Pharmacology Biochemistry & Behavior, Vol. 36, pp. 45–50. © Pergamon Press plc, 1990. Printed in the U.S.A. 0091-3057/90 $3.00 + .00

Interfering With Glutamatergic Neurotransmission by Means of NMDA Antagonist Administration Discloses the Locomotor Stimulatory Potential of Other Transmitter Systems

MARIA CARLSSON[1] AND ANDERS SVENSSON

Department of Pharmacology, University of Göteborg, Göteborg, Sweden

Received 14 August 1989

CARLSSON, M. AND A. SVENSSON. *Interfering with glutamatergic neurotransmission by means of NMDA antagonist administration discloses the locomotor stimulatory potential of other transmitter systems.* PHARMACOL BIOCHEM BEHAV **36**(1) 45–50, 1990.—In the present paper it is shown that when either of the noncompetitive NMDA antagonists MK-801 or ketamine are combined with the α-adrenergic agonist clonidine, a pronounced stimulation of locomotion is produced in monoamine-depleted mice. Likewise, when a subthreshold dose of MK-801 is combined with the muscarinic antagonist atropine, a forceful synergism with regard to locomotor activity in monoamine-depleted mice is observed. Furthermore, the present study shows that also in monoamine-depleted *rats* MK-801, as well as the competitive NMDA antagonist AP-5 (DL-2-amino-5-phosphonovaleric acid), interact synergistically with clonidine to enhance locomotor activity. Taken together, our findings suggest that central glutamatergic systems exert a powerful inhibitory influence on locomotion. Interfering with this inhibitory force by administration of an NMDA antagonist promotes locomotion and discloses the activational potential of other transmitter systems. The results are discussed in relation to 1) the pathophysiology of schizophrenia, with emphasis on the glutamate hypothesis of schizophrenia, and 2) implications for the treatment of Parkinson's disease.

MK-801 Clonidine Glutamate Locomotor activity Rat Mouse Parkinson's disease Schizophrenia

PREVIOUS work in our laboratory has shown that the selective, noncompetitive NMDA antagonist MK-801 [(+)-5-methyl-10,11-dihydroxy-5H-dibenzo(a,d)cyclohepten-5,10-imine; (26)] causes a pronounced locomotor stimulation in monoamine-depleted mice (5,6). From this finding it can be inferred that 1) dopamine (DA) is not indispensable for initiation and generation of locomotion, 2) central glutamatergic systems exert a powerful inhibitory influence on locomotion, 3) central glutamatergic and catecholaminergic systems are functionally opposed with regard to locomotion—possibly this antagonistic interaction takes place within the striatum, in analogy to the presumed cholinergic/dopaminergic antagonism within this structure [see (1)].

Moreover, previous work has demonstrated a forceful synergism in monoamine-depleted mice when MK-801 in a low dose, which does not per se affect motor activity, is combined with a high dose of the α-adrenergic agonist clonidine. A synergistic effect with regard to motor activity is also observed when MK-801 is combined with a low (subthreshold) dose of the dopaminergic agonist apomorphine (6). The present paper compares the behavioural effects produced in monoamine-depleted mice when MK-801 or the noncompetitive NMDA antagonist ketamine is combined with a high dose of clonidine or a high dose of the muscarinic antagonist atropine. Finally, the behavioural effects of MK-801 and the competitive NMDA antagonist DL-2-amino-5-phosphonovaleric acid (AP-5) and their interactions with clonidine in monoamine-depleted *rats* are reported.

METHOD

Animals

Male albino mice of the NMRI strain (20–30 g) and male Sprague-Dawley rats (160–180 g) were purchased from ALAB, Sollentuna.

Drugs

Idazoxan (Reckitt & Colman) was dissolved in distilled water.

[1]Requests for reprints should be addressed to Maria Carlsson, Department of Pharmacology, Box 33031, S-400 33 Göteborg, Sweden.

