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MK 801 reverses haloperidol-induced catalepsy from both striatal and extrastriatal sites in the rat brain

Simranjit Kaur, Hülya Özer, Michael Starr *

Department of Pharmacology, School of Pharmacy, 29–39 Brunswick Square, London WC1N 1AX, UK

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Abstract

The present study investigated whether the anticataleptic effect of (+)-5-methyl-10,11-dihydro-5H-dibenzo(a,d)-cyclohepten-5,10-imine (MK 801) is due to a blockade of *N*-methyl-D-aspartate (NMDA) receptors in striatal output pathways as well as in the striatum. Catalepsy induced by haloperidol (1 mg/kg i.p.) was more effectively reversed by MK 801 (0.2 mg/kg i.p.) given 10 min prior to rather than 45 min after the neuroleptic. Catalepsy evoked by intrastriatal haloperidol (7 μg/side) was also strongly attenuated by systemic MK 801 (0.2 mg/kg i.p.). We also found that the cataleptic rigidity induced by systemic haloperidol (1 mg/kg i.p.) could be prevented by prior injection of MK 801 into the striatum (10 μg), subthalamic nucleus (5 μg), entopeduncular nucleus (5 μg) or substantia nigra pars reticulata (1 μg). These results suggest that the anticataleptic action of systemic MK 801 versus haloperidol, is due to the blockade of NMDA receptors in the striatum as well as in striatal output circuits through the subthalamus. However, systemic MK 801 (0.2 mg/kg i.p.) was without effect on the catalepsy elicited by injecting muscimol into the globus pallidus (25 ng) or ventromedial thalamus (50 ng). These findings suggest that MK 801 has little influence over thalamic excitatory feedback to the cortex, and that hypoactivity of the pallidum may not be a prerequisite for hyperactivity in the subthalamus. © 1997 Elsevier Science B.V.

Keywords: Catalepsy; Haloperidol; Muscimol; MK 801

1. Introduction

There is growing evidence that dopamine depletion, as occurs in Parkinson's disease, results in an overactivity of glutamate-containing neurones within the basal ganglia and that this pathological increase in glutamate release contributes to the poverty of movement and the postural abnormalities that are the hallmarks of this disorder (for reviews see Greenamyre and O'Brien, 1991; Greenamyre, 1993; Ossowska, 1994; Starr, 1995a,b; Blandini et al., 1996). It is widely supposed that the glutamatergic cortical input to the striatum, as well as the glutamatergic neurones that make up the efferent projections from the subthalamic nucleus and which serve as a way-station for striatal output through the external globus pallidus, become disinhibited in the Parkinsonian brain, as illustrated in Fig. 1 (see also Albin et al., 1989; Gerfen, 1992). This being the case, a pharmacological blockade of glutamate receptors both within the striatum and subthalamic circuits, should theoretically reduce the heightened inhibitory feedback from the basal ganglia to the cortex and alleviate the motor deficiencies of Parkinsonism. In keeping with this proposal, there is now a large body of experimental evidence to indicate that glutamate receptor antagonists do indeed possess anti-Parkinsonian properties in animal models, both alone and when administered in conjunction with the standard anti-Parkinson agent L-dihydroxphenylalanine (L-DOPA; Klockgether and Turski, 1989; Klockgether et al., 1990; Klockgether et al., 1994).

The akinesia and muscular rigidity of Parkinsonism is conveniently reproduced by the administration of a typical neuroleptic agent, such as haloperidol and haloperidol-induced catalepsy has consequently been widely used to investigate the functional relationship between glutamate overactivity and dopamine deficiency with respect to motor behaviour (Kornhuber et al., 1993; Ossowska, 1994). The catalepsy induced by haloperidol is thought to derive principally from the striatum, and using intracerebral microinjection of haloperidol Yoshida et al. (1994) have identified a hot-spot for haloperidol-evoked catalepsy in the rostral ventromedial aspect of this structure. Of the glutamate receptor antagonists examined for anticataleptic

* Corresponding author. Tel.: (44-171) 753-5901; Fax: (44-171) 753-5902; e-mail: mstarr@cua.ulsop.ac.uk

