ELSEVIER

European Journal of Pharmacology 378 (1999) 9–16

ejp

www.elsevier.nl/locate/ejphar

Site-specific NMDA receptor antagonists produce differential effects on cocaine self-administration in rats

Petri Hyytiä [a,*], Pia Bäckström [a], Sture Liljequist [b]

[a] *Department of Mental Health and Alcohol Research, National Public Health Institute, P.O.B. 719, FIN-00101 Helsinki, Finland*
[b] *Department of Clinical Neuroscience, Division of Drug Dependence Research, Karolinska Institutet, S-171 76 Stockholm, Sweden*

Received 1 March 1999; received in revised form 15 June 1999; accepted 18 June 1999

Abstract

The effects of site-specific NMDA receptor antagonists on intravenous cocaine self-administration were examined in rats trained to self-administer cocaine (0.25 mg/infusion) on a fixed ratio (FR) 5 schedule with a 20-s time-out (TO) after each reinforcer. The non-competitive NMDA receptor antagonists, dizocilpine (MK-801, (+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine hydrogen maleate) (0.05–0.2 mg/kg i.p.) and memantine (1,3-dimethyl-5-amino-adamantane hydrochloride) (2.5–20 mg/kg i.p.), dose-dependently decreased cocaine self-administration, while the competitive NMDA receptor antagonist, CGP 39551 (DL-(*E*)-2-amino-4-methyl-5-phosphono-3-pentanoic acid carboxyethylester) (2.5–15 mg/kg i.p.), and the NMDA/glycine receptor antagonist, L-701,324 (7-chloro-4-hydroxy-3(3-phenoxy)-phenyl-2(*H*)quinolone) (1.25–10 mg/kg p.o.), were without effect. Under a progressive ratio (PR) schedule, dizocilpine (0.15 mg/kg i.p.) increased the number of cocaine infusions in a manner similar to increasing the unit dose of cocaine, suggestive of potentiation of cocaine reward. Conversely, memantine (10 mg/kg i.p.) produced rate-decreasing effects on the PR schedule. These results demonstrate that NMDA receptor antagonists acting at different modulatory sites of the NMDA receptor do not share dizocilpine's cocaine reward enhancing effects although they are all known to be effective blockers of NMDA receptor activity.

Keywords: Cocaine; Self-administration; NMDA receptor antagonist; Dizocilpine (MK-801); Memantine; CGP 39551; L-701,324

1. Introduction

Manipulation of glutamatergic neurotransmission produced by glutamate receptor antagonists alters a wide spectrum of functional responses in rodents, including lethality, convulsions, circulatory effects and locomotor stimulation following acute administration of cocaine and other psychostimulants (see Rockhold, 1998, for review). Glutamate receptor antagonists prevent also the development of sensitization to locomotor stimulation induced by repeated administration of cocaine (Karler et al., 1989); in addition, there is now increasing evidence for glutamatergic participation in the reinforcing actions of cocaine, assessed in various self-administration paradigms (Danysz and Parsons, 1998).

Alteration of cocaine self-administration by dizocilpine (MK-801), a non-competitive antagonist of the NMDA receptor, has been demonstrated best. Systemic pretreatment with dizocilpine reduced cocaine self-administration in rats maintained on a fixed ratio (FR) schedule in a manner similar to increasing the unit dose of cocaine (Pierce et al., 1997) and increased the breaking point of cocaine responding on a progressive ratio (PR) schedule (Ranaldi et al., 1996). Taken together, these findings suggest that dizocilpine enhances the reinforcing properties of cocaine. This effect, however, can be seen only in a very narrow dose range (0.1–0.15 mg/kg), whereas higher doses of dizocilpine produce a loss of discriminative responding for cocaine and motor impairment (Schenk et al., 1993). Furthermore, dizocilpine blocks enhanced acquisition of intravenous cocaine self-administration produced by pre-exposure to amphetamine (Schenk et al., 1993) and causes reinstatement of responding for cocaine following extinction (DeVries et al., 1998).

Attempts to modulate cocaine self-administration with other NMDA receptor antagonists than dizocilpine have produced conflicting results. For example, infusion of the

* Corresponding author. Tel.: +358-9-133-2896; fax: +358-9-133-2781; E-mail: petri.hyytia@ktl.fi

0014-2999/99/$ - see front matter
PII: S0014-2999(99)00446-X

competitive NMDA receptor antagonist, 2-amino-5-phosphonovaleric acid (APV), into the nucleus accumbens increased cocaine self-administration in rats, indicative of antagonism of cocaine reward by APV (Pulvirenti et al., 1992). In contrast, when the non-competitive antagonist, dextrometorphan, was given systemically, it reduced cocaine responding both on a continuous reinforcement and PR schedule (Pulvirenti et al., 1997).

Although these findings suggest that manipulation of NMDA receptor activity may alter the reinforcing properties of cocaine, little is known about the underlying neuropharmacological mechanisms involved in this phenomenon. Since antagonists acting at distinct modulatory sites of the NMDA receptor complex have different pharmacological and behavioural profiles, and could thus produce differential effects on cocaine reinforcement, the purpose of the present study was to examine how cocaine self-administration is modulated by CGP 39551 (Fagg et al., 1990), an antagonist acting competitively at the endogenous agonist recognition site, dizocilpine (Wong et al., 1986) and memantine (Bormann, 1989) that bind to a non-competitive site within the NMDA receptor channel, and L-701,324 (Kulagowski et al., 1994), an antagonist at the NMDA/glycine recognition site. In this study, dizocilpine and memantine were selected as representatives for high- and low-affinity channel blockers, respectively.