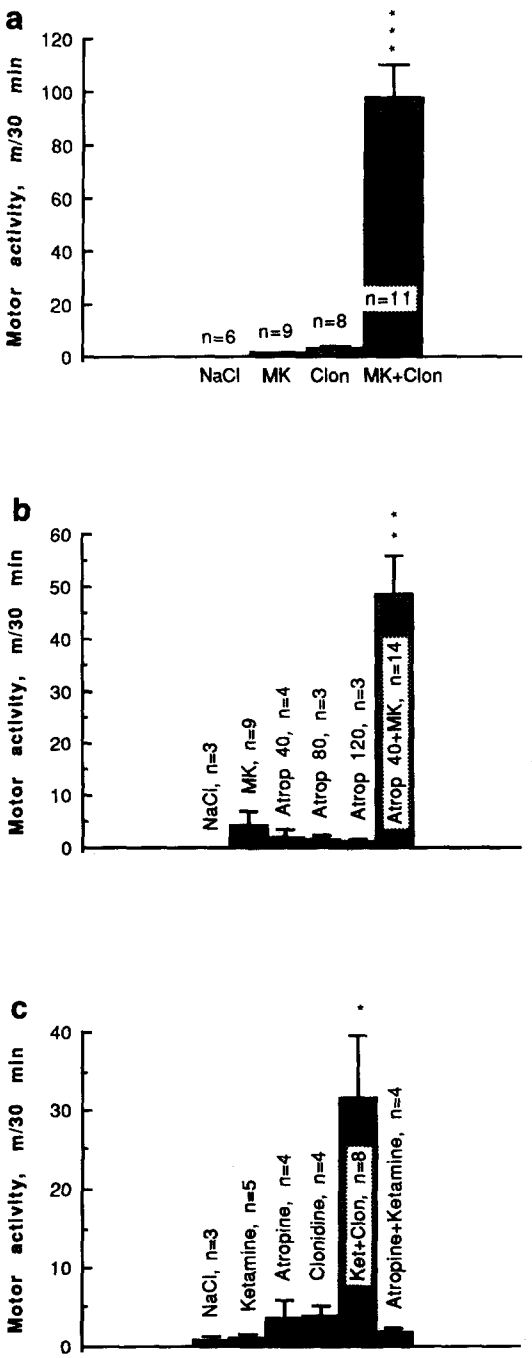

FIG. 1. (a) Effects of MK-801 (1 mg/kg IP) and clonidine (2 mg/kg IP) on motor activity in monoamine-depleted mice. Reserpine (10 mg/kg IP) was administered 18 hours and α-MT (250 mg/kg IP) 30 minutes prior to MK-801 treatment. Clonidine was administered immediately before the registration of motor activity started, i.e., 60 minutes after MK-801 treatment. Motor activity was registered during 30 minutes. Shown are the means ± s.e.m. Statistics: Kruskal-Wallis analysis of variance ($H = 25.5$, $p = 0.0001$) followed by Mann-Whitney U-test. ***$p<0.001$ vs. the other groups. (These data are from J. Neural Transm. 77:65–71; 1989.) (b) Effects of MK-801 (1 mg/kg IP) in combination with atropine (40 mg/kg SC) on motor activity in monoamine-depleted mice. Reserpine (10 mg/kg IP) was administered 18 hours, α-MT (250 mg/kg IP) 60 minutes and atropine 30 minutes prior to MK-801 treatment. Shown are also the effects of atropine administered separately in three different doses (40, 80 and 120 mg/kg SC). Motor activity was registered during 30 minutes starting 60 minutes after MK-801 administration. Shown are the means ± s.e.m. Statistics: Kruskal-Wallis analysis of variance ($H = 25.9$, $p = 0.0001$) followed by Mann-Whitney U-test. **$p<0.01$ vs. the other groups. (c) Effects of ketamine in combination with clonidine or atropine on motor activity in monoamine-depleted mice. Reserpine (10 mg/kg IP) was administered 18 hours, α-MT (250 mg/kg IP) 60 minutes and atropine (40 mg/kg SC) 30 minutes prior to ketamine (50 mg/kg IP) treatment. Clonidine (2 mg/kg IP) was administered immediately before the registration of motor activity started, i.e., 60 minutes after ketamine treatment. Motor activity was registered during 30 minutes. Shown are the means ± s.e.m. Statistics: Kruskal-Wallis analysis of variance ($H = 17.8$, $p = 0.0032$) followed by Mann-Whitney U-test. *$p<0.02$ vs. the other groups.

Reserpine (Ciba-Geigy), yohimbine HCl (Sigma), prazosin HCl (Pfizer) and clozapine (Wander) were dissolved in a few drops of glacial acetic acid and 5.5% glucose solution. α-Methyl-para-tyrosine methylester HCl (α-MT; Sigma), clonidine HCl (Boehringer Ingelheim), atropine sulphate (Aldrich) and ketamine HCl (Sigma) were dissolved in physiological saline. DL-2-amino-5-phosphonovaleric acid (AP-5; Sigma) was dissolved in 1.0 M NaOH before being diluted to final volume with physiological saline; the solution was adjusted to neutral pH by adding a few drops of 1.0 M HCl. 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, England, was dissolved in physiological saline in an ultrasonic bath. All drugs were injected IP, except atropine which was given SC and AP-5 which was given ICV. In mouse all drugs were given in a volume of 10 ml/kg, except reserpine which was administered in a volume of 20 ml/kg. In rat the injection volume was 5 ml/kg.

ICV Surgery

Polyethylene cannulae were implanted into each lateral ventricle under chloral hydrate (400 mg/kg IP) anaesthesia according to a technique described previously (12). The rats were allowed one week's recovery before the experiment was performed. Twenty μl of vehicle or AP-5 was injected into each ventricle.

Procedure

In mouse, the model for measuring motor activity consisted of a circular track, 5 cm wide and 1 meter in circumference, the inner and outer walls being transparent plastic cylinders, 15 and 25 cm high, respectively. The number of turns (= meters) the animal covered in 30 minutes was registered manually or by means of IR detectors. In rat 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). Motor activity was registered during 30 or 90 minutes (for details see figure legends). Two hours after the animals had been injected with reserpine and throughout the experiment the ambient temperature was held at 28°C (mice) or 27°C (rats). The behaviour and gross appearance of the animals were observed throughout the experiments.