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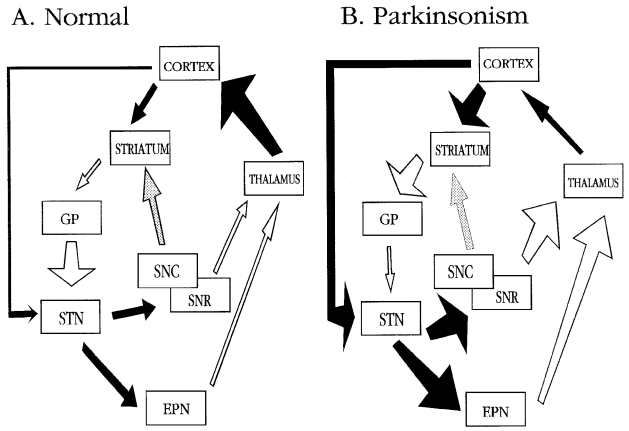

Fig. 1. Schematic view of the functional anatomy of the basal ganglia in the normal and parkinsonian brain. The size of the arrows reflects the activity of the pathways. Inhibitory GABAergic projections are indicated by open arrows, excitatory glutamatergic projections by solid arrows and the nigrostriatal dopamine projection by the stippled arrow. GP, globus pallidus; STN, subthalamic nucleus; EPN, entopeduncular nucleus; SNC, substantia nigra pars compacta; SNR, substantia nigra pars reticulata.

activity, the non-competitive (NMDA) receptor-channel blocker (+)-5-methyl-10,11-dihydro-5H-dibenzo(a,d)-cyclohepten-5,10-imine (MK 801) turns out to be one of the most potent (reviewed in Schmidt et al., 1992; Ossowska, 1994). Thus MK 801 actively reversed the catalepsy that was elicited by administering neuroleptic drugs systemically (Elliott et al., 1990; Mehta and Ticku, 1990; Verma and Kulkarni, 1992; Papa et al., 1993), or when a neuroleptic was injected directly into the striatum (Elliott et al., 1990). Clearly the striatum is an important locus for the motor restorative action of glutamate receptor antagonists in this model, since in a parallel microinjection study Yoshida et al. (1994) uncovered a similar hot-spot for the anticataleptic action of the competitive NMDA receptor antagonist 2-amino-5-phosphonopentanoic acid (AP-5) in the dorsorostral striatum, just above that for haloperidol. Such is the interest in the prospect of developing selective antagonists of basal ganglia NMDA receptors for the symptomatic treatment of Parkinson's disease, that current research is focussing on the differential distribution of NMDA receptor subunits in the basal ganglia and the feasibility of developing pharmacological agents that block these NMDA receptors selectively (Standaert et al., 1994).

As already mentioned, however, the efferent projections from the subthalamic nucleus to the internal globus pallidus (entopeduncular nucleus in rodents) and substantia nigra pars reticulata are also believed to utilise glutamate as their neurotransmitter and to become hyperactive when striatal dopaminergic activity is compromised (see Albin et al., 1989). The importance of this excitatory pathway in the expression of Parkinsonian symptomatology, is evidenced by the fact that high frequency electrical stimulation-inactivation of the subthalamic nucleus (Limousin et al., 1995) and pallidotomy in man (Klockgether et al., 1994; Lozano et al., 1995) are able to restore a significant measure of voluntary movement to sufferers of Parkinson's disease. A pharmacological blockade of glutamate receptors in the subthalamic nucleus, entopeduncular nucleus and substantia nigra pars reticulata has also been shown to reverse reserpine-induced akinesia (Klockgether and Turski, 1990) and Schuster (1990) has reported that intranigral injections of the competitive NMDA receptor antagonist AP-5 can attenuate haloperidol-induced catalepsy. Otherwise the effects of blocking NMDA receptors in these nuclei on neuroleptic-induced catalepsy have not been systematically studied and so this was one of the aims of the present investigation.

A second aim of this study concerned the role of the external pallidum in the so-called indirect striatal output pathway. Fig. 1 shows the external pallidum receiving information from the striatum via a γ-aminobutyric acidergic (GABAergic) connection and in turn sending a GABAergic projection to the subthalamic nucleus, in line with current thinking (Albin et al., 1989). The interposition of the external pallidum in this output circuit has recently been challenged, however, with Levy et al. (1997) presenting evidence that argues against hypoactivity of the external pallidum as being the direct cause of hyperactivity of the subthalamic nucleus. We have attempted to address this question by inducing catalepsy in rats with bilateral injections of muscimol into the globus pallidus (Scheel-Krüger et al., 1981), since this should mimic any hypoactivity of the external pallidum resulting from the blockade of striatal dopamine receptors and hence be equally susceptible to the anticataleptic effect of MK 801. As a further control, the effects of MK 801 on the catalepsy evoked by depositing muscimol into the ventromedial nucleus of the thalamus (Starr and Summerhayes, 1983), which resides further along the presumed striatal output chain, were also investigated.