2. Materials and methods

2.1. Subjects

Forty-two male Wistar rats (Wistar:Han/HY, Department of Laboratory Animals, University of Helsinki) weighing 140–160 g upon arrival were used. Animals were group housed (two per cage) in a room with controlled temperature (20 ± 2°C) and humidity (55 ± 5%) on a reverse 12-h light–dark cycle (lights on 6 p.m.–6 a.m.) with free access to tap water and RM1(E) pellet food (SDS, Witham, UK), except during initial food training (see Section 2.5). All behavioural testing occurred during the dark phase of the light–dark cycle between 10 a.m. and 5 p.m. All surgical and experimental procedures using animals were approved by the Institutional Animal Care and Use Committee.

2.2. Drugs

Cocaine hydrochloride was obtained from Sigma (St. Louis, MO). Dizocilpine (MK-801, (+)-5-methyl-10,11-dihydro-5*H*-dibenzo[*a*,*d*]cyclohepten-5,10-imine hydrogen maleate) and memantine (1,3-dimethyl-5-amino-adamantane hydrochloride) were obtained from Research Biochemicals (Natick, MA). CGP 39551 (DL-(*E*)-2-amino-4-methyl-5-phosphono-3-pentanoic acid carboxyethylester) was a generous gift from the Ciba-Geigy Laboratories in Basel, Switzerland. L-701,324 (7-chloro-4-hydroxy-3(3-phenoxy)-phenyl-2(*H*)quinolone) was generously supplied by Dr. Paul Leeson, Merck Sharpe and Dohme Research Laboratories, Harlow, UK). Cocaine, dizocilpine, memantine and CGP 39551 were dissolved in saline. Dizocilpine, memantine and CGP 39551 were administered intraperitoneally (i.p., 1 ml/kg) 15 min before cocaine self-administration sessions. L-701,324 was given p.o. (3 ml/kg) as a suspension in 0.5% methylcellulose 30 min before testing (Bristow et al., 1996). All doses refer to the weights of the respective salts.

2.3. Apparatus

Both the initial food training and cocaine self-administration took place in operant chambers (Model ENV-112B, MED Associates, Georgia, VT), enclosed in ventilated sound-attenuating cubicles. The chambers were equipped with a food hopper in the middle of the front panel and two retractable response levers on both sides of the food hopper. A white stimulus light was mounted above both levers. A food dispenser located behind the front panel delivered 45 mg Noyes pellets to the food hopper. Intravenous infusions were delivered at the volume of 0.1 ml by means of activating an infusion pump outside the sound-attenuation cubicle for 3.5 s. The infusion pump was attached to a counterbalanced liquid swivel through Tygon tubing (Fisher Scientific, Pittsburgh, PA). From the swivel, Tygon tubing protected by a steel spring passed through the hole of the operant chamber and was connected to the catheter base at the midscapular region of the animal. Schedule contingencies and data collection were controlled by an IBM compatible computer using the MED-PC behavioural software (MED Associates).

2.4. Surgery

Rats were anaesthetized with a halothane–air mixture and implanted with a chronic silastic catheter into the right external jugular vein, as described previously (Caine et al., 1993). Briefly, the catheter assembly consisted of a 13-cm length of silastic tubing (inside diameter 0.31 mm; outside diameter 0.64 mm), attached to a guide cannula that was bent at a right angle. The cannula was embedded into an dental cement base and anchored with a 2×2-cm of surgical polypropylene mesh. The catheter was passed subcutaneously from the rat's back to the jugular vein where it was inserted and secured with suture and cyanoacrylate glue. The catheter base was then mounted on the animal's back and the guide cannula was sealed with a plastic cap. After surgery, the catheters were flushed once a day for the next 10 days with a 0.1-ml infusion of an antibiotic (Borgalmite, Hoechst Veterinär) and a 0.1-ml infusion of 0.9% saline containing heparin (30 U/ml) to

prevent infections and blood coagulation in the catheters. Thereafter, the catheters were flushed with heparinized saline once every day. Catheter patency was tested by infusing a short-acting anaesthetic methohexital (Brietal, Eli Lilly and Co., Indianapolis, IN) through the catheter whenever an animal not receiving drug pretreatment displayed self-administration outside baseline performance. Animals with patent catheters exhibited a rapid loss of muscle tone within 2 s of the methohexital infusion.

2.5. Cocaine self-administration

Prior to implantation of i.v. catheters, rats were trained to lever press for food reinforcement. Rats were restricted to 4 g of standard pellet food per day for 48 h and then to 18 g daily during the course of training. Food training began on a fixed ratio 1 (FR1) schedule with a time-out (TO) duration of 1 s on both response levers during 60-min sessions until rats earned 100 pellets during the session. The session length was then shortened to 30 min and the TO duration was increased to 10 s. After this, the FR was increased to 5. Animals were allowed to respond on the FR5 TO 10 s schedule until they earned 50 pellets during the 30-min session. Once rats had reached this criterion after 4–5 days of training, they were returned to ad libitum food and implanted with i.v. catheters, as described before.