Statistics

Mann-Whitney U-test, preceded by Kruskal-Wallis analysis of variance, was used throughout for comparisons between groups.

RESULTS

Mouse

Interaction between MK-801 and clonidine in monoamine-depleted mice. One mg/kg of MK-801 and 2 mg/kg of the

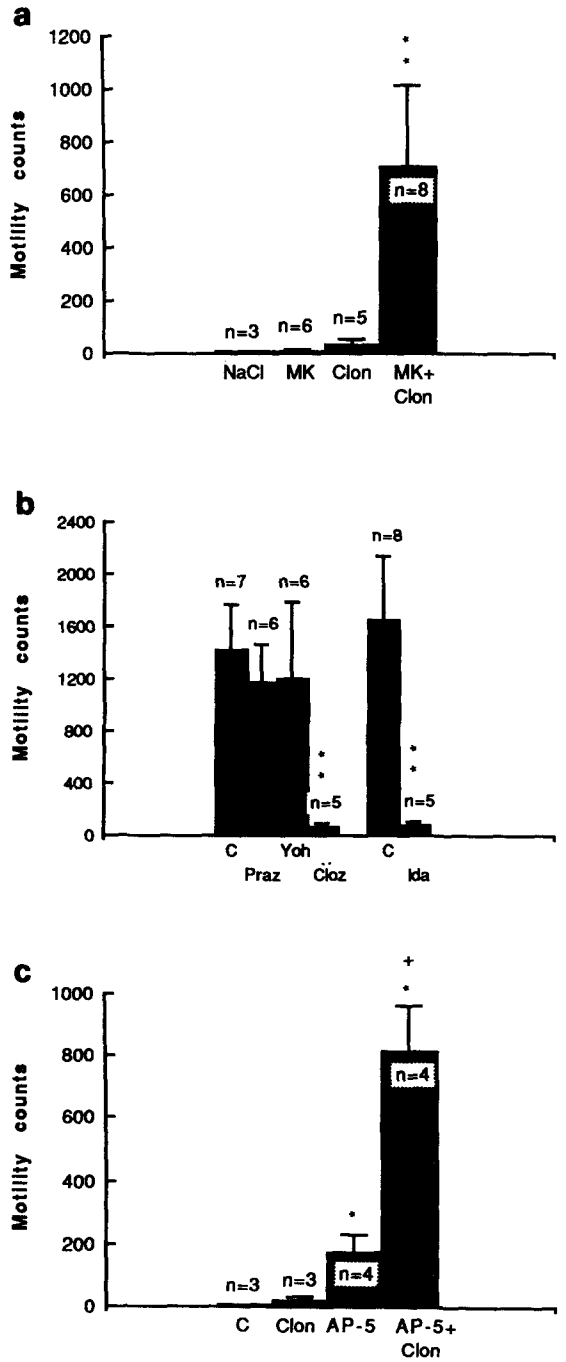

FIG. 2. (a) Effects of MK-801 in combination with clonidine on motor activity in monoamine-depleted rats. Reserpine (10 mg/kg IP) was administered 16 hours and α-MT (250 mg/kg IP) 60 minutes prior to MK-801 (0.1 mg/kg IP) treatment. Clonidine (2 mg/kg IP) was administered immediately before the registration of motor activity started, i.e., 30 minutes after MK-801 treatment. Motor activity was registered during 90 minutes. Shown are the means ± s.e.m. Statistics: Kruskal-Wallis analysis of variance ($H = 13.4$, $p = 0.0039$) followed by Mann-Whitney U-test. $^{**}p <$ or $= 0.01$ vs. the other groups. (b) Effects of different catecholaminergic blockers on the locomotor-stimulatory effects of MK-801 + clonidine in monoamine-depleted rats. Reserpine (10 mg/kg IP) was administered 16 hours and α-MT (250 mg/kg IP) 60 minutes prior to MK-801 treatment. Prazosin (1 mg/kg IP), yohimbine (12 mg/kg IP) and clozapine (20 mg/kg IP) were administered 30 minutes and idazoxan (10 mg/kg IP) 60 minutes prior to clonidine treatment. Motor activity was registered during 90 minutes beginning 10 minutes after the clonidine injection, except in the idazoxan experiment in which the registration of motor activity began 50 minutes after clonidine administration. Shown are the means ± s.e.m. Statistics: Kruskal-Wallis analysis of variance (for the experiment with prazosin, yohimbine and clozapine; $H = 10.1$, $p = 0.018$) followed by Mann-Whitney U-test. $^{**}p < 0.01$ vs. controls (C). (c) Effects of AP-5 in combination with clonidine on motor activity in monoamine-depleted rats. Reserpine (10 mg/kg IP) was administered 18 hours and α-MT (250 mg/kg IP) 60 minutes prior to AP-5 (0.05 mg in 40 μl ICV) treatment. Clonidine (2 mg/kg IP) was administered immediately after the AP-5 administration. Motor activity was registered during 30 minutes beginning 5 minutes after clonidine treatment. Shown are the means ± s.e.m. Statistics: Kruskal-Wallis analysis of variance ($H = 10.6$, $p = 0.014$) followed by Mann-Whitney U-test. $^{*}p < 0.05$ vs. controls (= C = vehicle ICV + saline IP). $+p < 0.025$ vs. AP-5.