2. Materials and methods

2.1. Animals

Male Wister albino rats (A.R. Tuck) weighing 180–300 g were used. The animals were housed in groups of six at 22 ± 1°C under fluorescent lighting between 10.00 and 17.00 h and allowed free access to rat chow and water. Experiments were conducted between 9.30 and 17.30 h and each animal was used not more than twice, with a washout period of one week between experiments. All experiments were carried out in accordance with the Animals (Scientific Procedures) Act 1976.

2.2. Induction and measurement of catalepsy

In one set of experiments catalepsy was induced by injecting haloperidol (1 mg/kg i.p.) and the rats were

placed singly into Perspex observation cages (28 × 24 × 21 cm high). 30 min later, the rats were placed with their front paws over a horizontal bar at a height of 8 cm above the floor (Morelli and Di Chiara, 1985). Descent latencies (s) were measured up to a maximum of 360 s, every 15 min for a total period of 2 h.

In a second set of experiments, rats were anaesthetised with halothane (4% (w/v) in oxygen for induction, 2% (w/v) in oxygen for maintenance) and secured in a Kopf stereotaxic frame. The scalp was resected and fine burr holes drilled in the skull to permit the introduction of a 10 μl Hamilton syringe, after rupturing the meninges with a hypodermic needle. Catalepsy was elicited by microinjecting haloperidol (7 μg) bilaterally into the striatum, or by injecting muscimol bilaterally into the globus pallidus (25 ng) or ventromedial thalamus (50 ng). Injections were delivered slowly over a period of 2.5 min and a further 2 min allowed to elapse before slowing withdrawing the injection needle. Injection coordinates were determined with reference to the stereotaxic atlas of Paxinos and Watson (1986) as follows: striatum A + 1.2 mm from bregma, L 1.5 mm from midline, V 5.5. mm from brain surface; globus pallidus A − 0.8, L 2.8, V 6.2; ventromedial thalamus A − 2.3, L 1.2, V 6.9. The wound was then cleaned with an antiseptic (Savlon) and a local anaesthetic cream (Emla) and closed with a suture. After surgery, the rats were allowed to recover for 30 min in a Perspex observation box as above and measurements of catalepsy commenced after 30 min.

2.3. Effects of MK 801 on haloperidol-induced catalepsy

To investigate the anticataleptic effect of MK 801 versus systemic haloperidol, the NMDA receptor antagonist (0.2 mg/kg i.p.) was either given 10 min prior to, or 45 min after the injection of haloperidol. In those experiments in which catalepsy was induced with intrastriatal haloperidol (see Section 2.2), MK 801 (0.2 mg/kg i.p.) was administered 60 min post-haloperidol, at which time the catalepsy was fully established. Controls received an equivalent volume of distilled water.

In a further study, we first injected MK 801 bilaterally into the striatum (10 μg), subthalamic nucleus (5 μg), entopeduncular nucleus (5 μg) or substantia nigra pars reticulata (1 μg), using standard stereotaxic procedures as described above. Injection coordinates according to Paxinos and Watson (1986) were: striatum A + 1.2, L 1.5, V 5.5; subthalamic nucleus A − 3.8, L 2.5, V 7.6; entopeduncular nucleus A − 2.8, L 2.9, V 7.4; substantia nigra pars reticulata A − 5.3, L 2.5, V 7.8. Controls received an equivalent volume of distilled water. The animals were allowed to recover consciousness and were injected 45 min later with haloperidol (1 mg/kg i.p.) and catalepsy measurements begun after a further 15 min.

2.4. Effects of MK 801 on catalepsy derived from the globus pallidus or ventromedial thalamus

Rats were injected with muscimol bilaterally into the globus pallidus or ventromedial thalamus under halothane anaesthesia as described above. They were then allowed to regain consciousness and catalepsy measurements begun 30 min later. At $t = 60$ min the rats then received an i.p. injection of MK 801 (0.2 mg/kg) or distilled water (controls) and catalepsy measurements continued for a further 90 min.

