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# Prazosin inhibits MK-801-induced hyperlocomotion and dopamine release in the nucleus accumbens

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**Abstract**

This study examined the putative inhibitory effect of the $\alpha_1$-adrenoceptor antagonist prazosin (1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)piperazine) on changes evoked by the psychotomimetic, non-competitive NMDA receptor antagonist, MK-801((+)-5-methyl-10,11-dihydroxy-5*H*-dibenzo-(*a*,*d*)cyclohepten-5,10-imine), in locomotor activity and extracellular concentrations of dopamine and its metabolites, dihydroxyphenylacetic acid (DOPAC) and homovanillic acid (HVA), and the serotonin metabolite 5-hydroxyindoleacetic acid (5-HIAA) in the nucleus accumbens as assessed by microdialysis in freely moving rats. MK-801 (0.1 and 0.3 mg/kg, s.c.) induced a significant, dose-dependent increase in horizontal locomotor activity but did not affect rearing. Prazosin administration alone (1 mg/kg, s.c.) only slightly reduced horizontal activity during an initial 10 min measurement period, although it consistently reduced rearing. However, pretreatment with prazosin effectively suppressed the locomotor stimulation caused by either dose of MK-801 throughout the whole observation period, i.e. 40 min. Both doses of MK-801 significantly increased extracellular levels of dopamine in the nucleus accumbens up to approximately 90%. In addition, MK-801 dose dependently increased dopamine metabolite concentrations in the nucleus accumbens, but 5-HIAA was significantly increased only by the high dose of MK-801. When given alone, prazosin did not affect either dopamine, DOPAC, HVA or 5-HIAA levels. However, prazosin pretreatment effectively blocked MK-801-evoked increases in dialysate dopamine concentrations. Consequently, the potent and selective $\alpha_1$-adrenoceptor antagonist prazosin was found to specifically suppress MK-801-evoked, but not basal dopamine release in the nucleus accumbens, while effectively blocking MK-801-evoked locomotor stimulation with only negligible effects on basal locomotor activity. Thus, $\alpha_1$-adrenoceptor antagonism may act by reducing the sensitivity of the mesolimbic dopamine system to pharmacological or environmental challenge. Since most antipsychotic drugs exhibit both dopamine $D_2$ receptor and $\alpha_1$-adrenoceptor antagonistic properties, they may alleviate psychosis not only through blockade of postsynaptic dopamine receptors, but also presynaptically on the mesolimbic dopamine system, through their $\alpha_1$-adrenoceptor antagonistic action. This latter action may contribute to reduce evoked dopamine hyperactivity, e.g. in response to stress.

*Keywords:* $\alpha_1$-Adrenoceptor antagonist; Microdialysis; NMDA receptor; Dizocilpine maleate; Locomotion

## 1. Introduction

During the last 35 years many reports have described a drug-related psychosis remarkably similar to schizophrenia, induced by phencyclidine (PCP). Unlike the amphetamine-induced paranoid psychosis, the PCP-induced psychosis may exhibit both positive symptoms of schizophrenia, such as auditory hallucinations and paranoid ideations, as well as negative symptoms, i.e. flattening of affect, impaired attention and motivation. The PCP-induced psychosis also frequently incorporates the formal thought disorder and neuropsychological deficits typically associated with schizophrenia (see Javitt and Zukin, 1991).

PCP has been shown to interact with several neuronal binding sites in the brain, including NMDA receptors and $\sigma$ binding sites, as well as the reuptake carriers for both catecholamines and serotonin. However, in psychotomimetic doses, PCP appears to predominantly act as a non-competitive antagonist at NMDA receptors (see Javitt and Zukin, 1991), as does the approximately 15-fold more potent, and considerably more selective, ligand dizocilpine (MK-801, Wong et al., 1986; see Kornhuber and Weller, 1995), which also blocks peripheral nicotinic receptors. When administered to rodents, PCP-like, non-competitive

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NMDA receptor antagonists, including MK-801, induce effects such as hyperlocomotion, ataxia and stereotypies, a behavioral syndrome which has been proposed as an animal model of schizophrenia (Contreras et al., 1987). This model is also consonant with findings of reduced glutamatergic activity in the brain in schizophrenic patients (see Moghaddam, 1994). The hyperlocomotion evoked by PCP or MK-801 administration in low doses can be abolished or largely attenuated by depletion of dopamine from neuronal stores by pretreatment with reserpine and/or α-methyl-*p*-tyrosine (Fessler et al., 1980; Clineschmidt et al., 1982; Criswell et al., 1993; Willins et al., 1993), or by administration of dopamine receptor antagonists (Clineschmidt et al., 1982; Ögren and Goldstein, 1994), indicating that the major behavioral effects of PCP and MK-801 are dopamine-dependent. Thus, the threshold dose of MK-801 to induce locomotor stimulation has been found to be approximately 10-fold lower in monoaminergically intact animals than in those depleted of brain monoamines (Clineschmidt et al., 1982; Carlsson and Carlsson, 1989; Willins et al., 1993; Martin et al., 1994). Nevertheless, evidence also exists that systemically administered MK-801 can, indeed, evoke some locomotor activity in monoamine-depleted animals, although only in rather high doses (i.e. $> 0.25$ mg/kg). Such data suggest that catecholamine-independent mechanisms may also be involved in the behavioral stimulant action of MK-801 (Carlsson and Carlsson, 1989; Criswell et al., 1993; Ouagazzal et al., 1994). However, the relative contributions of the dopamine-dependent, presynaptic, and the dopamine-independent, postsynaptic, mechanisms for the locomotor stimulation induced by non-competitive NMDA receptor antagonists remain to be unequivocally established.

