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The NMDA antagonist MK-801 causes marked locomotor stimulation in monoamine-depleted mice

Short Note

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Summary. It was shown in the present study that the selective non-competitive N-methyl-D-aspartate (NMDA) antagonist MK-801 [(+)-5-methyl-10,11-dihydroxy-5H-dibenzo(a,d)cyclohepten-5,10-imine] caused a pronounced and dose-dependent increase in locomotion in mice pretreated with a combination of reserpine and α-methyl-para-tyrosine. Haloperidol pretreatment did not antagonize the MK-801-induced stimulation of locomotion. The findings are discussed in relation to the concept of a corticostriatothalamocortical negative feedback loop serving to protect the cortex from an overload of information and hyperarousal. Such a feedback loop would encompass i.a. corticostriatal glutamatergic neurons and it would be modulated by mesencephalostriatal dopaminergic neurons.

Keywords: MK-801, NMDA receptors, glutamate, dopamine, brain, mouse.

Introduction

The existence of a corticostriatothalamocortical negative feedback loop serving to protect the cortex from an overload of information and hyperarousal has recently been proposed (Carlsson, 1988). Since cortical neurons projecting onto the striatum seem to be mainly glutamatergic, and thus excitatory, whereas striatothalamic projections appear to be basically inhibitory (possibly GABAergic) it is clear that an anatomical substrate for a negative feedback loop exists. The thalamus might be looked upon as a filter for sensory inputs and activaton of the corticostriatothalamic loop would serve to close this filter. Conversely, activation of another neuronal system, namely the mesencephalostriatal dopaminergic pathway would yield opposite effects, i.e. a widening of the filter, hence increasing the flow of information from the outer world to the cortex. Via collaterals from striatothalamic GABAergic neurons these two neu-

ronal systems may in an analogous manner control the impulse flow from the mesencephalic reticular formation to the cortex and hence the degree of arousal.

If the above presented scheme is correct it may be predicted that the behavioural consequences of a decreased activity in the corticostriatal glutamatergic neurons would be reminiscent of those produced by an increased activity in the mesencephalostriatal dopaminergic neurons, i.e. increased wakefulness, locomotion and mood elevation. Conversely, an enhanced activity in the corticostriatal glutamatergic neurons would influence behaviour in the same direction as a decreased activity in the dopaminergic mesencephalostriatal neurons, i.e. produce hypokinesia, sedation and have mood-lowering effects.

To test the hypothesis presented above we have initiated a series of experiments in mice aimed at elucidating interactions between central glutamatergic and dopaminergic systems. In the present paper we describe the results of some preliminary experiments in which the selective non-competetive N-methyl-D-aspartate (NMDA) antagonist MK-801 ([(+)-5-methyl-10,11-dihydroxy-5H-dibenzo(a,d)cyclohepten-5,10-imine] hydrogen maleate) (Wong et al., 1986) was used as pharmacological tool. Like phencyclidine (PCP) and ketamine, MK-801 binds to a site in the NMDA receptor-associated ion channel when in its open state. Functionally MK-801 has been shown to exert neuroprotective actions in experimentally induced ischemia (Gill et al., 1987). It has also been shown to have anticonvulsive (Clineschmidt et al., 1982a; McNamara, 1988) and anxiolytic (Clineschmidt et al., 1982c) properties as well as exerting PCP-like stimulatory effects on locomotion (Clineschmidt et al., 1982b; Koek et al., 1988). Some of the actions of MK-801 appear to be mediated via catecholaminergic mechanisms (Clineschmidt et al., 1982a, b, c).

Materials and methods

Male albino mice of the NMRI strain, weighing 20–30 g, were purchased from ALAB, Sollentuna.