α-adrenergic agonist clonidine administered separately did not significantly increase locomotion in monoamine-depleted mice, but the combined treatment caused a dramatic enhancement of motor activity (Fig. 1a). The animals walked/ran essentially in one and the same direction during the entire test period in a stilty, swaying fashion.

Interaction between MK-801 and atropine in monoamine-depleted mice. Atropine per se, even in doses as high as 80 and 120 mg/kg, could not reverse the akinesia induced by reserpine and α-MT treatment. However, when atropine (40 mg/kg) was combined with 1 mg/kg of MK-801, a pronounced stimulation of motor activity was observed (Fig. 1b). Similarly to the mice receiving MK-801 in combination with clonidine, the mice treated with MK-801 and atropine moved along the track in essentially one and the same direction, but they differed considerably from the former in appearance. Thus, whereas the MK-801/clonidine-treated animals had a stilty gait, their bodies lifted high above the ground, the mice treated with atropine and MK-801 displayed crawling, lizard-like movements, their bodies flat against the ground.

Interaction between ketamine and clonidine/atropine in monoamine-depleted mice. Neither 50 mg/kg of the noncompetitive NMDA antagonist ketamine, nor 2 mg/kg of the α-adrenergic agonist clonidine administered separately significantly affected locomotion, but the combined treatment caused a pronounced enhancement of motor activity. In contrast, when ketamine was combined with 40 mg/kg of atropine, no enhancement of motor activity was observed (Fig. 1c). The appearance of the mice receiving ketamine in combination with clonidine was very similar to that observed in mice treated with MK-801 and clonidine; thus, the animals ran or walked in a stilty, swaying fashion, moving along the track in essentially one and the same direction during the entire test period.

Rat

Interaction between MK-801/AP-5 and clonidine in monoamine-depleted rats. When MK-801 (0.1 mg/kg) and clonidine (2 mg/kg) were administered separately, no enhancement of motor activity was registered in the motility meters. In contrast, when the two drugs were combined, a pronounced enhancement of motor activity was observed (Fig. 2a). Part of the time the animals walked around close to the walls of the motility meter box. However, most of the time the rats were stuck in the corners, displaying intensive jumping and rearing.

The stimulatory effect on motor activity induced by the MK-801/clonidine treatment was antagonized by the α_2-adrenoceptor antagonist idazoxan as well as by the "atypical" neurolep-