Previously, we and others have demonstrated that systemic administration of PCP or MK-801 indeed stimulates the activity of most mesolimbic dopamine neurons within the ventral tegmental area, as expressed by both an increased firing rate and an increased percentage of spikes in bursts (Pawlowski et al., 1990; Zhang et al., 1992; French et al., 1993; Murase et al., 1993). Moreover, several studies indicate that burst activity in midbrain dopamine neurons is associated with a much larger release of dopamine in terminal areas than regular activity with the same average frequency (Gonon, 1988; Bean and Roth, 1991). Our recent work has also shown that burst activity in midbrain dopamine neurons preferentially activates postsynaptic neurons, as judged by their expression of *c-fos*, whereas regular activity is ineffective in this regard (Chergui et al., 1996). Thus, the MK-801-induced stimulation of mesolimbic dopamine neuronal activity should result in an enhanced release of dopamine within target areas, e.g. the nucleus accumbens, and also in a significant effect on the activity of postsynaptic neurons. Accordingly, several biochemical studies report an increase in dopamine turnover within the nucleus accumbens after MK-801 administration (Bubser et al., 1992; Löscher et al., 1993; Dai et al., 1995). Similarly, some studies utilizing microdialysis report elevated extracellular dopamine levels in the nucleus accumbens and prefrontal cortex after systemic MK-801 administration (Wolf et al., 1993; Wędzony et al., 1993; Kashiwa et al., 1995), although others report a decrease in, or no effect on, dopamine in dialysates from the dorsal striatum after the same treatment (Kashihara et al., 1990; Weihmuller et al., 1991). Generally, stimulation of dopamine receptors within the nucleus accumbens has been found to be associated with behavioral activation and locomotor stimulation in rodents (for review, see Dunnett and Robbins, 1992). Thus, the locomotor stimulant action of at least low doses of MK-801 may well be due largely to an increased release of dopamine in the nucleus accumbens (vide supra).

Interestingly, previous studies have shown that MK-801-induced hyperlocomotion can be abolished by pretreatment with the $\alpha_1$-adrenoceptor antagonist prazosin (Clineschmidt et al., 1982; Svensson et al., 1995b). The mechanism(s) by which relatively low doses of prazosin, which neither affect dopamine release in the nucleus accumbens nor reduce blood pressure (Sommermeyer et al., 1995), antagonize MK-801-evoked locomotor stimulation remain(s) to be clarified. Previously,we have shown that systemic administration of prazosin markedly attenuates burst firing in ventral tegmental area dopamine neurons, without affecting their basal firing rate (Grenhoff and Svensson, 1993). In addition, in previous experiments prazosin administration was found to abolish MK-801-induced stimulation of burst firing in ventral tegmental area dopamine neurons without affecting the average firing rate (Svensson et al., 1995b).

The present study was undertaken to establish the effects of relatively low doses of MK-801, systemically administered, on dopamine release in the nucleus accumbens in freely moving rats as well as its effect on locomotor activity. Furthermore, the tentative, inhibitory action of pretreatment with prazosin on these two effects of MK-801 was investigated.

## 2. Materials and methods

### 2.1. Animals

Male Bkl:WR rats weighing between 250–350 g were used (Bantin & Kingman Universal AB). Animals arrived at least one week before use and were housed five per cage under standard laboratory conditions, maintained on a 12 h light : dark cycle with lights on at 06:00. Animals had access to R34 rat chow and water ad libitum. Only experimentally naive rats were used. All animals were handled for at least 5 min per day, during the last two days before experiments.

### 2.2. Surgery and microdialysis experiments

Rats were anesthetized with sodium pentobarbital, 60 mg/kg, injected intraperitoneally. They were subsequently mounted in a stereotaxic apparatus and their body temperature was maintained at 37°C with a thermostatically controlled heating pad. Vertical probes of concentric type were stereotaxically implanted into the nucleus accumbens, AP + 1.6 mm, ML −1.4 mm, DV −8.2 mm relative to bregma. Dialysis occurred through a 2.25 mm semipermeable membrane (copolymer of acrylonitrile and sodium methallyl sulfonate, i.d. = 0.24 mm, 40000 Da molecular weight cutoff, AN69 Hospal).

After surgery, the animals were housed individually in plexiglass cages (32 × 35 × 50 cm) and given ad libitum access to food and water. All experiments were conducted approximately 48 h after surgery in awake, freely moving animals during the light cycle. After stable baseline conditions were achieved (< 10% variation), rats were injected subcutaneously with vehicle, prazosin or MK-801 (cf. below). In two groups of animals, rats were injected with prazosin, and 20 min later with MK-801 (0.1 or 0.3 mg/kg, s.c.). Treatment groups consisted of 6-8 rats each. Immediately after drug injection and subsequently during the whole experiment, the behavior of the animals was periodically observed to ascertain any overt behavioral changes.

Microdialysis was performed using automated on-line sampling (Nomikos et al., 1989, 1994). The dialysis probe was perfused with perfusion solution (147 mM sodium chloride, 3.0 mM potassium chloride, 1.3 mM calcium chloride, 1.0 mM magnesium chloride, and 1.0 mM sodium phosphate, pH 7.4) at a rate of 2.5 μl/min set by a microinfusion pump (Harvard Apparatus). The perfusate was loaded directly into the sample loop of the injector (Valco). Samples were automatically injected into the analytical system every 20 min. An IBM compatible computer controlled the loading and injection modes of the injector. Upon completion of the experiments, rats were killed by an overdose of sodium pentobarbital and the brains were removed and stored in 5% formalin and 25% sucrose. Each brain was sectioned on a microtome (50 μm), stained with neutral red, and examined for probe placement. Only rats with probes verified to be located within the nucleus accumbens, according to the anatomical atlas of Paxinos and Watson (1986), were included in this study.

### 2.3. Biochemical assay

Concentrations of dopamine, dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA), and 5-hydroxyindoleacetic acid (5-HIAA) were determined by high-performance liquid chromatography with electrochemical detection as described previously (Nomikos et al., 1994). Separation of dopamine and the acid metabolites was achieved by reverse-phase liquid chromatography (150 × 4.6 mm, Nucleosil 5 μm, C18) with a mobile phase consisting of 0.055 M sodium acetate with 0.1 mM octanesulfonic acid, 0.01 mM $Na_2EDTA$, and 5% methanol, pH 3.8, adjusted with glacial acetic acid. The mobile phase was delivered by an high performance liquid chromatography (HPLC) pump (LKB; 2150) at 0.8 ml/min. Chromatograms were recorded by an IBM compatible computer (Turbochrom software, Perkin Elmer) as well as by a two-pen chart recorder (Kipp & Zonen).