One week after surgery, subjects were allowed to respond for a 0.1-ml infusion of cocaine (0.25 mg/infusion, dissolved in 0.9% physiological saline) on an FR1 TO 20-s schedule during daily 2-h sessions, 5 days a week. At the onset of each session, the house light was turned off and the two response levers were extended. Responding on the active lever resulted in an infusion that was signalled by illumination of the stimulus light for a 20-s TO. Responding on the inactive lever was recorded but had no scheduled consequence. If animals failed to earn cocaine infusions during the entire 2-h session, they were given two non-contingent priming infusions every 30 min during the next session. Once rats had acquired reliable responding on FR1 TO 20-s schedule, they were raised to FR2, FR3 and

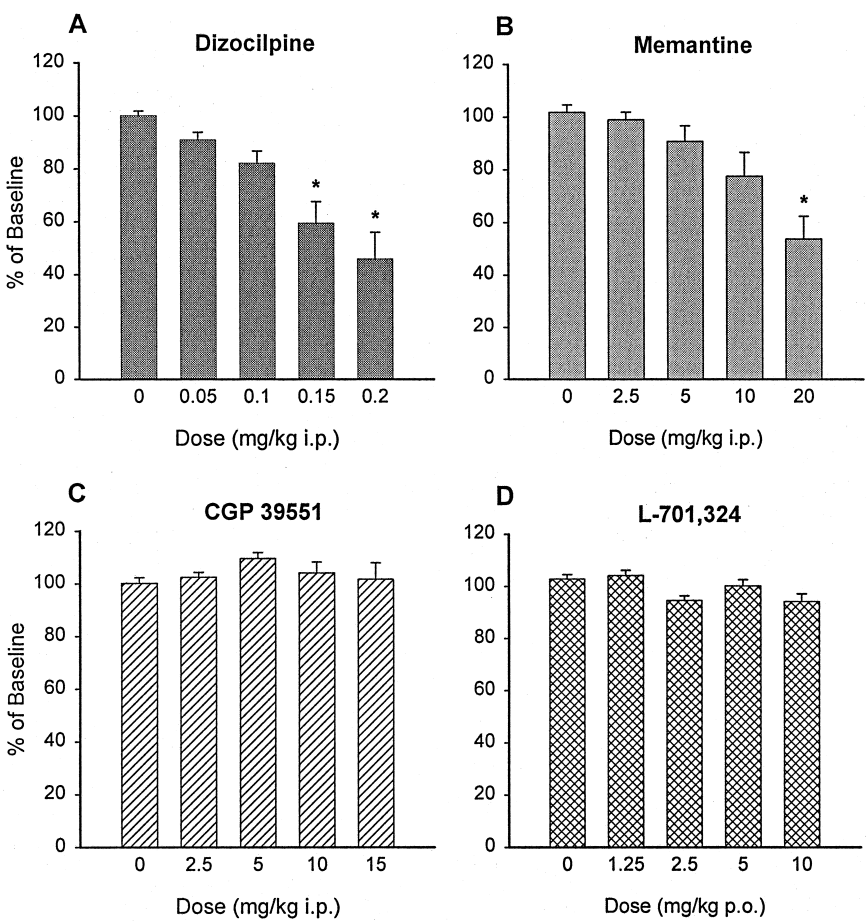

Fig. 1. Effects of dizocilpine (A), memantine (B), CGP 39551 (C) and L-701,324 (D) on cocaine self-administration (0.25 mg/infusion) on an FR5 TO 20-s schedule. Data points represent the mean ± S.E.M. (dizocilpine: $n = 7$; memantine: $n = 10$; CGP 39551: $n = 8$; L-701,324: $n = 9$). Asterisks indicate statistically significant differences from the vehicle injections ($P < 0.05$) by post hoc comparisons with Bonferroni correction after a significant main effect by ANOVA.

FR5 on consecutive days. No priming infusions were used during the drug testing phase.

Drug pretreatment testing began following establishment of stable baseline responding for cocaine on the FR5 TO 20-s schedule. Criterion for a stable baseline was three consecutive self-administration sessions with less than 10% variation in the total number of infusions earned. After the first drug test, subsequent doses were tested after at least two sessions with no drug pretreatment and after at least two sessions with less than 10% deviation in the total number of infusions. The mean total number of cocaine infusions (±S.E.M.) during all baseline sessions for the dizocilpine, memantine, CGP 39551 and L-701,324 treatment groups were 28.5 ± 1.1, 30.5 ± 1.6, 25.6 ± 0.6 and 29.4 ± 1.6, respectively. The effects of dizocilpine ($n = 7$), memantine ($n = 10$) and CGP 39551 ($n = 8$) on cocaine self-administration were examined in a between-sessions, within-subjects Latin square design. L-701,324 ($n = 9$) was tested using an ascending dosing regime for each subject.

