ELSEVIER

European Journal of Pharmacology 295 (1996) 19–25

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Modulation of cocaine intravenous self-administration in drug-naive animals by dihydropyridine Ca^{2+} channel modulators

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Received 1 September 1995; revised 25 September 1995; accepted 29 September 1995

Abstract

The dihydropyridine Ca^{2+} channel blocker nimodipine and the dihydropyridine Ca^{2+} channel activator BayK 8644 (1,4-dihydropyridine-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)-pyridine-5-carboxylate) were administered to drug-naive mice and rats that were tested for intravenous cocaine self-administration. A range of cocaine doses was tested to investigate the nature of the effect. The results indicate that nimodipine and BayK 8644 shifted the dose-response curve for cocaine's reinforcing action to the right and left, respectively. Thus, the Ca^{2+} channel blocker nimodipine decreases the sensitivity of mice and rats to the reinforcing effects of cocaine while the Ca^{2+} channel activator BayK 8644 makes the animals more sensitive to cocaine reward. The results suggest that a dihydropyridine-sensitive mechanism is implicated in the initiation of cocaine self-administration.

Keywords: Cocaine; Nimodipine; BayK 8644; Self-administration, i.v.; (Rat); (Mouse)

1. Introduction

Cocaine is a widely abused drug but until now treatment of cocaine dependence has not been very successful. Cocaine acts primarily on monoaminergic systems, by blocking the reuptake of dopamine, noradrenaline and serotonin. The reinforcing properties of cocaine have been associated with its effect on dopamine transporter sites (Woolverton and Johanson, 1992). The cocaine-induced increase in synaptic dopamine has been shown to be sensitive to the level of extracellular Ca^{2+} ions (Hurd and Ungerstedt, 1989). Systemic administration of dihydropyridine Ca^{2+} channel antagonists inhibits cocaine-induced dopamine release and cocaine-induced motor activation (Pani et al., 1990). Assuming the proposed critical role of dopamine in cocaine reinforcement, dihydropyridine Ca^{2+} channel blockers are expected to inhibit the reinforcing effects of cocaine. Accordingly it has been shown that isradipine, a potent dihydropyridine Ca^{2+} channel blocker, inhibits in a dose-related manner cocaine-induced place conditioning (Pani et al., 1991) and antagonizes cocaine intake in rats, during the maintenance phase of intravenous self-administration (Martellotta et al., 1994). Moreover, nimodipine, a dihydropyridine Ca^{2+} channel blocker, but not haloperidol, a non-selective dopamine receptor antagonist, blocks the expression of the behavioral component of cocaine-induced sensitization (Reimer and Martin-Iverson, 1994). Thus, it was of interest to evaluate the influence of dihydropyridine Ca^{2+} channel blockers and activators on the reinforcing effects of cocaine, using the method of initiation of drug self-administration. During initiation in particular the reinforcing effects of cocaine are assessed while during maintenance other effects of cocaine contibute to drug intake (Van Ree, 1979).

Thus, the dihydropyridine Ca^{2+} channel blocker nimodipine and the Ca^{2+} channel activator BayK 8644 (1,4-dihydropyridine-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)-pyridine-5-carboxylate) were administered to drug-naive mice and rats, that were tested

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SSDI 0014-2999(95)00630-3

for initiation of intravenous cocaine self-administration. A range of cocaine doses was tested to analyze the nature of the effect.

2. Materials and methods

2.1. Animals

Male albino mice, weighing 20–22 g (Rappolovo State Breeding Laboratory, Russia), and male Wistar rats, weighing 180–220 g (TNO Zeist, The Netherlands), were used. Before the experiments the animals were kept under standard laboratory conditions (temperature 20–21°C, 60–65% relative humidity and 12/12 h light regime with lights on at 10 a.m. [mice] and at 7 a.m. [rats]) with unlimited access to food and water.