### 2.4. Behavioral experiments

Locomotor activity was assessed in separate animals by means of computer-monitored photocell-equipped boxes as previously described (Ericson et al., 1991). Each animal

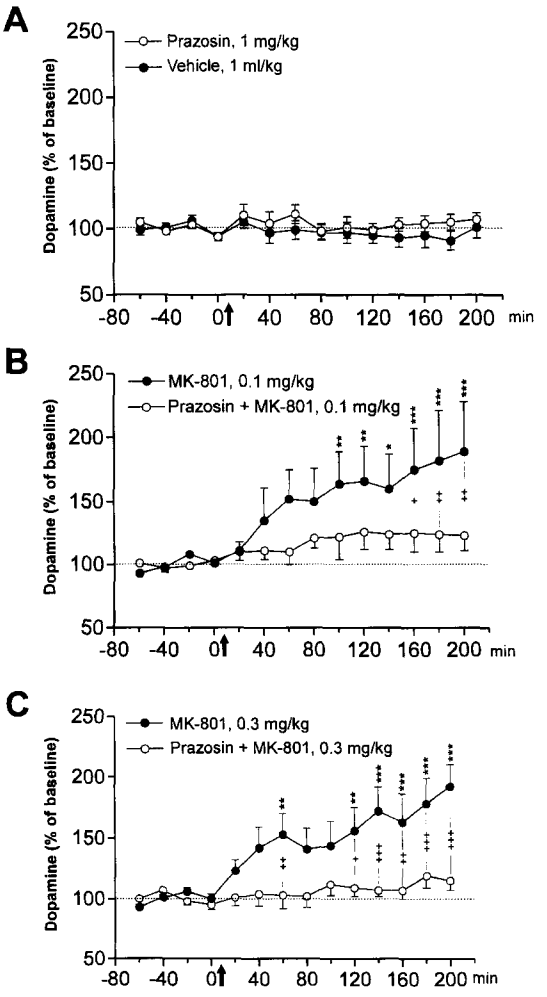


Fig. 1. Effects of vehicle (1 ml/kg, s.c.) and prazosin (1 mg/kg s.c.) (A), MK-801 (0.1 mg/kg, s.c.) alone and after pretreatment with prazosin (1 mg/kg, s.c.) (B), and MK-801 (0.3 mg/kg, s.c.) alone and after prazosin pretreatment (1 mg/kg, s.c.) (C) on extracellular concentrations of dopamine in the nucleus accumbens ($n = 6–8$), as assessed by microdialysis in freely moving rats. Data are presented as mean ± S.E.M. percentage changes from basal values before drug injection. Arrow heads indicate injection of prazosin or vehicle (A) or MK-801 (B and C). $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$ as compared to last baseline sample. $^{+}P < 0.05$, $^{++}P < 0.01$ and $^{+++}P < 0.001$, MK-801 alone compared to MK-801 after prazosin pretreatment.

was placed in a square plexiglass open-field arena (68 × 68 × 45 cm) within a sound-attenuated and fan-ventilated box, which was kept dark during the duration of the testing session. Two rows of photocells lined the exterior of the arena. All photobeam interruptions were recorded and stored on disk by an IBM-compatible computer. Computer recordings of horizontal activity (lower row interruptions) and rearing (upper row interruptions) were taken.

On the day of the experiment, rats were brought to the behavioral testing room in their home cages and allowed to become accustomed to the new environment for at least 60 min. Rats were first injected subcutaneously with either prazosin or vehicle (cf. below) and then placed in a clean holding cage. Twenty minutes later, they received a second subcutaneous injection of MK-801 or saline (cf. below) and were immediately placed in the locomotor activity boxes. The treatment groups consisted of 8–13 rats.

Each behavioral monitoring session lasted for 40 min, since the peak locomotor stimulatory effect of MK-801 has previously been shown to occur within this time period (Willins et al., 1993; Ouagazzal et al., 1994; Ögren and Goldstein, 1994). The interior of the locomotor activity boxes was wiped clean after each session. All behavioral monitoring was conducted during the light cycle between 08:30 and 17:00.

### 2.5. Drug treatment

Prazosin hydrochloride (1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)piperazine hydrochloride, Apoteksbolaget) was dissolved in a drop of glacial acetic acid and titrated to volume using 5.5% glucose solution. (+)-MK-801 hydrogen maleate ((+)-5-methyl-10,11-dihydroxy-5*H*-dibenzo-(*a*,*d*)cyclohepten-5,10-imine hydrogen maleate, Research Biochemicals Incorporated) was dissolved in 0.9% sodium chloride. Vehicle injections refer to a drop of glacial acetic acid in 5.5% glucose solution. The aforementioned drugs, saline or vehicle was administered subcutaneously in a volume of 1 ml/kg.

### 2.6. Data analysis

For graphical representation of microdialysis data, the average of four baseline samples immediately preceding drug injection was defined as 100%. All subsequent measurements were transformed to a mean percentage of baseline values for each subsequent 20 min sampling period (Fig. 1). For calculation of overall output of dopamine, DOPAC, HVA and 5-HIAA, the mean percentage changes over 200 min were calculated (Fig. 2). Behavioral data are presented as horizontal activity over four sequential 10 min measurement periods (Fig. 3). Also, total horizontal activity (Fig. 4A) and rearing (Fig. 4B) over the entire 40-min measurement session are presented. For statistical evaluation, a one- and two-way (treatment × time) analysis of variance (ANOVA) with repeated measures was used, and a post-hoc Newman-Keuls test for multiple comparisons; a $P$ value $< 0.05$ was considered significant.

Behavioral data are presented as raw values of horizontal activity and rearing. Data were analyzed by a two-way ANOVA, followed by the Newman-Keuls test for multiple comparisons. A $P$ value $< 0.05$ was considered significant.