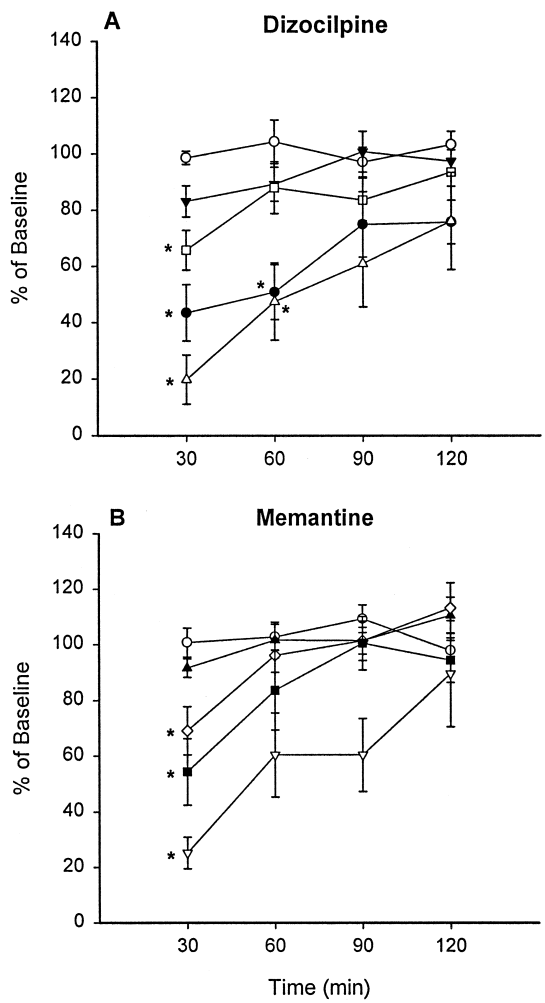

Fig. 2. Effects of dizocilpine (A) and memantine (B) on the temporal pattern of cocaine self-administration (0.25 mg/infusion) on an FR5 TO 20-s schedule. The data from Fig. 1 are presented in 30-min blocks over the 2-h session. (A) ○, Vehicle; ▼, 0.05 mg/kg; □, 0.1 mg/kg; ●, 0.15 mg/kg; △, 0.2 mg/kg. (B) ○, Vehicle; ▲, 2.5 mg/kg; ◇, 5 mg/kg; ■, 10 mg/kg; ▽, 20 mg/kg. Data points represent the mean ± S.E.M. (dizocilpine: $n = 7$; memantine: $n = 10$). Asterisks indicate statistically significant differences from the vehicle injections ($P < 0.05$) by post hoc comparisons with Bonferroni correction after a significant main effect by ANOVA.

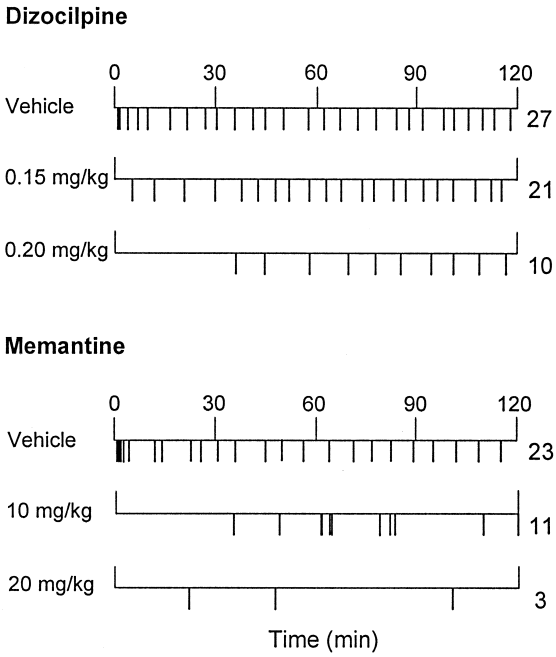

Fig. 3. Typical patterns of responding for cocaine (0.25 mg/infusion) on an FR5 TO 20-s schedule following dizocilpine and memantine administration. Each vertical mark on the horizontal time line indicates delivery of a single cocaine infusion. The numbers to the right of each line denote the total number of cocaine infusions during the 2-h session.

Because dizocilpine and memantine altered cocaine self-administration on the FR5 TO 20-s schedule, their effects were further studied using a PR schedule of cocaine self-administration. A separate group of rats ($n = 6$) was first trained to self-administer cocaine on the FR5 TO 20-s as described above. Once stable self-administration was achieved, animals were allowed to respond for cocaine (0.25 mg/infusion) on a PR schedule using an incrementing series of response ratios that were derived from the following equation (Richardson and Roberts, 1996): Response ratio $= [5e^{(\text{injection number} \times 0.16)}] - 5$. At the start of each 5-h session, the ratio value was reset to 1. Drug testing begun when less than 10% variation in the total number of cocaine infusions was seen during three consecutive sessions. Each subject was tested after an injection of saline, dizocilpine (0.15 mg/kg i.p.) and memantine (10 mg/kg i.p.), with at least two intervening sessions without drug pretreatment and with less than 10% deviation in the total number of infusions obtained. During the 5-h sessions, all rats achieved the criterion of the breaking point that was defined as the total number of cocaine infusions obtained by a rat prior to a 1-h period during which a ratio was not completed.