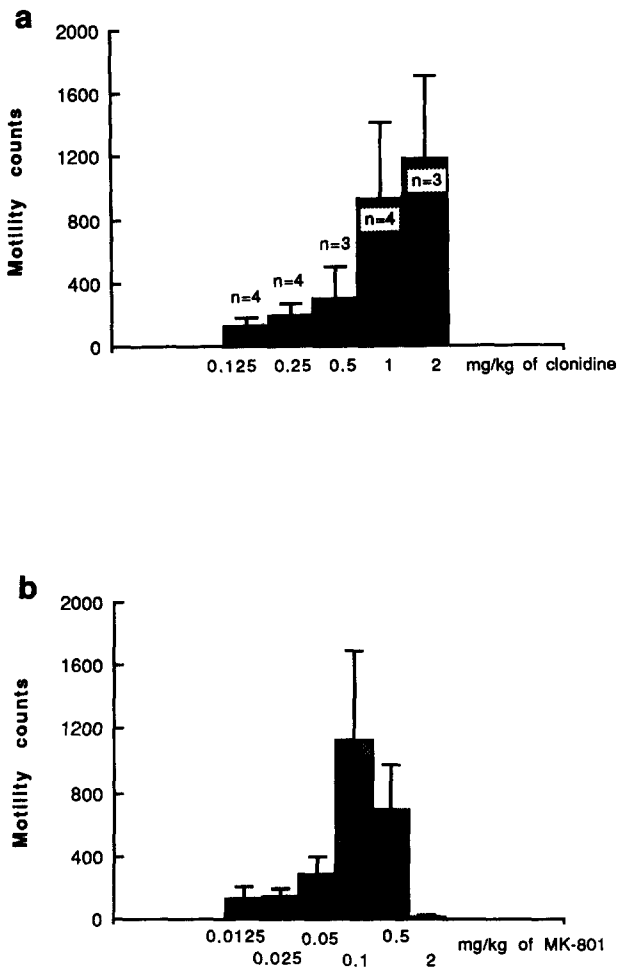

FIG. 3. (a) Effects of varying doses of clonidine combined with 0.1 mg/kg of MK-801 on motor activity in monoamine-depleted rats. Reserpine (10 mg/kg IP) was administered 16 hours and α-MT (250 mg/kg IP) 60 minutes prior to MK-801 treatment. Clonidine was given 20 minutes after MK-801 treatment. Motor activity was registered for 90 minutes beginning 10 minutes after clonidine treatment. Shown are the means ± s.e.m. There was a significant correlation between clonidine dose and motility counts [ANOVA: $F(16)=8.9$; $r=.59$, $p<0.01$]. (b) Effects of varying doses of MK-801 combined with 2 mg/kg of clonidine on motor activity in monoamine-depleted rats. Reserpine (10 mg/kg IP) was administered 7 hours and α-MT (250 mg/kg IP) 60 minutes prior to MK-801 treatment. Clonidine was given 20 minutes after MK-801 treatment. Motor activity was registered for 90 minutes beginning 10 minutes after clonidine administration. Shown are the means ± s.e.m. $N=4$. There was a significant positive correlation between dose of MK-801 in the range 0.0125-0.1 mg/kg and motility counts [ANOVA: $F(14)=8.5$; $r=.62$, $p=0.01$] and a significant negative correlation between dose of MK-801 in the range 0.1–2 mg/kg and motility counts [ANOVA: $F(10)=5.1$; $r=-.58$, $p<0.05$].

tic clozapine, but it was not significantly decreased by the α_2-adrenoceptor antagonist yohimbine or the α_1-adrenoceptor antagonist prazosin (Fig. 2b).

The competitive NMDA receptor antagonist AP-5 induced a certain degree of locomotor stimulation when administered alone, and this effect was markedly potentiated by coadministration of clonidine (Fig. 2c). Similarly to the MK-801/clonidine-treated animals, the AP-5/clonidine-treated rats exhibited intensive jumping and darting behaviour, in this case reminiscent of a rabbit's way of jumping.

Dose-response studies with clonidine and MK-801 in monoamine-depleted rats. Clonidine in doses ranging from 0.125 to 2 mg/kg was administered to rats receiving a fixed dose of MK-801 (0.1 mg/kg). A dose-related increase in motor activity was observed; the dose-response curve did not plateau, even at the highest doses (Fig. 3a). Thus, 2 mg/kg of clonidine may not be a supramaximal dose with regard to locomotor stimulatory effect. On the other hand, when a dose-response study with MK-801 was conducted against a fixed dose (2 mg/kg) of clonidine, a bell-shaped response curve was obtained, the anaesthetic effects (see below) of MK-801 prevailing over the activational effects in higher doses (Fig. 3b).

DISCUSSION

The outstanding locomotor stimulatory actions of the noncompetitive NMDA antagonist MK-801 in rats and mice was firstly described by Clineschmidt *et al.* (9). These authors suggested that the stimulatory effects were brought about by catecholamine release, via a mechanism similar to that of methylphenidate. Subsequent studies have shown that MK-801 causes an activation of catecholaminergic neurons [(13), Carlsson *et al.*, unpublished observations], probably by virtue of its NMDA receptor blocking action. However, the present and previous (5,6) studies have demonstrated that MK-801 is able to cause a marked locomotor stimulation in mouse also via a *catecholamine-independent* mechanism. This is illustrated by the finding that MK-801 causes a pronounced and dose-dependent stimulation of locomotion in mice that are depleted of monoaminergic stores. Moreover, the present and previous (5,6) studies have shown that administration of NMDA antagonists to monoamine-depleted mice and rats discloses the activational potential of other transmitter systems. This is illustrated by the marked synergism produced when the NMDA antagonists MK-801 or AP-5 are combined with an adrenergic or a dopaminergic agonist, or a muscarinic antagonist.

Thus, it appears that NMDA antagonists interact with catecholamines also on a postsynaptic level. Interesting in this context is a study showing that MK-801 potentiated the effects of noradrenaline-induced depolarization of motoneurons in isolated immature spinal cord preparations (8). Thus, the powerful stimulatory actions of MK-801 in intact animals might be mediated by at least three different, possibly synergistic, mechanisms involving blockade of NMDA receptors: 1) via a mechanism unrelated to catecholaminergic systems, 2) via release of catecholamines from presynaptic nerve terminals, 3) via reinforcement of the actions of catecholamines on a postsynaptic level, possibly via receptor-receptor interactions.

We do not know at this stage which brain region(s) that might be involved in the behavioural effects produced by MK-801 given alone or in combination with another agent. Hopefully, future experiments with topical drug application in discrete brain regions will shed some light on this issue. One important subcortical structure to consider is the striatum; application of AP-5 into the anterodorsal striatum has been shown to result in behavioural stimulation, i.e., increased locomotion, rearing and sniffing in intact rats (22). Likewise, MK-801 infused into the nucleus accumbens of intact rats has been found to produce a dose-related increase in locomotor activity (21).