## 3. Results

### 3.1. Microdialysis experiments

There were no differences in mean values of basal dopamine and its metabolites, or 5-HIAA among the treat-

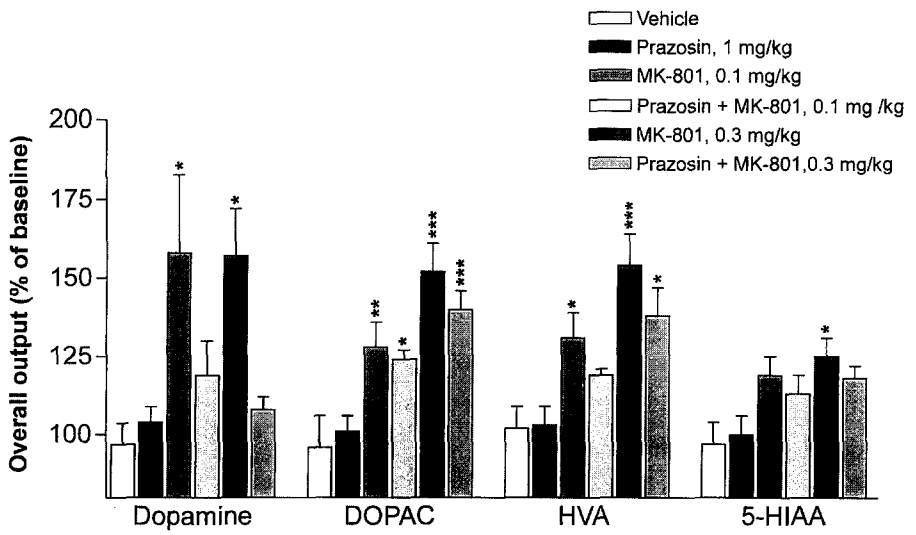


Fig. 2. Effects of vehicle (1 ml/kg, s.c.), prazosin (1 mg/kg s.c.), MK-801 (0.1 mg/kg or 0.3 mg/kg, s.c.) alone and after pretreatment (20 min) with prazosin (1 mg/kg, s.c.), on extracellular concentrations of dopamine, dihydroxyphenylacetic acid (DOPAC), homovanillic acid (HVA) and 5-hydroxyindoleacetic acid (5-HIAA) in the nucleus accumbens ($n = 6$–8). Data are presented as mean + S.E.M. percentage changes over 200 min (overall effect) following injection of vehicle, prazosin or MK-801. * $P < 0.05$, ** $P < 0.01$, and *** $P < 0.001$ compared to vehicle.

ment groups. The overall mean ± standard error of the mean (S.E.M.) of basal values of dopamine, DOPAC, HVA and 5-HIAA was 1.9 ± 0.16, 620 ± 39, 327 ± 24, and 439 ± 31 fmol/min from the NAC ($n = 44$), respectively.

Administration of prazosin (1 mg/kg) or vehicle (1 ml/kg) did not significantly affect dopamine or metabolite levels throughout the entire sampling session (Fig. 1A and Fig. 2). Similarly to vehicle-treated rats, animals receiving prazosin alone did not show any overt behavioral signs.

MK-801 administration in both doses, 0.1 and 0.3 mg/kg, evoked a significant increase in dopamine levels in dialysates, (158.4 ± 25.5% and 156.7 ± 15.2% overall, respectively, both $P < 0.05$, Fig. 2).

MK-801 0.1 mg/kg induced a progressive elevation of dialysate dopamine levels, reaching statistical significance 100 min after administration. Dialysate DA levels remained significantly elevated throughout the duration of the experiment, reaching a maximum of 189.5 ± 38.6% during the last sampling period ($P < 0.001$, Fig. 1B). A slight increase in locomotion was observed in this group of animals, as well as some circling ipsi- and contralateral to the dialysis probe, sniffing, head-weaving, flat body posture, and very mild ataxia, lasting for approximately 1 h, although these parameters were not quantified.

MK-801 0.3 mg/kg evoked a similar increase in dialysate levels of dopamine in the nucleus accumbens; this increase was also relatively slow to develop, reaching significance 60 min after administration. Dopamine levels increased progressively during the experiment, reaching a maximal level in the last sample, 200 min, 192.4 ± 15.2% compared to baseline ($P < 0.001$, Fig. 1C). Marked locomotion and both ipsi- and contralateral circling were evident in these rats, which also displayed sniffing, head weaving, flat body posture and pronounced ataxia, lasting for approximately 2 h.

Dialysate DOPAC concentrations increased in response to both doses of MK-801 (0.1 and 0.3 mg/kg, 128.5 ± 7.8% and 152.4 ± 8.8% overall, $P < 0.01$ and $P < 0.001$, respectively, Fig. 2). Similarly, MK-801, 0.1 and 0.3 mg/kg, evoked significant increases in extracellular levels of HVA (130.7 ± 8.5% and 153.5 ± 9.8% overall, $P < 0.05$ and $P < 0.001$, respectively, Fig. 2). Generally, DOPAC and HVA concentrations increased in a time course which parallelled that of dopamine (data not shown). However, only the 0.3 mg/kg dose of MK-801 significantly elevated dialysate concentrations of 5-HIAA (124.6 ± 6.1% overall, $P < 0.05$, Fig. 2).

In animals pretreated with prazosin, MK-801 administration at both dose levels, 0.1 and 0.3 mg/kg, failed to significantly affect dialysate levels of dopamine (119.6 ± 10.8% and 108.0 ± 4.5% overall, respectively, Fig. 1B,C). Extracellular concentrations of DOPAC, however, were significantly elevated by both doses of MK-801 (124.2 ± 3.1% and 139.7 ± 6.1% overall, $P < 0.05$ and $P < 0.001$, respectively, Fig. 2) in prazosin-pretreated animals. Only the high dose of MK-801 elevated dialysate concentrations of HVA significantly in prazosin-pretreated animals (138.5 ± 8.8%, $P < 0.05$, Fig. 2). In the presence of prazosin, MK-801 did not significantly affect 5-HIAA levels at either dose (Fig. 2). Prazosin pretreatment largely reduced the hyperactivity and circling induced by MK-801. The MK-801-induced ataxia was still evident in prazosin-pretreated animals. These parameters were not quantitatively analyzed in the microdialysis experiments.