Reserpine (Ciba-Geigy) was dissolved in a few drops of glacial acetic acid and 5.5% glucose solution. α-Methyl-para-tyrosine methylester HCl (α-MT; Sigma) was dissolved in physiological saline. Haloperidol (Leo) was dissolved in a few drops of glacial acetic acid and physiological saline. MK-801 ([(+)-5-methyl-10,11-dihydroxy-5H-dibenzo(a,d)cyclohepten-5,10-imine] hydrogen maleate), generously supplied by Dr. G. N. Woodruff at the MSD laboratories, was dissolved in physiological saline. The drugs were injected i.p. in a volume of 20 ml/kg.

Motor activity was measured by means of a "M/P 40 Fc Electronic Motility Meter" (Motron Products, Stockholm) with 40 photoconductive sensors (5 rows × 8, centre-centre distance 40 mm). Two hours after the mice had been injected with reserpine and throughout the experiment they were kept in a room holding at least 27 °C.

Results

All mice received 10 mg/kg of reserpine and 250 mg/kg of α-MT 19 hours and 30 minutes, respectively, before the administration of saline or various doses of MK-801. 45 minutes following treatment with saline or MK-801 the animals

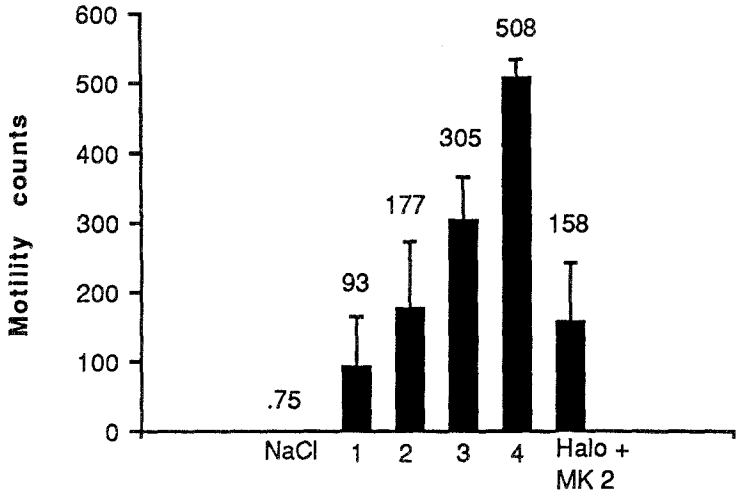

Fig. 1. Effects of various doses of MK-801 on motor activity in monoamine-depleted mice. Shown are the means ± s.e.m. N is 4, 3, 4, 4, 2, and 3, respectively in the control, 1, 2, 3, 4 mg/kg, and haloperidol + 2 mg/kg groups. The number of animals is 3 × n, since the mice were tested three at a time in the motility meters. The motility counts for the different groups are shown above the respective bars. There was a significant correlation between dose and motility counts ($r = 0.54$, $p < 0.02$)

were placed, three at a time, in motility meters and their motor activity was recorded for 90 minutes. Control mice receiving reserpine and α-MT in combination with saline displayed virtually no locomotion at all. In contrast, animals receiving MK-801 exhibited a pronounced increase in motor activity in a dose-related manner. Haloperidol in a dose of 1 mg/kg given 15 minutes prior to MK-801 was unable to reduce the effect of MK-801 (2 mg/kg) on motor activity (Fig. 1). Maximal stimulation of locomotion was observed about 1½ hour following the injection of MK-801 (not shown).

Apart from causing increased locomotion, MK-801 produced intensive sniffing, Straub tail, hindleg ataxia, an elongated body posture and occasional head twitches as well as increased irritability and increased sensitivity to tactile and auditory stimuli. The highest doses of MK-801 produced convulsions; in the 3 mg/kg group 5 (42%) mice died before the 90-minute test period had ended and in the 4 mg/kg group 3 (50%). When the animals were placed in an open field they exhibited higher motor activity and less propensity for convulsions than when confined to the motility meters or their home cages, where they tended to get stuck in the corners, displaying intensive treading and sniffing.