Local drug application may also be helpful when attempting to understand why the anaesthetic actions are more pronounced with an agent like ketamine, whereas with MK-801 the activational effects prevail. The present study has shown that ketamine, similarly to MK-801 causes a clear-cut locomotor stimulation in

monoamine-depleted mice when combined with clonidine. However, the synergism is not as marked with the ketamine/clonidine combination as with the MK-801/clonidine combination. Furthermore, ketamine per se does not seem to cause any stimulation of motor activity. Likewise, when ketamine is combined with atropine, no locomotor stimulatory effect in monoamine-depleted mice is observed. This is to be compared with the powerful synergism obtained when MK-801 is combined with atropine. Could it be that ketamine predominantly interferes with glutamatergic transmission in sensory afferents and thalamocortical pathways, whereas MK-801 preferentially decreases glutamatergic transmission within the striatum? Are we dealing with subtypes of NMDA receptors?

Monoamine-depleted rats receiving MK-801 in combination with clonidine attempted to force obstacles instead of walking around them, thus reminiscent of the compulsive forward locomotion seen in mice receiving this treatment. In fact, there is an interesting parallel between the behavioural effects obtained in mouse and rat in this study and the effects previously observed in cat following removal of the cerebral hemispheres (25). In both cases locomotion is stimulated, the animals tend to walk incessantly and they do not turn and change direction when encountering an obstacle, thus bumping into walls and getting stuck in corners. Corticofugal projections seem to be essentially glutamatergic [see (10)]. Thus, administration of a glutamatergic antagonist like MK-801 might produce a "pharmacological decortication," which in turn might release, e.g., brainstem locomotor programs, resulting in the described bizarre behaviour.

It should be kept in mind in this context that different underlying mechanisms as well as different brain regions may be involved in the behaviours produced by the various drug combinations. Supporting such a notion is the observation that the gross appearance of the animals varied following the different drug combinations. Although all MK-801-treated mice displayed compulsive forward locomotion, the addition of atropine produced crawling movements, whereas the addition of clonidine produced a stilty gait. Furthermore, since mouse and rat differ in their responses to NMDA antagonists given alone or in combination with clonidine, the neuroanatomical substrates and underlying mechanisms involved in the behavioural responses may be different in the two species. For instance, in the monoamine-depleted mouse MK-801 has been found to produce a dose-dependent increase in locomotion, with convulsions appearing in higher doses (5). In the monoamine-depleted rat, in contrast, MK-801 per se did not stimulate locomotion if the rats were placed in motility meter cages. However, 0.1 mg/kg of MK-801 induced a behavioural activation, lasting for 30–60 minutes, if the rats were placed in an open field. These animals explored the surroundings spontaneously but tended to get stuck in corners and displayed a certain degree of ataxia. In higher doses, on the other hand, the anaesthetic effects prevailed, with, e.g., muscular hypotension and loss of righting reflex, effects that were observed also after high doses of AP-5.

In the mouse the pronounced synergism between MK-801 and clonidine was effectively antagonized by both yohimbine, idazoxan and clozapine, but not by prazosin, indicating the involvement of an α_2-adrenergic mechanism (6). In rat, on the other hand, idazoxan and clozapine, but not yohimbine or prazosin, antagonized the clonidine effect, although both the yohimbine-treated and the prazosin-treated groups were *qualitatively* affected. (For instance, the yohimbine-treated rats spent relatively more time walking than jumping compared to controls and the prazosin-treated animals exhibited a greater degree of ataxia than controls.) According to the classification proposed by Bylund (2) there are three subtypes of α_2-adrenoceptors, α_{2A}, α_{2B} and α_{2C}. Possibly a different population of α_2-adrenoceptors participates in the interaction with MK-801 in rat, as compared to mouse. Alternatively, nonadrenergic receptors may be involved, considering the imidazole nature of clonidine and idazoxan (2, 19, 24). Speaking against such a notion, however, is the observation that clozapine, which is not an imidazole, effectively antagonized the clonidine effect in all cases. In any event, α_1-adrenoceptors do not seem to be involved, since prazosin was consistently ineffective in antagonizing the behavioural responses evoked by MK-801 + clonidine.

In the experiment in which a dose-response curve on MK-801 was performed (Fig. 3b) the interval between reserpine treatment and MK-801 was only 7 hours, as compared to 16–18 hours in the other experiments. One should be aware of the possibility that these different time regimens might differentially affect the responsiveness of the α-adrenergic receptors and thereby the behavioural response to clonidine. However, speaking against such a notion is the observation that the enhancement of locomotion following 0.1 mg/kg of MK-801 in combination with 2 mg/kg of clonidine in the experiment with 7 hours elapsing between reserpine and MK-801 was not lower than in two other experiments using a 16-hour reserpine interval (Figs. 2a and 3a). Regarding the effects of reserpine on the granular storage mechanism, this appears to be equally effective after 16–18 hours as after 7 hours (4). Thus, the depletion of catecholamines ought to be optimal with both time regimens, particularly considering the fact that the tyrosine hydroxylase inhibitor α-MT was always given as additional pretreatment.