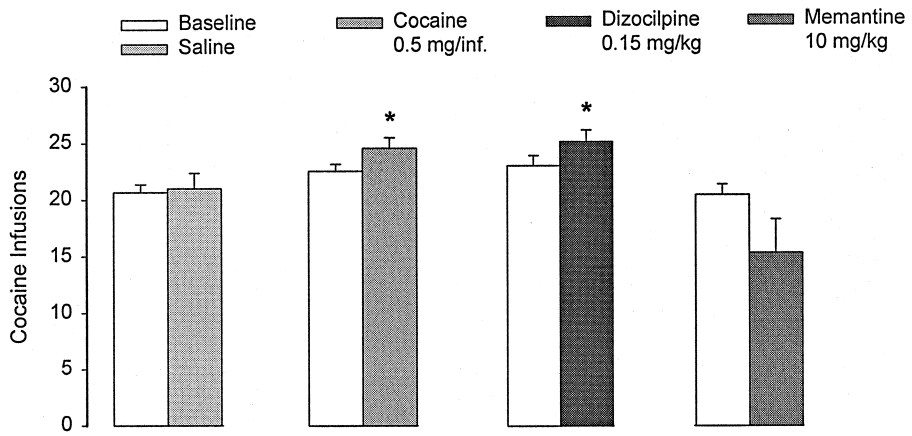

Fig. 4. Effects of increasing the cocaine unit dose (from 0.25 mg to 0.5 mg/infusion) and dizocilpine (0.15 mg/kg) and memantine (10 mg/kg) pretreatment on cocaine self-administration (0.25 mg/infusion) on a PR schedule ($n = 6$). The data, expressed as mean ± S.E.M., represent the number of cocaine infusions obtained during the session before a 1-h period during which no infusions were obtained. Asterisks indicate statistically significant differences from the baseline ($P < 0.05$) by paired *t*-tests.

2.6. Statistical analysis

The effects of each drug dose on cocaine self-administration on the FR5 TO 20-s schedule were expressed as percentage of the mean of total number of infusions during the two preceding baseline days and analysed with one-way within-subjects analyses of variance (ANOVA) with repeated measures on dose. Following a significant main effect of dose, each individual drug dose was compared with the vehicle condition using a post hoc means comparison with Bonferroni correction. For analysing cocaine responding as a function of elapsed time, the 2-h sessions were further divided into four 30-min blocks during which the effects of each dose were expressed as percentage of the mean number of responses during the two baseline days. These data were examined using a two-way within-subjects ANOVA with repeated measures on both dose and time block, followed by post hoc mean comparisons between each dose and vehicle at each time block using Bonferroni correction. The number of infusions earned on the PR schedule after drug pretreatment was compared with the mean of the two preceding baseline sessions using paired *t*-tests. Criterion for significance was set at the 0.05 level.

3. Results

Data presented in Fig. 1 show that both non-competitive NMDA receptor antagonists, dizocilpine and memantine, dose-dependently decreased cocaine self-administration during the 2-h sessions [main effects, dizocilpine: $F(4,24) = 18.16$, $P < 0.0001$; memantine: $F(4,36) = 12.06$, $P < 0.0001$]. In contrast, the competitive NMDA receptor antagonist CGP 39551 and the NMDA/glycine antagonist, L-701,324, failed to reliably alter the number of cocaine infusions [CGP 39551: $F(4,28) = 0.89$, $P > 0.05$; L-701,324: $F(4,32) = 2.34$, $P > 0.05$].

Figs. 2 and 3 indicate that pretreatment with dizocilpine and memantine, especially with the highest doses, altered the general pattern of responding for cocaine infusions. Although cocaine responding was suppressed throughout the 2-h session, the most conspicuous decreases were seen during the first 30-min block. A two-way (dose, time) repeated measures ANOVA conducted on the rate of responding during the four 30-min blocks revealed significant main effects for dose [dizocilpine: $F(4,24) = 13.88$, $P < 0.0001$; memantine: $F(4,36) = 9.96$, $P < 0.0001$] and time [dizocilpine: $F(3,18) = 20.33$, $P < 0.0001$; memantine: $F(3,27) = 21.22$, $P < 0.0001$], and a significant dose × time interaction [dizocilpine: $F(12,72) = 2.56$, $P < 0.01$; memantine: $F(12,108) = 2.40$, $P < 0.01$]. No significant main effects or interactions were found for the CGP 39551 or L-701,324 data.

In order to examine further the decreases found in cocaine self-administration after dizocilpine and memantine pretreatment, the effects of these drugs on cocaine self-administration were tested also using a PR schedule. Fig. 4 shows that pretreatment with 0.15 mg/kg dizocilpine increased the number of cocaine infusions earned on the PR schedule in the same manner as increasing the cocaine unit dose from 0.25 mg to 0.50 mg/infusion, suggesting that the decreases found on the FR5 TO 20-s schedule resulted at least partly from dizocilpine's effect on the reinforcing efficacy of cocaine. In contrast, memantine pretreatment tended to decrease the number of cocaine infusions on the PR schedule, suggestive of a nonspecific motor effect of memantine both on FR5 TO 20-s and PR schedules.

4. Discussion

In the present study, we investigated the modulation of intravenous cocaine self-administration by NMDA recep-

tor antagonists acting at three different modulatory sites on the NMDA receptor: the site for the endogenous transmitter glutamate (CGP 39551), the non-competitive binding site within the NMDA receptor channel (dizocilpine, memantine) and the NMDA/glycine-specific binding site (L-701,324). The cocaine unit dose (0.25 mg/infusion) and the reinforcement schedule (FR5 TO 20-s) used in the present experiments resulted in reliable responding for intravenous cocaine. Previously, responding for this unit dose of cocaine on the FR5 TO 20-s schedule has been demonstrated to be sensitive to changes in the unit dose and pretreatment with dopamine antagonists: a decrease in the unit dose or pretreatment with a dopamine D_1 receptor antagonist SCH23390 increases the number of cocaine infusions, whereas increasing the unit dose decreases cocaine responding (e.g., see Caine and Koob, 1994; Epping-Jordan et al., 1998).

