cortical synaptic transmission and in subcortical structures that receive glutamatergic afferents from the cortex. In the anterodorsal striatum of the rat, a blockade of glutamatergic transmission at the NMDA-preferring receptor, using local injections of 2-amino-5-phosphonovaleric acid (AP-5), produces behavioural stimulation, e.g., hypermotility and stereotyped sniffing that is antagonized by neuroleptics (12). Within the nucleus accumbens, AP-5 stimulates locomotion as well (3). AP-5 injected into the ventricles produces similar symptoms, e.g., locomotion, sniffing and swaying (8).

Peripheral application of (+)-5-Methyl-10,11-dihydro-5H-dibenzo-(a,d)cyclohepten-5,10-imine maleate (MK-801), which in contrast to AP-5 readily penetrates the blood-brain barrier, elicits amphetamine-like effects on locomotion in mice and on circling behaviour in rats with unilateral 6-hydroxydopamine lesions to the nigrostriatal system (4).

Recent data concerning the mechanism of action of MK-801 have led to the hypothesis that this drug binds to the phencyclidine (PCP) site and blocks the NMDA receptor response by binding inside the open ion channel, thereby impeding transmembrane ion fluxes (5). Further, like other NMDA antagonists it has anticonvulsant properties (6).

The behavioural effects of AP-5 and MK-801 are reminiscent of some effects that are produced by dopamine agonists. Thus, the question is raised whether NMDA antagonists have one further property in common with dopamine agonists: do NMDA antagonists attenuate catalepsy, a state of postural immobility, that is induced by blocking dopaminergic transmission?

Thus, we tested whether catalepsy, induced by the dopamine-antagonist haloperidol, is antagonized by MK-801.

METHOD

Subjects were 59 male Sprague-Dawley rats (Interfauna, Tuttlingen, F.R.G.). They received intraperitoneal (IP) injections of 0.5 mg/kg haloperidol (injectable solution from ampoules, Janssen, Neuss, F.R.G.) in order to induce a moderate degree of catalepsy. Simultaneously, either MK-801 (Merck Sharp & Dohme, Munich, F.R.G.) dissolved in saline (final pH = 5.0) or saline adjusted to pH = 5.0 were injected IP.

Thirty and 60 min after the injections the degree of catalepsy was measured in each rat. Three established tests were carried out in the following order of succession (11):

1) Placing both forelegs on a horizontal bar 9 cm above the surface.

2) Placing one foreleg on a podium (3 cm high).

3) Hanging on a vertical wire grid.

The time span from placement of the paws until the first movement of one of these paws (descent latency) was measured (at the most for 180 sec).

Differences between groups were analyzed using the two-tailed Mann-Whitney U-test (14). A p-value <0.05 was considered to indicate a significant difference between groups.

RESULTS

The rats having received haloperidol plus saline exhibited a higher degree of catalepsy when tested 30 and 60 min after the injections than those having received haloperidol plus MK-801. This was evident for the medium and high doses of MK-801 (0.16 and 0.33 mg/kg) in all three tests ($p \leqq 0.02$) and for the lowest dose of MK-801 (0.08 mg/kg) in the grid test ($p \leqq 0.02$), whereas in the bar and the podium test the lowest dose of MK-801 had no