2.5. Histology

At the end of each intracerebral microinjection experiment the animals were guillotined and their brains removed and placed in formol saline (pH 7.2). After three weeks fixation the brains were placed on a freezing microtome and 20 μm sections cut for microscopic inspection. Only those animals exhibiting correct placement of needle tracks in a designated brain nucleus were used for data analysis.

2.6. Statistics

Descent latencies (s) for MK 801-treated rats were compared with controls by analysis of variance (ANOVA) with post hoc analysis of individual differences by one-tailed Student's *t*-test. In all cases significance was taken as $P < 0.05$.

2.7. Drugs

Haloperidol (Sigma, Poole, UK), muscimol (Sigma) and (+)-5-methyl-10,11-dihydro-5H-dibenzo(a,d)-cyclohepten-5,10-imine (MK 801; Research Biochemicals International, Natick, MA, USA) were dissolved in distilled water. The solution of haloperidol was added to a minimum volume of glacial acetic acid and made up to volume with water. All intracerebral microinjections were delivered in a volume of 0.5 μl, while systemic injections of drugs were given in a volume of 1 ml/kg. Controls received an equivalent volume of distilled water. In most cases the choice of drug dose was based either on a survey of the literature or on pilot dose–response studies conducted in this laboratory.

3. Results

Haloperidol, 1 mg/kg i.p., produced marked catalepsy within 30 min of injection with the animals remaining on the horizontal bar for the full 360 s test period (Fig. 1).

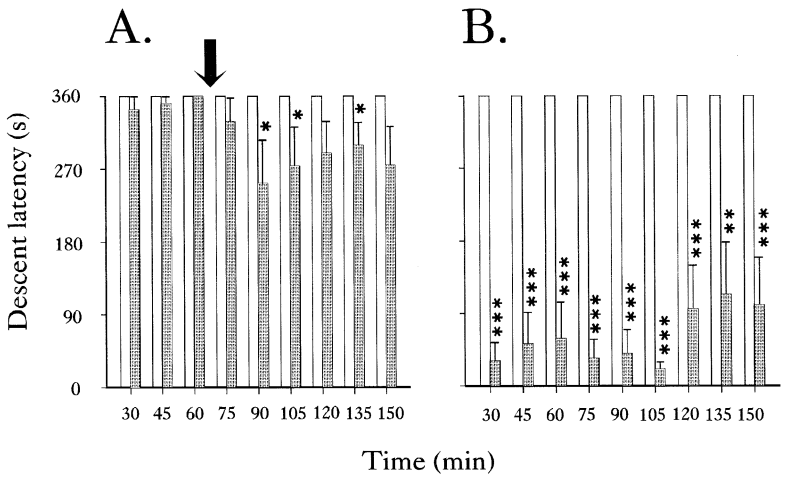

Fig. 2. Suppression of haloperidol-induced catalepsy by MK 801. (A) Rats were injected with haloperidol, 1 mg/kg i.p. and tested for catalepsy every 15 min for 150 min by the horizontal bar test (see Section 2 for details). At the arrow rats received a control injection of distilled water (1 ml/kg i.p., open bars) or MK 801 (0.2 mg/kg i.p., stippled bars). Each result is the mean ± S.E.M. of six experiments. * $P < 0.05$ versus controls by Student's *t*-test. (B) Experiments were conducted as in (A), except that vehicle and MK 801 injections were administered 10 min before the neuroleptic. ** $P < 0.005$, *** $P < 0.001$ versus controls by Student's *t*-test.

This response remained undiminished for the duration of the experiment (150 min). MK 801, 0.2 mg/kg i.p., administered 45 min after the neuroleptic, significantly reduced the descent latency after a delay of 45 min ($P < 0.05$, Fig. 1A). By contrast, when the same dose of MK 801 was given as a pretreatment, 10 min before the haloperidol, a much more profound and long-lasting suppression of the resultant catalepsy was obtained ($P < 0.001$, Fig. 2B). In this instance the MK 801 elicited behavioural stimulation which included forward ambulation and pronounced sniffing.