Of the four NMDA receptor antagonists tested, the non-competitive antagonists, dizocilpine and memantine, produced significant and dose-dependent decreases in the number of cocaine infusions on the FR5 TO 20-s schedule, while the competitive glutamate site antagonist, CGP 39551, and the NMDA/glycine site antagonist, L-701,324, failed to significantly alter cocaine responding. Examination of the temporal pattern of cocaine responding during the session revealed that dizocilpine and memantine, at doses that significantly reduced the number of cocaine infusions, increased the inter-infusion intervals mostly during the first half of the session. Particularly after higher dizocilpine and memantine doses, the typical burst of responding at the onset of the session was eliminated in many subjects. While reductions in the total number of cocaine infusions resemble changes produced by increases in the unit dose, the response patterns suggest that both dizocilpine and memantine could also have nonspecific effects on responding, e.g., by impairing motor performance. Therefore, the effects of these drugs on cocaine self-administration were tested also using a PR paradigm that has been used widely for investigating the effects of various compounds on the rewarding value of self-administered drugs (Richardson and Roberts, 1996). Consistently with previous findings (Ranaldi et al., 1996), both increasing the cocaine unit dose and pretreatment with 0.15 mg/kg dizocilpine increased the number of cocaine infusions obtained; moreover, the mean FR value reached at the breaking point after dizocilpine was very high (369 ± 72), indicating that at this dose dizocilpine's effects on motor performance were negligible. Together, our results both from the dose-response analysis and the PR probe support the view presented earlier that dizocilpine enhances the reinforcing efficacy of self-administered cocaine (Ranaldi et al., 1996; Pierce et al., 1997).

In contrast to dizocilpine, memantine produced variable effects on the PR schedule, with most animals showing decreases in the number of cocaine infusions earned. Memantine is a low-affinity non-competitive NMDA receptor antagonist that has been shown to produce full substitution in dizocilpine- and phencyclidine-trained rats only at doses (10–17 mg/kg) that significantly reduce response rate in drug discrimination paradigms (Grant et al., 1996; Nicholson et al., 1998). At the dose range used, any measurement of memantine's effects on the reinforcing efficacy of cocaine on a PR schedule that requires emitting hundreds of responses for a single reinforcer is thus probably influenced by impairment in motor ability. The reasons for the rate-reducing effects of memantine are not known; they could be caused by memantine's NMDA receptor blocking activity or by its effects on other neurotransmitter systems.

The lack of effects by CGP 39551 and L-701,324 on cocaine self-administration cannot be explained by insufficient dosing of the compounds. For example, systemic doses of CGP 39551 used in the present study have been shown to have anticonvulsant activity (De Sarro et al., 1996); L-701,324 has anxiolytic actions and attenuates both spontaneous and amphetamine-induced locomotor activity in the dose range used (Bristow et al., 1996; Kotlinska and Liljequist, 1998). Since these compounds have the same mechanism of action as dizocilpine and memantine, i.e., antagonism of glutamatergic neurotransmission, their differential effects on cocaine self-administration could perhaps be explained by their interactions with other transmitter systems. Indeed, NMDA receptor antagonists differ remarkably from each other in their ability to facilitate the mesocorticolimbic dopamine function that has been hypothesized to have a central role in the mediation of cocaine reinforcement (Koob, 1992). There is a good correlation between the ability of various antagonists to enhance dopaminergic neurotransmission and increase horizontal locomotor activity. For example, both dizocilpine and memantine increase dopamine release and metabolism in the nucleus accumbens (Bubser et al., 1992; Löscher et al., 1993; Spanagel et al., 1994; Miller and Abercrombie, 1996); these drugs also increase locomotor activity (Bubser et al., 1992; Löscher et al., 1993; Danysz et al., 1994). In contrast, CGP 39551 and L-701,324 fail to significantly alter dopaminergic function in any brain area (Bubser et al., 1992; Löscher et al., 1993) and either they do not affect locomotor activity in the dose range used or, depending on the rodent species and strain, may even depress it (Liljequist, 1991; Bristow et al., 1996).

It is not clear, however, whether stimulation of locomotor activity and the putative enhancement of cocaine reward by dizocilpine are entirely dependent on the mesocorticolimbic dopamine. Dizocilpine-induced locomotor stimulation cannot be blocked by bilateral 6-hydroxydopamine lesions to the nucleus accumbens or dopamine D_1 receptor antagonists (Ouagazzal et al., 1994; Mele et al., 1996) and dizocilpine can stimulate locomotion at doses that do not result in detectable increase in extracellular dopamine in the nucleus accumbens (Whitton et al., 1992a). Moreover, self-administration of non-competitive NMDA receptor antagonists into the nucleus accumbens is not altered by

co-infusion of the dopamine D_2 receptor antagonist sulpiride (Carlezon and Wise, 1996). These findings have led to the hypothesis that dopamine agonists and NMDA receptor antagonists may have similar yet independent actions in the nucleus accumbens: they may both act to decrease the activity of the γ-aminobutyric acid (GABA)-ergic medium spiny output neurons that are postulated to serve as the final path of drug reinforcement (Carlezon and Wise, 1996; Ranaldi et al., 1997). Therefore, the differential effects of the NMDA receptor antagonists on cocaine self-administration in the present study may not solely depend on their actions on mesocorticolimbic dopamine function. It should also be noted that neuronal pathways other than the mesocorticolimbic dopamine system are modulated by the action of antagonists at the NMDA receptor complex, e.g., the serotonergic and cholinergic systems that could contribute to cocaine reward. Dizocilpine increases serotonin release and metabolism in various brain regions, while CGP 39551 does not (Whitton et al., 1992b; Löscher et al., 1993). Similarly, antagonists acting at different sites of the NMDA receptor complex have different effects on hippocampal and striatal acetylcholine efflux (Hutson and Hogg, 1996).

