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 activation of the corticostriatothalamocortical 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-competitive 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. a-Methyl-para-tyrosine methylester HCl (a-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/P40 Fc Electronic Motility Meter” (Motron Products, Stockholm) with 40 photoconductive sensors (5 rows x 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 a-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