A similarly robust catalepsy was evoked by injecting haloperidol, 7 μg in 0.5 μl, bilaterally into the rostral ventromedial striatum, corresponding to the hot-spot for haloperidol-induced catalepsy described by other investigators (Ellenbroek et al., 1985; Yoshida et al., 1994). All animals that were treated in this way recorded maximum 360 s descent latencies 90 min post-injection (Fig. 3). MK

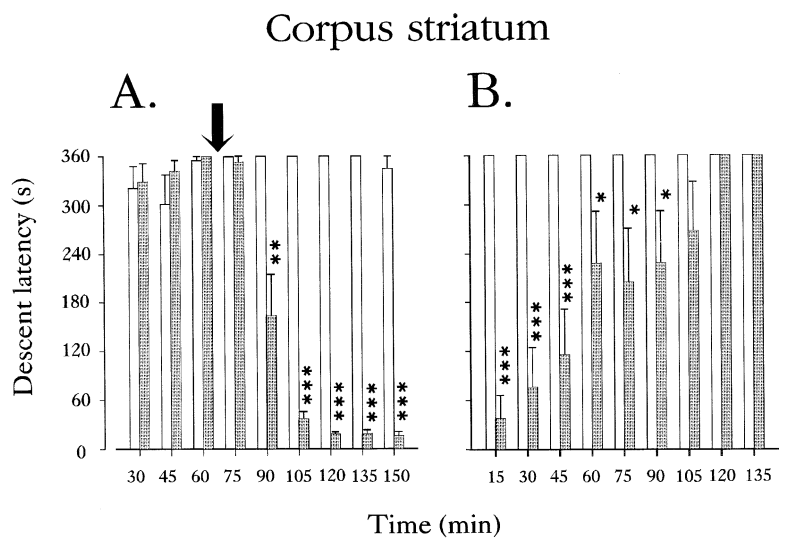

Fig. 3. Antagonism of haloperidol-induced catalepsy by MK 801. (A) Rats were anaesthetised with halothane and prepared for acute bilateral injection of haloperidol (7 μg/side) into the anteroventral striatum (see Section 2 for details). Following injection, the rats were allowed to recover consciousness and assessed for cataleptic rigidity at $t = 30$ min, every 15 min for 150 min, using the horizontal bar test. At the arrow, rats received a control injection of distilled water (1 ml/kg i.p., open bars) or MK 801 (0.2 mg/kg i.p., stippled bars). Each result is the mean ± S.E.M. of six determinations. ** $P < 0.01$, *** $P < 0.001$ versus controls by Student's *t*-test. (B) Similar experiment to (A), except that MK 801 (10 μg/side, stippled columns) or distilled water (0.5 μl/side, controls, open columns) was injected bilaterally into the striatum under halothane anaesthesia and the rats allowed to recover consciousness and then injected 45 min later with haloperidol (1 mg/kg i.p.). * $P < 0.05$, *** $P < 0.001$ versus controls by Student's *t*-test.

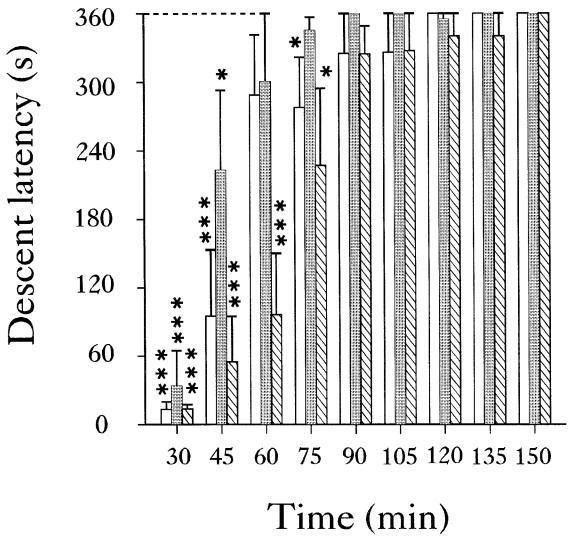

Fig. 4. Effects of MK 801 injected into the indirect striatal output pathway on the development of haloperidol-induced anaesthesia. Rats were anaesthetised with halothane and injected bilaterally with MK 801 or vehicle in the substantia nigra pars reticulata (1 μg MK 801, open columns), entopeduncular nucleus (5 μg MK 801, stippled columns) or the subthalamic nucleus (5 μg MK 801, hatched columns). The rats were then allowed to regain consciousness and injected 45 min later with haloperidol (1 mg/kg i.p.). Testing for catalepsy by the horizontal bar test began 15 min later. Control animals received distilled water in place of MK 801 into the appropriate nuclei and in each case registered a maximum 360 s descent latency (shown by the dotted line) at the first 15 min test period. Each result is the mean ± S.E.M. of six determinations. * $P < 0.05$, *** $P < 0.001$ versus controls by Student's *t*-test.