In summary, NMDA receptor antagonists acting at different sites of the NMDA receptor complex were found either to decrease cocaine self-administration or to have no effect. Only the non-competitive channel blockers, dizocilpine and memantine decreased cocaine responding on the FR5 TO 20-s schedule; a further analysis using a PR schedule suggested that dizocilpine's effects were due to enhancement of cocaine reward, whereas memantine's rate decreasing effects excluded analysis of its effects on the reinforcing properties of cocaine. The failure of the competitive NMDA receptor antagonist CGP 39551 and the NMDA/glycine-site antagonist L-701,342 to affect cocaine self-administration suggests that the endogenous agonist binding site and the NMDA/glycine recognition site are not as important as the non-competitive binding site in the modulation of cocaine reinforcement. However, we have to be cautious about this conclusion because the pharmacological profiles of NMDA receptor antagonists are probably influenced both by their specific actions at the recognition site on the NMDA receptor and by their complex interaction with other neurotransmitter systems that could result from the unique properties of each compound determined by their chemical structures.

Acknowledgements

Supported by the Swedish Medical Research Council (Project No. 7688), and funds from the Karolinska Institutet (Stockholm) and the National Public Health Institute (Helsinki).

References

Bormann, J., 1989. Memantine is a potent blocker of *N*-methyl-D-aspartate (NMDA) receptor channels. Eur. J. Pharmacol. 166, 591–592.

Bristow, L.J., Flatman, K.L., Hutson, P.H., Kulagowski, J.J., Leeson, P.D., Young, L., Tricklebank, M.D., 1996. The atypical neuroleptic profile of the glycine/*N*-methyl-D-aspartate receptor antagonist, L-701,324, in rodents. J. Pharmacol. Exp. Ther. 277, 578–585.

Bubser, M., Keseberg, U., Notz, P.K., Schmidt, W.J., 1992. Differential behavioural and neurochemical effects of competitive and non-competitive NMDA receptor antagonists in rats. Eur. J. Pharmacol. 229, 75–82.

Caine, S.B., Koob, G.F., 1994. Effects of dopamine D-1 and D-2 antagonists on cocaine self-administration under different schedules of reinforcement in the rat. J. Pharmacol. Exp. Ther. 270, 209–218.

Caine, S.B., Lintz, R., Koob, G.F., 1993. Intravenous drug self-administration techniques in animals. In: Sahgal, A. (Ed.), Behavioral Neuroscience: A Practical Approach. Oxford Univ. Press, Oxford, pp. 117–143.

Carlezon, W.A. Jr., Wise, R.A., 1996. Rewarding actions of phencyclidine and related drugs in nucleus accumbens shell and frontal cortex. J. Neurosci. 16, 3112–3122.

Danysz, W., Parsons, C.G., 1998. Glysine and *N*-methyl-D-aspartate receptors: physiological significance and possible therapeutic applications. Pharmacol. Rev. 50, 597–664.

Danysz, W., Essmann, U., Bresink, I., Wilke, R., 1994. Glutamate antagonists have different effects on spontaneous locomotor activity in rats. Pharmacol. Biochem. Behav. 48, 111–118.

De Sarro, G., De Sarro, A., Ammendola, D., Patel, S., 1996. Lack of development of tolerance to anticonvulsant effects of two excitatory amino acid antagonists, CGP 37849 and CGP 39551 in genetically epilepsy-prone rats. Brain Res. 734, 91–97.

DeVries, T.J., Schoffelmeer, A.N., Binnekade, R., Mulder, A.H., Vanderschuren, L.J., 1998. MK-801 reinstates drug-seeking behaviour in cocaine-trained rats. NeuroReport 9, 637–640.

Epping-Jordan, M.P., Markou, A., Koob, G.F., 1998. The dopamine D-1 receptor antagonist SCH 23390 injected into the dorsolateral bed nucleus of the stria terminalis decreased cocaine reinforcement in the rat. Brain Res. 784, 105–115.

Fagg, G.E., Olpe, H.-R., Pozza, M.F., Baud, J., Steinmann, M., Smutz, M., Portet, C., Baumann, P., Thedinga, K., Bittiger, H., Allgeier, H., Heckendorn, R., Angst, C., Brundish, D., Dingwall, J.G., 1990. CGP 37849 and CGP 39551: novel and potent competitive *N*-methyl-D-aspartate receptor antagonists with oral activity. Br. J. Pharmacol. 99, 791–797.

Grant, K.A., Colombo, G., Grant, J., Rogawski, M.A., 1996. Dizocilpine-like discriminative stimulus effects of low-affinity uncompetitive NMDA receptor antagonists. Neuropharmacology 35, 1709–1719.

Hutson, P.H., Hogg, J.E., 1996. Effects of and interactions between antagonists for different sites on the NMDA receptor complex on hippocampal and striatal acetylcholine efflux in vivo. Eur. J. Pharmacol. 295, 45–52.