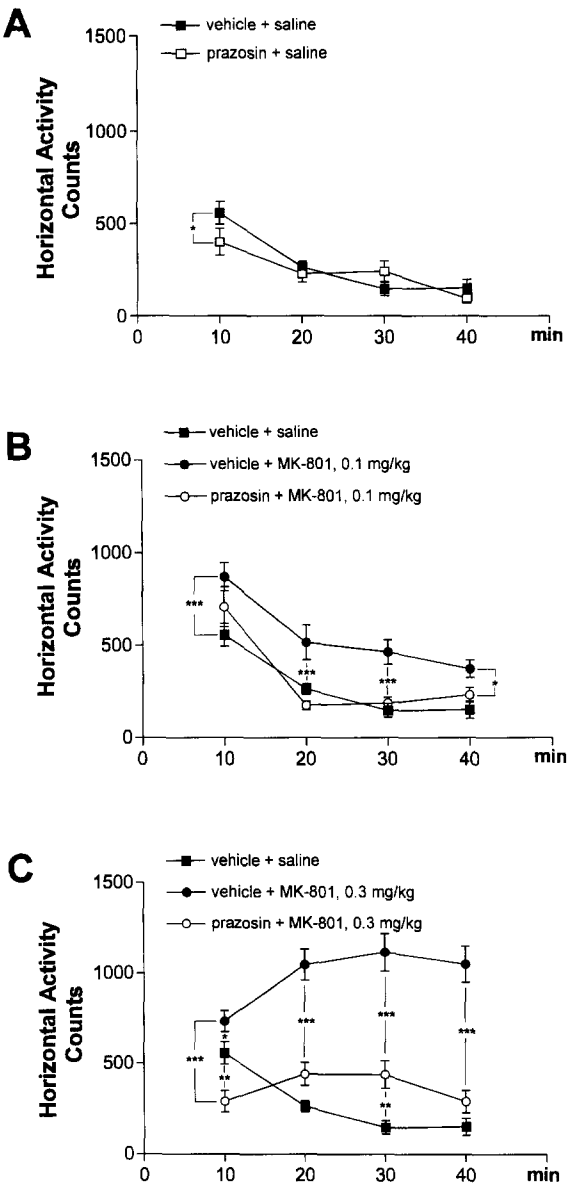


Fig. 3. Temporal effects of vehicle (1 ml/kg, s.c.) and prazosin (1 mg/kg s.c.) (A), MK-801 (0.1 mg/kg, s.c.) alone and after pretreatment with prazosin (1 mg/kg, s.c.) (B), and MK-801 (0.3 mg/kg, s.c.) alone and after prazosin pretreatment (1 mg/kg, s.c.) (C), on rat locomotor activity ($n = 8–13$), as assessed by horizontal activity measurements in an open field. Data are presented as mean ± S.E.M. values for each of four 10 min measurement periods. * $P < 0.05$, * * $P < 0.01$ and * * * $P < 0.001$, between-group comparisons.

### 3.2. Behavioral experiments

Prazosin administration (1 mg/kg) did not affect overall horizontal activity during the entire 40 min session, compared to control (Fig. 4A), although a significant reduction in horizontal activity was observed during the first (10 min) measurement period (Fig. 3A). However, prazosin significantly reduced spontaneous rearing in these animals ($P < 0.05$, Fig. 4B).

MK-801 administration at both 0.1 and 0.3 mg/kg significantly enhanced locomotor activity over each consecutive time period as compared to that of control rats ($P$ values $< 0.05$–$0.001$, Fig. 3B,C), and also caused an overall significant increase in locomotor activity during the entire 40 min test session ($P < 0.01$ and $P < 0.001$ overall, respectively, Fig. 4A). Rearing activity was not affected by MK-801 administration at either dose (Fig. 4B).

Prazosin pretreatment abolished horizontal hyperactivity induced by MK-801 0.1 mg/kg at each measured time point ($P$ values $< 0.05$-$0.001$, Fig. 3B). The locomotor activity in this group was nearly identical in magnitude and pattern over time to that of the control group. Also, the total horizontal activity evoked by MK-801 0.1 mg/kg was significantly lower in the prazosin-pretreated group than in the rats receiving vehicle and MK-801. Furthermore, after administration of MK-801, 0.1 mg/kg, total rearing scores in this prazosin-pretreated group were not significantly different from those of the control group injected with vehicle and saline.

Prazosin pretreatment significantly attenuated horizontal activity induced by MK-801 0.3 mg/kg ($P$ values $< 0.001$) at all time points (Fig. 3C). Similarly, total horizontal activity scores over the 40 min session were significantly lower in prazosin-pretreated rats than in rats receiving vehicle and MK-801 0.3 mg/kg (Fig. 4A), although at 40 min locomotor activity was significantly greater than in control animals ($P < 0.01$, Fig. 3C). The reduction of rearing counts induced by MK-801 0.3 mg/kg was significantly reduced further by prazosin pretreatment ($P < 0.001$, Fig. 4B).

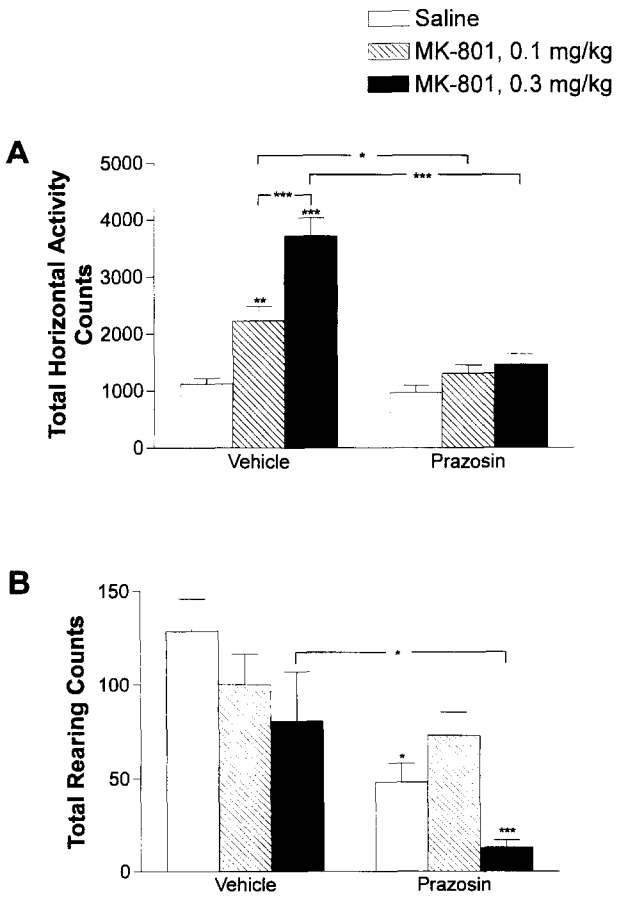


Fig. 4. Effects of vehicle (1 ml/kg, s.c.), prazosin (1 mg/kg s.c.), MK-801 (0.1 mg/kg or 0.3 mg/kg, s.c.) alone and after pretreatment with prazosin (1mg/kg, s.c.) ($n = 8$–$13$) on rat locomotor activity, as assessed by horizontal activity (A) and rearing (B) in an open field. Data are presented as mean + S.E.M. values for the entire 40 min measurement period (overall effect). $^{*}P < 0.05$, $^{**}P < 0.01$ and $^{***}P < 0.001$, drug treatment compared to saline + vehicle, or between-group comparisons, as indicated.