801, 0.2 mg/kg i.p., administered 60 min after haloperidol, rapidly and almost completely reversed the attendant catalepsy ($P < 0.001$), whilst vehicle-treated control rats remained profoundly cataleptic (Fig. 3A). The converse experiment, in which MK 801 (10 μg in 0.5 μl) was microinjected bilaterally into the striatum under halothane anaesthesia, followed by recovery and injection of haloperidol (1 mg/kg i.p.) 45 min later, is shown in Fig. 3B. Vehicle-treated rats were fully cataleptic within 15 min of receiving the neuroleptic, whereas MK 801-treated animals displayed a gradually increasing level of muscle rigidity over a period of 2 h, reflecting an anticataleptic action of MK 801 within the striatum that subsided with time.

To determine if the anticataleptic response to systemic MK 801 was confined to the striatum, we repeated the latter experiment by microinjecting MK 801 into presumed glutamatergic nuclei lying within the indirect striatal output pathway. Fig. 4 demonstrates that prior treatment of the substantia nigra pars reticulata, entopeduncular nucleus or subthalamic nucleus with 1, 5 and 5 μg MK 801, respectively, was sufficient in each case to delay the onset of catalepsy induced by the subsequent systemic administration of 1 mg/kg haloperidol. MK 801 appeared to be equiactive in this respect at all three brain sites at the first test period, 1 h post-injection (i.e., 15 min after haloperidol), but the anticataleptic effect then wore off more rapidly in the entopeduncular nucleus than in the substantia nigra pars reticulata or subthalamic nucleus (Fig. 4). Rats receiving control injections of water into the substantia nigra pars reticulata, entopeduncular nucleus or subthalamic nucleus developed a full cataleptic response (360 s descent latency) which remained constant for the duration of the experiment.

A profound but shorter-lived catalepsy was also obtained by injecting the $GABA_A$ receptor agonist muscimol bilaterally into the globus pallidus (25 ng) or ventromedial thalamus (50 ng), as illustrated in Fig. 5. In each case, the subsequent injection of MK 801 (0.2 mg/kg i.p. at $t = 60$

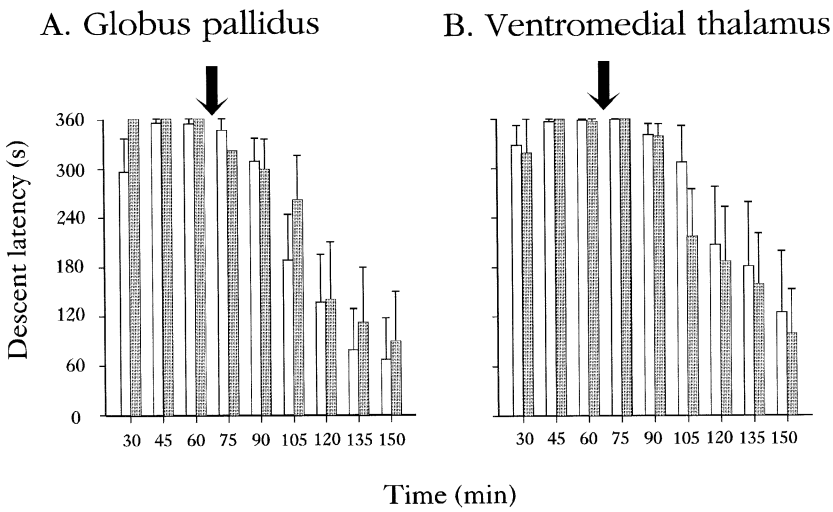

Fig. 5. Lack of effect of MK 801 on catalepsy induced by muscimol injected bilaterally into the globus pallidus (A) or ventromedial nucleus of the thalamus (B). Rats were anaesthetised with halothane and muscimol was then injected into the pallidum (25 ng) or thalamus (50 ng). Catalepsy developed rapidly on recovery from the anaesthetic and reached a plateau after 60 min. At the arrow, rats were injected with water (controls, open columns) or MK 801 (0.2 mg/kg i.p., stippled columns). Each result is the mean ± S.E.M. of six determinations.

min) did not affect the animals' rate of recovery from catalepsy, as compared with vehicle-treated controls.