Discussion

The present preliminary study has demonstrated that the highly selective NMDA antagonist MK-801 causes a marked behavioural stimulation in monoamine-depleted mice. It has previously been suggested that the stimulatory effect

exerted by MK-801 on locomotion is mediated via a catecholaminergic mechanism (Clineschmidt et al., 1982a). This is probably true in part (see below), but the present experiments clearly show that MK-801 produces a pronounced locomotor stimulation via a mechanism that is independent of dopamine (DA) and noradrenaline release. It is tempting to suggest that such a mechanism might involve a corticostriatothalamic feedback loop as outlined in the Introduction. Hence, the behavioural stimulation observed in the MK-801-treated animals would be the result of an opening of the thalamic filter a well as an activation of the mesencephalic reticular formation, leading to an increased flow of information from the outer world to the cortex and hyperarousal. In line with such a speculation is the finding that, apart from the marked increase in motor activity, an enhanced sensitivity to tactile and auditory stimuli was observed in the MK-801-treated mice.

In line with the concept of a corticostriatothalamic feedback loop is a recent paper, reporting that injection of NMDA bilaterally into the anterodorsal striatum of rats reduced locomotion, sniffing and rearing, whereas injection of the NMDA receptor blocker DL-2-amino-5-phosphonovaleric acid (AP-5) into the same area resulted in increased locomotion, rearing and sniffing (Schmidt and Bury, 1988). Furthermore, a recent study has shown that MK-801, as well as the other two non-competitive NMDA antagonists PCP and ketamine, protect against methamphetamine-induced neurotoxicity (Sonsalla et al., 1988); since this latter compound causes massive DA release it is tempting to suggest that it induces activation of a corticostriatothalamocortical negative feedback loop, resulting in excessive release of glutamate from terminals in the striatum, in turn leading to destruction of monoaminergic neurons in this area.

Clineschmidt et al. (1982a, b) have suggested that the anticonvulsant and locomotor stimulatory effects of MK-801 are mediated via a catecholaminergic mechanism. Indeed, preliminary biochemical data from our laboratory have shown that MK-801 increases central DA turnover (unpublished observations). Thus, MK-801 probably produces behavioural stimulation in mice both via activation of catecholaminergic neurons and via a mechanism independent of catecholamines. Why is it then that blockade of NMDA receptors causes activation of central catecholaminergic neurons? One possibility is that inhibition of glutamergic transmission in the striatum, a region with a high density of NMDA receptors, leads to a decreased firing in the GABAergic striatonigral neurons, in turn resulting in a decreased inhibition of impulse flow in the nigrostriatal DA neurons and hence an increased dopaminergic transmission in the striatum.

MK-801 is reported to exert anticonvulsive effects, but in our hands higher doses of this agent were found to be proconvulsive. This discrepancy may partly be explained by the fact that reserpine lowers the threshold for seizures. Moreover, there is evidence that the anticonvulsive effects exerted by MK-801 are mediated via a catecholaminergic mechanism (Clineschmidt et al., 1982a). However, even in unpretreated animals we have observed proconvulsive effects of MK-801.

In summary, the present study demonstrates that the selective NMDA antagonist MK-801 causes marked locomotor stimulation in monoamine-depleted mice. The findings are discussed in relation to the concept of a corticostriatothalamocortical negative feedback loop, encompassing glutamatergic and modulated by dopaminergic neuronal systems, serving to protect the cortex from an overload of information and hyperarousal. Should this hypothesis prove to be correct, a new strategy for the pharmacological treatment of i.a. Parkinson's disease and schizophrenia may be envisaged. Thus, low doses of a NMDA antagonist may prove to be effective in Parkinson's disease, whereas a NMDA agonist may be a useful complement in the treatment of schizophrenia.

Similar views regarding schizophrenia have been expressed by Kornhuber et al. (1984) and Kim et al. (1985). After completion of the present paper we learned about experiments showing an anticataleptic action of MK-801 in haloperidol-treated rats (Schmidt and Bubser, 1989).

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