## 4. Discussion

The present results show that administration of MK-801, in two doses, 0.1 and 0.3 mg/kg, significantly increased the levels of dopamine and its metabolites DOPAC and HVA in the nucleus accumbens of the freely moving rat, in accordance with previous microdialysis data reported by Wolf et al. (1993). The low dose (0.1 mg/kg) of MK-801 was selected since the locomotor stimulatory effect of low doses of MK-801 has been found to be blocked by catecholamine depletion (Clineschmidt et al., 1982). A higher dose (0.3 mg/kg) was also studied since dopamine-independent effects have been suggested to be involved the hyperlocomotion induced by MK-801 in high doses in mice (Carlsson and Carlsson, 1989). However, doses higher than 0.3 mg/kg have been reported to induce severe locomotor incoordination in rats (Criswell et al., 1993). The increased dopamine levels, at the two doses, were of approximately the same magnitude, suggesting the possibility that already at the low dose a maximal dopamine release may be achieved in the rat brain. This effect of MK-801 in the nucleus accumbens is consistent with previous electrophysiological findings, which demonstrate that MK-801 in low doses, i.e. $< 0.25$ mg/kg, potently stimulates the activity, in particular burst firing, of ventral tegmental area dopamine neurons projecting inter alia to the nucleus accumbens (Zhang et al., 1992; French et al., 1993; Murase et al., 1993). Previous studies utilizing both in vivo voltammetry (Gonon, 1988) and microdialysis (Bean and Roth, 1991) have indeed revealed that burst firing is associated with a more pronounced release of dopamine from nerve terminals in the nucleus accumbens than regular firing of the same average frequency. Thus,

the increased dopamine release in the nucleus accumbens caused by systemic administration of low doses of MK-801 may well be causally related to the increased burst firing of mesolimbic dopamine neurons.

The mechanism(s) by which MK-801 stimulates ventral tegmental area dopamine cell firing and thereby increases extracellular levels of dopamine remain(s) to be clarified. Since local application of NMDA antagonists into the somatodendritic region of ventral tegmental area dopamine cells attenuates burst firing (Chergui et al., 1993), the stimulation of ventral tegmental area dopamine neuronal activity induced by systemic administration of non-competitive NMDA receptor antagonists is probably mediated through indirect mechanisms. Indeed, the activity of presumably γ-amino-butyric acid (GABA) containing interneurons within the ventral tegmental area is suppressed by administration of MK-801 (Zhang et al., 1993). In addition, regional differences in excitatory amino acid receptor regulation of ventral tegmental area dopamine neuronal subpopulations should be considered. Specifically, activation of non-NMDA excitatory amino acid receptors within the ventral tegmental area has been found to stimulate dopamine metabolism in the nucleus accumbens, but not in the prefrontal cortex, indicating that glutamatergic mechanisms could be involved (Kalivas et al., 1989). Local effects of MK-801 within the nucleus accumbens may possibly also be involved in increasing extracellular levels of dopamine when MK-801 is administered systemically. Preliminary experiments from our laboratory demonstrate that at least high concentrations of MK-801 (300 μM), locally administered into the nucleus accumbens via a microdialysis probe, can significantly increase extracellular concentrations of dopamine.

The time course for the increase in dopamine levels was rather similar with both the low (0.1 mg/kg) and high (0.3 mg/kg) doses of MK-801. At 0.1 mg/kg, MK-801 evoked a significant increase in the extracellular concentrations of dopamine 100 min after injection, whereas 0.3 mg/kg of MK-801 induced a faster increase in dopamine levels, the increase being significant 60 min after administration. Dopamine levels continued to increase slowly during the course of the experiment, reaching a maximum approximately 2.5 h after MK-801 administration at both doses. Recent studies show that MK-801-induced increases in dopamine levels in the prefrontal cortex develop over a similar time course when assessed by microdialysis (Wędzony et al., 1993; Kashiwa et al., 1995). Indeed, an increase in dopamine metabolism in the nucleus accumbens is not apparent until 120 min after MK-801 administration (Dai et al., 1995). There is, however, a certain temporal discrepancy between these microdialysis findings in awake animals, which showed a delayed response of extracellular dopamine levels in the nucleus accumbens, and the nearly immediate and pronounced stimulatory effect of MK-801 on neuronal activity in ventral tegmental area dopamine neurons previously observed in anesthetized rats (Zhang et al., 1992; French et al., 1993; Murase et al., 1993). In addition, recent experiments in our laboratory in which we used voltammetry in pargyline-pretreated anesthetized rats, demonstrated an essentially immediate dopamine-releasing effect of intravenous injections of MK-801 (Marcus et al., in preparation). Thus, the difference in onset of action of MK-801 in our electrophysiological and microdialysis experiments may reflect different routes of drug administration, as well as a slight delay associated with the microdialysis sampling technique per se. Also, the use of anesthesia may augment the responsiveness of some brain neurons to MK-801 and/or enhance excitability in midbrain dopamine cells (Mereu et al., 1995). Moreover, the faster onset of action of the stimulatory action of MK-801 on dopamine release observed in the voltammetric study appears not to be related to the use of pargyline and consequently to diminished elimination of dopamine by metabolism, since the time course of the increase of dopamine metabolites was nearly identical to that of dopamine in the present microdialysis study.