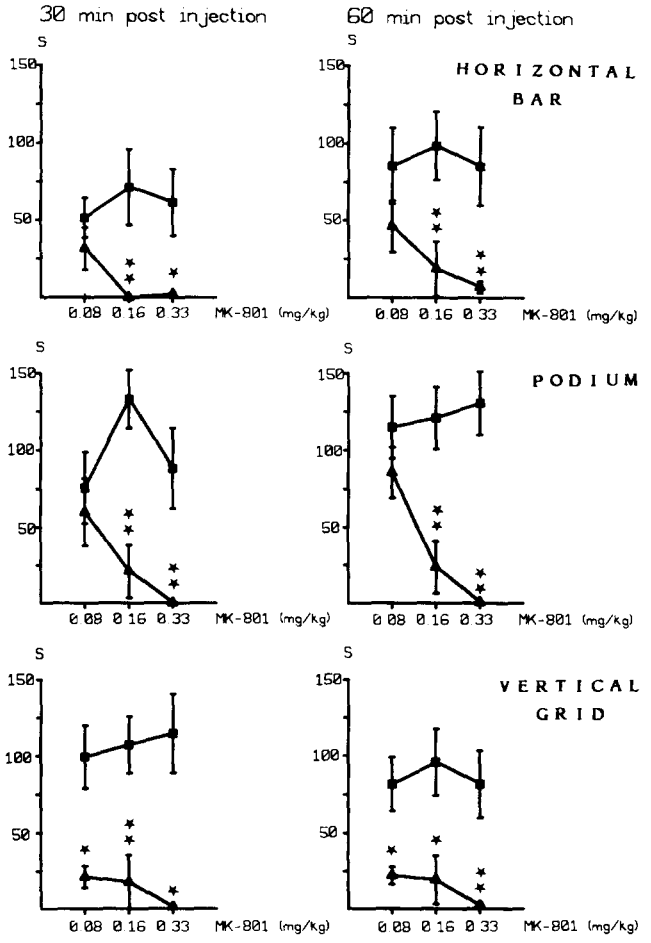

FIG. 1. Descent latencies of animals treated with: ■ haloperidol 0.5 mg/kg IP + saline IP; ▲ haloperidol 0.5 mg/kg IP + MK-801 IP at the indicated doses. Means ± S.E.M. are presented. N = 10 for each dose of MK-801 and N = 10 for the corresponding control runs (except saline control corresponding to 0.08 mg/kg MK-801: N = 9). ★$p \leq 0.02$, ★★$p \leq 0.002$ (Mann-Whitney U-test, two-tailed).

significant anticataleptic effects ($p > 0.05$; Fig. 1).

The anticataleptic effect of MK-801 appears to be dose-dependent.

DISCUSSION

The data show that the noncompetitive NMDA antagonist MK-801 counteracts haloperidol-induced catalepsy. This effect is not due to general debility or ataxia, but rather due to the muscle relaxant effects characteristic of all NMDA antagonists (16), and to an induction of forward locomotion: The rats crossed the obstacles of the experimental setup and exhibited vigorous locomotion. Also, in another paradigm, the 8-arm radial maze, rats are able to collect food at the same dose range of MK-801 alone or in combination with haloperidol, however in both cases severe working memory deficits were seen (2).

While it is generally acknowledged that striatal dopamine receptors are involved in the generation of haloperidol-induced catalepsy, the location of these dopamine receptors, either pre- or postsynaptically, is still controversial [for references see (7)]. But there is convincing evidence that axon sparing kainate lesions in the striatum attenuate haloperidol-induced catalepsy (10). Also quinolinic acid-induced lesions of the striatum abolish haloperidol-induced catalepsy (13). Quinolinic acid destroys spiny projecting neurons using GABA or substance P as their transmitter, but striatal interneurons and striatal afferents are preserved (1). The neurotoxic effects of quinolinic acid are preferentially mediated by NMDA receptors (15). Animals bearing quinolinic acid striatal lesions also show other behavioural changes reminiscent of MK-801 and of AP-5 locally injected into the striatum, e.g., locomotion and stereotyped sniffing (12). Thus, it is possible that MK-801, by transient blockade of NMDA receptor functions, exerts similar effects.

However, in this study, drugs were administered systemically, thus also structures other than the striatum may be involved.

The haloperidol-induced behavioural symptoms resemble those of Parkinson's disease in humans, and therefore catalepsy in animals is sometimes considered to represent a model for this disease. Tentatively, the present findings may suggest a therapeutic potential of MK-801 or of other NMDA antagonists as antiparkinsonian agents. In this connection it is of interest that commonly used antiparkinsonian drugs, known to have anticholinergic and/or antihistaminergic actions, have recently been shown to be NMDA antagonists as well (9).

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