Implications for the Pathophysiology of Schizophrenia

The agent that is reported to most faithfully mimic schizophrenia is phencyclidine [PCP; "angel dust"; (14,23)]. For instance, in contrast to amphetamine, which was previously the prototype in both human and animal models of schizophrenia, PCP has been reported to produce not only productive but also deficit symptoms. Amphetamine is an indirect dopaminergic agonist. PCP has also traditionally been considered to exert its effects mainly via interactions with central dopaminergic systems (15). However, recently it has been shown that PCP, similarly to MK-801 and ketamine, is a noncompetitive NMDA antagonist. This finding, in conjunction with the clinical features of PCP, fit nicely with the hypothesis formulated by Kornhuber and colleagues (17) that glutamate deficiency may be an important pathophysiological component in schizophrenia. Considering the fact that the major glutamatergic pathways in the brain originate in the cerebral cortex such an hypothesis would also be in line with the cortical atrophy observed in schizophrenia. Moreover, it is in line with reports of hypometabolism in parts of the cortex in schizophrenia. Finally, studies showing alterations in glutamate receptor densities in schizophrenia are also in agreement with the hypothesis of an aberration in central glutamatergic systems in schizophrenia (18,20).

A currently held belief is that the NMDA antagonist-induced behavioural activation depends on enhanced catecholamine release. Accordingly, it has been suggested that a putative glutamate deficiency may cause schizophrenia by increasing dopaminergic tone (11). However, our experiments show that NMDA antagonists can cause behavioural stimulation via a *catecholamine-independent* mechanism. Given that our behavioural model can be regarded as a "schizophrenia model" (cf. amphetamine) it may be speculated that schizophrenia induced by a primary glutamate deficiency can emerge regardless and independently of central dopaminergic tone.

As has previously been suggested (3, 5, 11), an NMDA agonist acting at the glutamate receptor or an allosteric site of the receptor complex might be an interesting therapeutic alternative in schizophrenia. If the glutamate hypothesis of schizophrenia is

correct this could then be regarded as a kind of "substitution therapy." Moreover, our results with MK-801 in rodents suggest that decreased glutamatergic transmission results in an increased activational power of other transmitter systems. Thus, just as DA receptor blockers are effective in schizophrenia, it is possible that manipulation with adrenergic and/or cholinergic transmission may be beneficial. Noteworthy in this context is the observation that the "atypical" neuroleptic clozapine effectively antagonized the pronounced behavioural stimulation produced by MK-801/clonidine treatment, probably due to blockade of α_2-adrenoceptors (6); it is well known that clozapine is clinically effective in a subgroup of therapy-resistant schizophrenics (16). Also interesting in this context, in view of the pronounced synergism between MK-801 and atropine, is a report showing beneficial effects of physostigmine in the treatment of PCP-induced psychosis (7).

Implications for the Treatment of Parkinson's Disease

Could a substance like MK-801 (or perhaps preferably an orally active *competitive* NMDA antagonist) be used in the treatment of Parkinson's disease? Considering the pharmacological similarity to phencyclidine (PCP), how great are the risks for psychotic side effects and abuse? If brain reward mechanisms are intimately linked to catecholamine release the risk for abuse of an NMDA antagonist (given alone) might be minimal in Parkinson's disease, at least in later stages when the degeneration of catecholaminergic neurons is extensive. Possibly, it is also in this late phase, when the patient no longer responds to conventional pharmacological therapy, that an NMDA antagonist might be an important therapeutic supplement.

Considering the powerful synergism between, on one hand, MK-801 and clonidine/apomorphine/atropine on the other, observed in the present and previous studies, an interesting clinical approach might be to combine an NMDA antagonist with a catecholaminergic agonist or a muscarinic antagonist, in order to achieve an optimal therapeutic effect and a minimum of side effects.

ACKNOWLEDGEMENTS

The present study was supported by grants from MRF (155 and 9067), Stiftelsen för Gamla Tjänarinnor, Syskonen Svenssons Fond, Torsten och Ragnar Söderbergs Stiftelser, Stiftelsen Sigurd och Elsa Goljes Minne, Svenska Läkaresällskapet, Stiftelsen Handlanden Hjalmar Svenssons Forskningsfond, Kerstin and Bo Pfannenstills Stiftelse and Lundbecks Fond. We wish to thank Dr. G. N. Woodruff (MSD) for generously supplying MK-801. The excellent technical assistance of Kirsten Sönniksen is also gratefully acknowledged. Finally, we wish to thank research engineer Stellan Ahl for constructing the IR detectors used to quantify motor activity in the present study.