The MK-801-induced increase in extracellular dopamine in the nucleus accumbens was observed as long as 3 h after injection of MK-801, in concordance with previous reports (Wędzony et al., 1993; Kashiwa et al., 1995). Indeed, the plasma half-life of MK-801 in rats is approximately 2 h (Hucker et al., 1983). In addition, the rate of dissociation of MK-801 from the NMDA receptor complex is quite slow, exhibiting only partial recovery after 3 h (Wong et al., 1986). We have previously observed similar long-lasting effects of MK-801 in single unit recordings of ventral tegmental area dopamine neurons in anesthetized rats, where MK-801 administration can induce a prolonged increase in firing rate and burst firing that lasts for well over 4 h (unpublished observations).

In animals receiving the $\alpha_1$-adrenoceptor antagonist prazosin alone, no significant changes of extracellular dopamine or metabolite levels were observed throughout the course of the experiment, in accordance with a previous microdialysis report (Sommermeyer et al., 1995). Systemic administration of prazosin has previously been shown to selectively reduce burst activity, but not the basal firing rate in ventral tegmental area dopamine neurons (Grenhoff and Svensson, 1993). Such an attenuation of burst firing would, in principle, be expected to reduce the terminal release of dopamine in the nucleus accumbens (cf. above). Indeed, some reports demonstrate decreased brain dopamine utilization and terminal synthesis following prazosin administration (Andén et al., 1978; Ålander et al., 1980). However, even a 10-fold higher dose of prazosin than that used in the present study failed to alter extracellular dopamine levels in the nucleus accumbens, as assessed by microdialysis (Sommermeyer et al., 1995).

Interestingly, in rats pretreated with prazosin, administration of MK-801 did not significantly increase extracellular dopamine levels in the nucleus accumbens. Thus,

dopamine levels were significantly lower in the prazosin-pretreated, as well as vehicle-treated groups, compared to the groups that received MK-801 alone. This effect cannot be related to a hypotensive action of prazosin, since previous studies show that significant hypotension in the rat is obtained only at a dose 10-fold higher than that used in the present study (Sommermeyer et al., 1995). Clearly, prazosin's inhibitory effect on MK-801-evoked dopamine release does not reflect an effect on basal dopamine levels, as shown by the present data with prazosin alone, but rather represents an effect of prazosin to reduce the sensitivity of the mesolimbic dopamine system to a challenge, i.e. MK-801 administration. Indeed, dopamine release in the nucleus accumbens evoked by administration of the dopamine $D_2/D_3$ receptor antagonist raclopride has also been found to be attenuated by pretreatement with prazosin (Andersson et al., 1994). Such a modulation of the mesolimbic dopamine system may occur through several different mechanisms, since $\alpha_1$-adrenoceptors are expressed in many regions of the rat brain (Jones et al., 1985). Previously, we have shown that electrical stimulation of noradrenergic cell bodies within the locus coeruleus induces burst firing in ventral tegmental area dopamine neurons, an effect which could be blocked by pretreatment with prazosin (Grenhoff et al., 1993). Furthermore, recent voltage clamp experiments indicate that $\alpha_1$-adrenoceptors locally depolarize ventral tegmental area dopamine cells by reducing membrane conductance for potassium, suggesting that $\alpha_1$-adrenoceptors directly influence the excitability of ventral tegmental area dopamine neurons (Grenhoff et al., 1995). Also, recent studies implicate interactions within the nucleus accumbens, since addition of prazosin to the perfusion solution during microdialysis reduces nucleus accumbens levels of dopamine (Sommermeyer et al., 1995). Furthermore, the increased phasic activity, but not the elevated tonic activity of ventral tegmental area dopamine cells, induced by MK-801 administration is abolished by systemic administration of prazosin (Svensson et al., 1995b). Thus, the attenuation of MK-801-evoked dopamine release by prazosin may well be related to decreased burst activity in dopamine cells, an effect that seems to be executed within the ventral tegmental area. Since previous data show that burst activity in midbrain dopamine neurons is much more effective than regular activity of the same, absolute mean discharge rate in releasing dopamine as well as in augmenting *c-fos* expression in target areas, the administration of prazosin should significantly influence information processing through the mesolimbic dopamine system.

In our behavioral experiments, MK-801 caused a significant, dose-dependent enhancement of locomotor activity, as reported in several previous studies (Clineschmidt et al., 1982; Carlsson and Carlsson, 1989; Willins et al., 1993; Ouagazzal et al., 1994; Ögren and Goldstein, 1994; Svensson et al., 1995a). Thus, the maximum locomotor stimulatory effect of MK-801 at 0.1 mg/kg was observed during the initial 10 min observation period, whereas at 0.3 mg/kg maximum locomotor activity was observed 30 min after administration. It is noteworthy that the locomotor stimulation evoked by MK-801 did not coincide temporally with the MK-801-evoked release of dopamine in the nucleus accumbens. Such an absence of a linear relationship between drug-induced extracellular dopamine concentrations and behavior is not surprising and has been noted in several previous reports (Sharp et al., 1987; Nomikos et al., 1989; Hertel et al., 1996). Yet, the absence of habituation over time with the high (0.3 mg/kg), but not with the low (0.1 mg/kg), dose of MK-801 in the present study might reflect an increased contribution of NMDA-receptor antagonist mechanisms at sites unrelated to dopamine (cf. Carlsson and Carlsson, 1989).

Generally it has, as yet, not been unequivocally established where low, behaviorally relevant doses of non-competitive NMDA receptor antagonists act in evoking locomotor activity. Thus, it may be that sites both within and outside the nucleus accumbens are involved, since local application of MK-801 within the nucleus accumbens can also evoke some locomotor activity (Raffa et al., 1989; Svensson et al., 1995a). Also, the threshold dose of MK-801 that induces behavioral stimulation is 10-fold lower in monoamine-intact than in monoamine-depleted animals, indicating that dopamine activity within the nucleus accumbens is important for mediating the locomotor stimulatory effects of MK-801 (Clineschmidt et al., 1982; Martin et al., 1994). It is also likely that mechanisms within the ventral tegmental area may be involved, since local application of MK-801 in this region evokes locomotor activity (Narayanan et al., 1994) and also increases dopamine metabolism in the pyriform cortex (Rao et al., 1990). The mechanisms involved here could include, for example, inhibition of local GABAergic interneurons in the ventral tegmental area (cf. above).