4. Discussion

Dopamine and glutamate are widely recognised as having opposite effects on motor behaviour, with dopamine being excitatory and glutamate inhibitory (Schmidt, 1986; Schmidt et al., 1992). This means that the poverty of movement which is so characteristic of Parkinson-like symptoms, can just as readily be ascribed to an increase in the activity of glutamate in the basal ganglia, as to a decrease in the activity of dopamine (Albin et al., 1989; Gerfen, 1992). Taking this argument a step further, antagonists of glutamate at its receptors should therefore provide an alternative pharmacological approach to the symptomatic treatment of Parkinsonism (Klockgether and Turski, 1989). By and large, this supposition is largely borne out by experiment, with a wide variety of glutamate receptor antagonists demonstrating anti-Parkinsonian qualities in dopamine-deficient animals (Klockgether et al., 1990; Greenamyre and O'Brien, 1991; Greenamyre, 1993; Ossowska, 1994; Starr, 1995a,b; Blandini et al., 1996). The unwelcome side effects exhibited by the newer, potent glutamate receptor antagonists (e.g., MK 801), would preclude their use in the treatment of Parkinsonism in man, whereas the recently discovered weaker glutamate receptor antagonistic properties of older generation anti-Parkinsonian drugs (e.g., amantadine, memantine, see Danysz et al., 1994) could help to explain their clinical efficacy, which has eluded us so far.

The ability of NMDA receptor antagonists to overcome the hypolocomotion (Hauber and Schmidt, 1990), catalepsy (Elliott et al., 1990; Verma and Kulkarni, 1992; Papa et al., 1993) or muscular rigidity (Ellenbroek et al., 1985) induced by dopamine receptor blockers, is frequently used to assess their anti-Parkinsonian potential. These tests reveal MK 801 as being one of the most potent agents, with maximum efficacy occurring in the dose range 0.04–0.5 mg/kg (see Ossowska, 1994). Our present data confirm this and further show that pretreatment with MK 801 is far more potent at preventing the catalepsy induced by haloperidol, than it is at reversing such catalepsy once it has already been established (Fig. 2). The reason for this difference is not immediately clear. In fact, if anything, we might have expected MK 801 to be more effective in the former situation. This is because haloperidol is believed to disinhibit glutamate release in the striatum, as lesioning the corticostriatal glutamatergic pathway has been found to inhibit haloperidol-induced catalepsy, whilst focal intrastriatal injection of NMDA into cortically-ablated rats was shown to restore it (Yoshida et al., 1991). Haloperidol consequently increases glutamatergic tone in the striatum and it is the blockade of this elevated excitatory tone by both competitive and non-competitive NMDA receptor antagonists that partially accounts for their anticataleptic action (Yoshida et al., 1991). However, since MK 801 is a use-dependent antagonist of the NMDA receptor-cation channel, it would be expected to produce a more profound degree of NMDA receptor blockade when glutamatergic tone is high and the associated ion channels are held open, as would occur when the injection of haloperidol preceded that of MK 801. That the reverse occurred suggests the behavioural interaction between MK 801 and haloperidol cannot be explained in these simple terms.

Haloperidol-induced catalepsy is reputed to have its origins in dopamine receptor blockade in the ventral aspect of the rostral striatal complex, as evidenced by the profound catalepsy that develops when haloperidol is injected discretely into the rostral ventromedial striatum (Ellenbroek et al., 1985; Yoshida et al., 1994), or into the subjacent nucleus accumbens (Ossowska et al., 1990). We also found that haloperidol elicited a profound cataleptic state in rats that received the drug in the anteroventral striatum and, interestingly, that this was practically abolished by a subsequent systemic dose of MK 801 (0.2 mg/kg i.p.) which was minimally effective versus haloperidol given systemically. This finding demonstrates that MK 801 is rapidly absorbed into the circulation from the peritoneal cavity and enters the brain within a few minutes of injection and so its relative inefficacy against systemic haloperidol cannot be due to problems of bioavailability. The densities of NMDA receptors are especially high in the striatum and nucleus accumbens (Albin et al., 1992) and MK 801 binds avidly to these structures (Sakurai et al., 1993). It is not unreasonable to assume, therefore, that a substantial part of MK 801's anticataleptic action derives from the striatal complex and that its ability to counteract striatally-derived catalepsy will also be greater. This assumption is supported by our finding that MK 801 also strongly attenuated haloperidol-induced catalepsy when the NMDA receptor antagonist was injected focally into the striatum (Fig. 3 above). This result concurs with the ability of intrastriatal AP-5 to attenuate haloperidol-induced catalepsy (Yoshida et al., 1991), but contrasts with the lack of motor stimulant effect of intrastriatal MK 801 in the reserpine-treated (Kaur and Starr, 1997) or 6-hydroxydopamine-lesioned rat (St-Pierre and Bédard, 1994), probably because the action of MK 801 depends to a large extent on the release of endogenous dopamine.