REFERENCES

1. Bartus, T. B.; Dean, R. L.; Flicker, C. Cholinergic psychopharmacology: an integration of human and animal research on memory. In: Meltzer, H. Y., ed. Psychopharmacology: The third generation of progress. New York: Raven Press; 1987:219–232.
2. Bylund, D. B. Subtypes of α_2-adrenoceptors: pharmacological and molecular biological evidence converge. Trends Pharmacol. Sci. 9:356–361; 1988.
3. Carlsson, A. The current status of the dopamine hypothesis of schizophrenia. Neuropsychopharmacology 1:179–186; 1988.
4. Carlsson, A. Drugs which block the storage and release of 5-hydroxytryptamine and related amines. In: Eichler, O.; Farah, A., eds. Handbook of experimental pharmacology. Vol. XIX: 5-Hydroxytryptamine and related indolealkylamines. Berlin: Springer-Verlag; 1965:529–592.
5. Carlsson, M.; Carlsson, A. The NMDA antagonist MK-801 causes marked locomotor stimulation in monoamine-depleted mice. J. Neural Transm. 75:221–226; 1989.
6. Carlsson, M.; Carlsson, A. Dramatic synergism between MK-801 and clonidine with respect to locomotor stimulatory effect in monoamine-depleted mice. J. Neural Transm. 77:65–71; 1989.
7. Castellani, S.; Gianni, A. J.; Adams, P. M. Physostigmine and haloperidol treatment of acute phencyclidine intoxication. Am. J. Psychiatry 139:508–510; 1982.
8. Childs, A. M.; Evans, R. H.; Watkins, J. C. The pharmacological selectivity of three NMDA antagonists. Eur. J. Pharmacol. 145: 81–86; 1988.
9. Clineschmidt, B. V.; Martin, G. E.; Bunting, P. R.; Papp, N. L. Central sympathomimetic activity of (+)-5-methyl-10,11-dihydro-5H-dibenzo(a,d)cyclohepten-5,10-imine (MK-801), a substance with potent anticonvulsant, central sympathomimetic and apparent anxiolytic properties. Drug Dev. Res. 2:135–145; 1982.
10. Cotman, C. W.; Monaghan, D. T. Chemistry and anatomy of excitatory amino acid systems. In: Meltzer, H. Y., ed. Psychopharmacology: The third generation of progress. New York: Raven Press; 1987:197–210.
11. Deutsch, S. I.; Mastropaolo, J.; Schwartz, B. L.; Rosse, R. B.; Morihisa, J. M. A "glutamatergic hypothesis" of schizophrenia. Clin. Neuropharmacol. 12:1–13; 1989.
12. Garcia-Sevilla, J. A.; Ahtee, L.; Magnusson, T.; Carlsson, A. Opiate-receptor mediated changes in monoamine synthesis in rat brain. J. Pharm. Pharmacol. 30:613–621; 1978.
13. Hiramatsu, M.; Cho, A. K.; Nabeshima, T. Comparison of the behavioural and biochemical effects of the NMDA receptor antagonists, MK-801 and phencyclidine. Eur. J. Pharmacol. 166:359–366; 1989.
14. Javitt, D. C. Negative schizophrenic symptomatology and the PCP (phencyclidine) model of schizophrenia. Hillside J. Clin. Psychiatry 9:12–35; 1987.
15. Johnson, K. M. Phencyclidine: behavioural and biochemical role supporting a role for dopamine. Fed. Proc. 42:2579–2583; 1983.
16. Kane, J. M.; Honigfeld, G.; Singer, J.; Meltzer, H. Clozapine in treatment-resistant schizophrenics. Psychopharmacol. Bull. 24:62–67; 1988.
17. Kornhuber, J.; Kornhuber, M. E. Presynaptic dopaminergic modulation of cortical input to the striatum. Life Sci. 39:669–674; 1986.
18. Kornhuber, J.; Mack-Burkhardt, F.; Riderer, P.; Hebenstreit, G. F.; Reynolds, G. P.; Andrews, H. B.; Beckmann, H. [^{3}H]MK-801 binding sites in postmortem brain regions of schizophrenic patients. J. Neural Transm. 77:231–236; 1989.
19. Michel, M. C.; Brodde, O.-E.; Schnepel, B.; Behrendt, J.; Tschada, R.; Motulsky, H. J.; Insel, P. A. [^{3}H]Idazoxan and some other α_2-adrenergic drugs also bind with high affinity to a nonadrenergic site. Mol. Pharmacol. 35:324–330; 1989.
20. Nishikawa, T.; Takashima, M.; Toru, N. Increased ^{3}H-kainic acid binding in the prefrontal cortex in schizophrenia. Neurosci. Lett. 40:245–250; 1983.
21. Raffa, R. B.; Ortegón, M. E. Robisch, D. M.; Martin, G. E. In vivo demonstration of the enhancement of MK-801 by L-glutamate. Life Sci. 44:1593–1599; 1989.
22. Schmidt, W. J.; Bury, D. Behavioural effects of N-methyl-D-aspartate in the anterodorsal striatum of the rat. Life Sci. 43:545–549; 1988.
23. Snyder, S. H. Phencyclidine. Nature 285:355–356; 1980.
24. Wikberg, J. E. S. High affinity binding of idazoxan to a non-catecholaminergic binding site in the central nervous system: description of a putative idazoxan-receptor. Pharmacol. Toxicol. 64:152–155; 1989.
25. Villablanca, J. R.; Marcus, R. J.; Olmstead, C. E. Effects of caudate nuclei or frontal cortical ablations in cats. I. Neurology and gross behavior. Exp. Neurol. 52:389–420; 1976.
26. Wong, E. H. F.; Kemp, J. A.; Priestley, T.; Knight, A. R.; Woodruff, G. N.; Iversen, L. L. The anticonvulsant MK-801 is a potent N-methyl-D-aspartate antagonist. Proc. Natl. Acad. Sci. USA 83:7104–7108; 1986.