Horizontal activity counts were only affected by prazosin administration during the initial 10 min observation period, and overall rearing counts were also significantly reduced. Generally, rats show high locomotor activity and rearing scores immediately after being placed in a novel environment, and several reports indicate that exploratory activity is associated with increased noradrenergic activation in the brain (see Clark et al., 1987). Therefore, the reduced locomotor activity and rearing during the first 10 min measurement period induced by prazosin administration may represent a functional consequence of blockade of noradrenergic receptor activation in the brain.

In prazosin-pretreated animals, MK-801 0.1 mg/kg failed to exert any significant effects on locomotor activity. Rearing after MK-801 administration was not significantly different from control, suggesting that the general increase in locomotor activity after administration of MK-801 may partially counteract the suppression of rearing induced by prazosin. Also, in rats receiving MK-801 0.3 mg/kg, pretreatment with prazosin blocked the overall locomotor

stimulatory effects of MK-801, although locomotor activity was significantly higher than that of the control 40 min after MK-801 administration. In animals pretreated with prazosin, MK-801 administration potentiated the reduction of rearing induced by prazosin alone. Although we did not rate the animals for ataxia, the animals receiving MK-801 0.3 mg/kg exhibited pronounced ataxia, i.e. markedly low body posture, abduction of the hindlimbs, and lack of hindlimb coordination during locomotion. Thus, ataxia alone induced by high doses of MK-801 may account for the further reduction in rearing in the prazosin-pretreated animals.

In the present study, locomotor activity was significantly greater in the group receiving 0.3 mg/kg than in the group receiving 0.1 mg/kg of MK-801, although the time course and the magnitude of the increase in dopamine levels in the nucleus accumbens were nearly the same after both doses of MK-801. It is likely that the locomotor stimulatory effect of the high dose of MK-801 is influenced by dopamine-independent effects of MK-801 to a greater extent than the locomotor stimulatory effect of the low dose. Indeed, in monoamine-depleted animals, locomotor activity can be induced if high doses of MK-801 are administered (Carlsson and Carlsson, 1989). Furthermore, 6-hydroxydopamine lesions of brain dopamine systems do not consistently block MK-801-induced hyperlocomotion (Criswell et al., 1993; Ouagazzal et al., 1994), although development of denervation supersensitivity of central dopamine systems may at least partially compensate for the effects of 6-hydroxydopamine lesions. The contribution of such dopamine-independent mechanisms to the psychotomimetic effects of non-competitive NMDA receptor antagonists, which are usually obtained with low doses of these agents, has not been clarified. Indeed, PCP-induced psychosis is most frequently observed after emergence from PCP anesthesia, when plasma concentrations of PCP are low (Javitt and Zukin, 1991). Also, it is noteworthy that MK-801 has approximately 10-fold higher affinity for NMDA receptors than PCP (Kornhuber and Weller, 1995). Thus, if comparable NMDA receptor occupancy as obtained with $> 0.2$ mg/kg MK-801 were to be obtained with PCP in humans, the doses required, i.e. $> 1$ mg/kg, would likely be lethal (Javitt and Zukin, 1991). These observations suggest that the effects of relatively low doses of non-competitive NMDA receptor antagonists are of particular interest with regard to the psychotomimetic effects of this group of compounds. Therefore, it is of considerable interest that the locomotor stimulatory effects of low doses of MK-801 can be abolished by depletion of dopamine with reserpine or antagonized by administration of dopamine receptor antagonists (Clineschmidt et al., 1982; Willins et al., 1993; Ögren and Goldstein, 1994). Indeed, the locomotor stimulation induced by low doses of MK-801 has been found to be inhibited by local infusion of the $GABA_B$ receptor agonist baclofen into the ventral tegmental area, where it inhibits neuronal activity (Narayanan et al., 1994). Taken together, these findings clearly indicate that in low doses, MK-801-induced locomotor hyperactivity is specifically associated with, and dependent upon, enhanced mesolimbic dopamine neuronal activity.

Interactions between brain noradrenaline and dopamine systems have been implicated in several brain disorders. In schizophrenia, acute psychosis as well as psychotic relapse has been found to be associated with enhanced noradrenergic activity in the brain (Van Kammen and Kelley, 1991; Maas et al., 1993; Van Kammen et al., 1994). Furthermore, most antipsychotic drugs also possess $\alpha_1$-adrenoceptor antagonistic properties (Peroutka and Snyder, 1980; Cohen and Lipinski, 1986), although the putative contribution of $\alpha_1$-adrenoceptor antagonism to the antipsychotic effects of neuroleptics remains to be established. Addition of prazosin to the standard neuroleptic treatment of a small group of schizophrenic patients failed to affect schizophrenic symptoms (Hommer et al., 1984). However, these findings may relate to the rather limited capacity of prazosin to reach the brain when orally administered to humans (Cubeddu, 1988; Van Kammen and Kelley, 1991), although it effectively enters the brain in rodents.

The present findings, that administration of a potent $\alpha_1$-adrenoceptor antagonist blocked the dopamine release in the nucleus accumbens evoked by the psychotomimetic, PCP-like drug MK-801, without exerting any effects on basal dopamine activity when given alone, suggest that $\alpha_1$-adrenoceptor antagonism exerts a preferential effect on evoked, but not on basal, dopamine release. Interestingly, in two other animal models of schizophrenia, i.e. prefrontal cortical dopamine hypofunction or neonatal hippocampal damage, an increased sensitivity of the mesolimbic dopamine system to challenge, e.g. environmental stress or administration of indirect dopamine agonists, has been observed (Deutch et al., 1990; Jaskiw et al., 1990). In effect, the $\alpha_1$-adrenoceptor antagonistic properties of most antipsychotic drugs may, accordingly, act in concert with their dopamine $D_2$ receptor blocking properties, and specifically reduce evoked, subcortical dopamine hyperactivity, e.g. evoked by environmental stimuli. Such an effect may help to explain the superior clinical efficacy of clozapine, which exerts a very potent $\alpha_1$-adrenoceptor antagonistic action.

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