Karler, R., Calder, L.D., Chaudhry, I.A., Turkanis, S.A., 1989. Blockade of ''reverse tolerance'' to cocaine and amphetamine by MK-801. Life Sci. 45, 599–606.

Koob, G.F., 1992. Drugs of abuse: anatomy, pharmacology and function of reward pathways. Trends Pharmacol. Sci. 13, 177–184.

Kotlinska, J., Liljequist, S., 1998. A characterization of anxiolytic like actions induced by the novel NMDA/glysine site antagonist, L-701,324. Psychopharmacology 135, 175–181.

Kulagowski, J.J., Baker, R., Curtis, N.R., Leeson, P.D., Mawer, I.M., Moseley, A.M., Ridgill, M.P., Rowley, M., Stansfield, I., Foster, A.C., Grimwood, S., Hill, R.G., Kemp, J.A., Marshall, G.R., Saywell, K.L., Tricklebank, M.D., 1994. 3′-(Arylmethyl)- and 3′-(aryloxy)-3-phenyl-4-hydroxyquinolin-2(1*H*)-ones: orally active antagonists of the glycine site on the NMDA receptor. J. Med. Chem. 37, 1402–1405.

Liljequist, S., 1991. Genetic differences in the effects of competitive and non-competitive NMDA receptor antagonists on locomotor activity in mice. Psychopharmacology 104, 17–21.

Löscher, W., Annies, R., Hönack, D., 1993. Comparison of competitive and uncompetitive NMDA receptor antagonists with regard to monoaminergic neuronal activity and behavioural effects in rats. Eur. J. Pharmacol. 242, 263–274.

Mele, A., Castellano, C., Felici, A., Cabib, S., Caccia, S., Oliverio, A., 1996. Dopamine–*N*-methyl-D-aspartate interactions in the modulation of locomotor activity and memory consolidation in mice. Eur. J. Pharmacol. 308, 1–12.

Miller, D.W., Abercrombie, E.D., 1996. Effects of MK-801 on spontaneous and amphetamine-stimulated dopamine release in striatum measured with in vivo microdialysis in awake rats. Brain Res. Bull. 40, 57–62.

Nicholson, K.L., Jones, H.E., Balster, R.L., 1998. Evaluation of the reinforcing and discriminative stimulus properties of the low-affinity *N*-methyl-D-aspartate channel blocker memantine. Behav. Pharmacol. 9, 231–243.

Ouagazzal, A., Nieoullon, A., Amalric, M., 1994. Locomotor activation induced by MK-801 in the rat: postsynaptic interactions with dopamine receptors in the ventral striatum. Eur. J. Pharmacol. 251, 229–236.

Pierce, R.C., Meil, W.M., Kalivas, P.W., 1997. The NMDA antagonist, dizocilpine, enhances cocaine reinforcement without influencing mesoaccumbens dopamine transmission. Psychopharmacology 133, 188–195.

Pulvirenti, L., Maldonado-Lopez, R., Koob, G.F., 1992. NMDA receptors in the nucleus accumbens modulate intravenous cocaine but not heroin self-administration in the rat. Brain Res. 594, 327–330.

Pulvirenti, L., Balducci, C., Koob, G.F., 1997. Dextromethorphan reduces intravenous cocaine self-administration in the rat. Eur. J. Pharmacol. 321, 279–283.

Ranaldi, R., French, E., Roberts, D.C.S., 1996. Systemic pretreatment with MK-801 (dizocilpine) increases breaking points for self-administration of cocaine on a progressive ratio schedule in rats. Psychopharmacology 128, 83–88.

Ranaldi, R., Bauco, P., Wise, R.A., 1997. Synergistic effects of cocaine and dizocilpine (MK-801) on brain stimulation reward. Brain Res. 760, 231–237.

Richardson, N.R., Roberts, D.C.S., 1996. Progressive ratio schedules in drug self-administration studies in rats: a method to evaluate reinforcing efficacy. J. Neurosci. Methods 66, 1–11.

Rockhold, R.W., 1998. Glutamatergic involvement in psychomotor stimulant action. In: Jucker, E. (Ed.), Progress in Drug Research. Birkhäuser Verlag, Basel, pp. 155–192.

Schenk, S., Valadez, A., McNamara, C., House, D.T., Higley, D., Bankson, M.G., Gibbs, S., Horger, B.A., 1993. Development and expression of sensitization to cocaine's reinforcing properties: role of NMDA receptors. Psychopharmacology 111, 332–338.

Spanagel, R., Eilbacher, B., Wilke, R., 1994. Memantine-induced dopamine release in the prefrontal cortex and striatum of the rat — a pharmacokinetic microdialysis study. Eur. J. Pharmacol. 262, 21–26.

Whitton, P.S., Biggs, C.S., Pearce, B.R., Fowler, L.J., 1992a. Regional effects of MK-801 on dopamine and its metabolites studied by in vivo microdialysis. Neurosci. Lett. 142, 5–8.

Whitton, P.S., Biggs, C.S., Pearce, B.R., Fowler, L.J., 1992b. MK-801 increases extracellular 5-hydroxytryptamine in rat hippocampus and striatum in vivo. J. Neurochem. 58, 1573–1575.

Wong, E.H., Kemp, J.A., Priestley, T., Knight, A.R., Woodruff, G.N., Iversen, L.L., 1986. The anticonvulsant MK-801 is a potent *N*-methyl-D-aspartate antagonist. Proc. Natl. Acad. Sci. U.S.A. 83, 7104–7108.