Systematic mapping studies of the behavioural sensitivity of the striatum to locally-applied NMDA receptor antagonists, have rather focussed attention on the anterior striatum as an important site for stimulating motor activity and for combatting the motor deficiencies associated with neuroleptic treatment. As a result, the effects of blocking hyperactive glutamatergic synapses in the striatal output pathway innervating the subthalamic nucleus (see Fig. 1), have tended to be overlooked, although it is well known that suppression of subthalamic nucleus activity is com-

mensurate with a strengthening of motor performance. Klockgether and Turski (1990) reported that NMDA and α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA) receptor antagonists infused into the substantia nigra pars reticulata, entopeduncular nucleus or subthalamic nucleus were capable of reversing reserpine-induced akinesia in the rat and Schuster (1990) has similarly recorded that haloperidol-induced rigidity is reversed by AP-5 injected into the nigra. The present work extends these limited observations and shows that MK 801 deposited into any one of these nuclei is similarly effective at overcoming haloperidol-induced catalepsy. With each treatment the rats showed little inclination to assume an imposed posture on the horizontal bar 1 h after MK 801 injection (i.e., 15 min after haloperidol), but in every case the effect had worn off by 2 h. Collectively these data provide evidence that the blockade of the glutamatergic output from the striatum, is potentially just as important as blocking the cortical input to the striatum as far as the motor stimulant effects of MK 801 are concerned.

When striatal dopamine function is reduced, as in Parkinsonism or when a neuroleptic is administered, inhibitory GABAergic input is increased both to the globus pallidus and the ventromedial thalamus (Fig. 1). Injecting GABA agonists into the pallidum or ventromedial thalamus of a normal animal should therefore also elicit catalepsy and indeed this is found to be the case (Scheel-Krüger et al., 1981; Starr and Summerhayes, 1983). Since the presumed feedback circuit from the thalamus to the cortex is probably glutamatergic, then blocking this excitatory feedback by administering a glutamate receptor antagonist would, if anything, reduce motor activity still further and might explain the deleterious effects of high doses of certain glutamate receptor antagonists on voluntary movement and posture (Löschmann et al., 1991). In the present study, however, we saw no evidence of an intensification of thalamus-derived catalepsy to support this proposal. However, it would be premature to discount a motor-inhibitory action of glutamate receptor antagonists within the cortex, since we currently have no satisfactory explanation as to why glutamate receptor antagonists are often able to overcome reserpine-induced akinesia when these are injected focally into basal ganglia nuclei, but not when they are administered systemically (see reviews by Starr, 1995a,b). The most parsimonious explanation for this discrepancy, is that the beneficial effects of glutamate receptor blockade in the striatum, nigra, entopeduncular nucleus and subthalamus are counterbalanced by a deleterious action at glutamatergic synapses situated further along this motor pathway and the cortex would seem to be an obvious choice.

The failure of MK 801 to alleviate the catalepsy derived from injecting a $GABA_A$ receptor agonist into the globus pallidus was not expected, however, and this finding could have an important bearing on whether we think that hypoactivity of the pallidum contributes to hyperactivity of the subthalamus in parkinsonian animals. Current models of the functional anatomy of the basal ganglia interpose the external globus pallidus between the striatum and subthalamus, within the so-called indirect output pathway from the striatum (Albin et al., 1989; Gerfen, 1992; Starr, 1995a,b). Levy et al. (1997) have recently challenged this view, quoting evidence from biochemical studies which failed to detect any reduction in the pallidum of the messenger RNA encoding for the synthesising enzyme for GABA, or in metabolic activity as revealed by the enzyme cytochrome oxidase. Since we found that MK 801 attenuated the catalepsy produced by haloperidol injected into the striatum, but not that elicited by muscimol injected into the globus pallidus, it could be argued that increased GABAergic activity in the pallidal complex does not per se lead to overactivity of glutamatergic efferents from the subthalamus. A more direct test of this argument would be to induce catalepsy with muscimol in the pallidum and then show this is not influenced by MK 801 deposited in the subthalamus.

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