2.2. Intravenous self-administration in mice

Mice were tested in pairs in identical test cages. Pairs of animals were selected on the basis of approximately equal levels of nose poking during preliminary testing without injections. Each cage had a frontal hole for nose poking that was equipped with infrared sensors interfaced to a computer. Both mice were partially immobilized by fixing their tails, which protruded through a vertical slot in the back wall, by Scotch tape to a horizontal surface. Each nose poke of the active mouse resulted in a contingent injection of 1.6 μl of either saline or cocaine solution to the lateral tail vein of both the active mouse and the yoked passive mouse. Nose pokes of the yoked passive mice were counted but had no programmed consequences. After 10 min of habituation to the test cage, an injection was made contingent upon each nose poke of the active animal. Cocaine was tested in graded concentrations (0.06–1.5 mg/ml); nimodipine (5.0–20.0 mg/kg, s.c.), BayK 8644 (0.1–0.4 mg/kg, s.c.) and their vehicle were administered to separate groups of animals 30 min prior to the self-administration session. As a gradual measure of the reinforcing effect of the drug solution (R criterion), the ratio between the cumulative number of the nose poke responses of the active and passive mice during a 30-min period of self-infusions minus one (the initial ratio of the responses of animals in the pair) was used (Kuzmin et al., 1994). The effect of the drug in each pair was considered reinforcing, neutral or aversive when R was higher, equal or smaller than 0, respectively. As a alternative measure of the reinforcing effect of the drug ($N+$ criterion), the number of pairs of animals in the group with R higher than the upper confidence limit (95%) of R in a group with saline self-administration ($R > 0.4$) was used (Kuzmin et al., 1994).

The differences between cocaine and saline self-administration (R criterion) were statistically analyzed with a one-way analysis of variance followed by Newman-Keuls test. $N+$ values were analyzed using Fisher exact test. The theoretical optimal concentration was calculated after construction of the theoretical equation of the dependence of R on the concentration of cocaine with the aid of multifactor regression method (first factor – cocaine concentration, second factor – square of cocaine concentration).

2.3. Intravenous self-administration in rats

Details of the experimental set-up and procedure have been published elsewhere (see Van Ree et al., 1978; Van Ree and Ramsey, 1987). Rats, which had no previous experience with operant behavior procedures, were equipped with a silicone intravenous cannula in the right jugular vein. After surgery each rat was housed individually and was left undisturbed for 4 days, after which the day-night cycle was reversed and food supply was restricted. Testing and treatment started 3 days later. Testing consisted of five consecutive 3-h daily sessions. Each session was terminated individually either after 3 h or when a maximum of 60 infusions had been reached within that period. Before each session the rats were weighed and their cannulas were flushed with saline. Rats were treated 30 min before each session with either nimodipine (20 mg/kg, s.c.) or BayK 8644 (0.5 mg/kg, s.c.) or vehicle. Testing was done in standard operant chambers with two levers protruding from one wall. Only one lever (reinforcement lever) was connected to an infusion pump, and had a red light above it. Depression of this lever triggered a 13 s infusion (0.25 ml, FR1), while depression of the other (the dummy lever) had no programmed consequences. Responding on the reinforcement lever while an infusion was taking place was not followed by another infusion. Responses on both levers were recorded. After the fifth and last session proper placement and functioning of the cannulas were verified.

In separate experiments, with different rats each time, the infusion fluid contained saline, or 15, 30 or 60 μg cocaine dissolved in saline per infusion. Thus in each experiment half of the rats were pretreated with nimodipine (20 mg/kg) or BayK 8644 (0.5 mg/kg) and the other half with vehicle, and all of them had the same cocaine dose available. Each rat was tested only once. The number of animals per treated group varied between 7 and 14. The number of self-infusions on sessions 2 to 5 was statistically analyzed using two-way analyses of variance with repeated measurements. The number of responses on the dummy lever was similarily analyzed. The data of day 1 were not included in the analysis because some rats did not show regular responding over time on that day. An overall analysis was

Table 1
Concentration-dependent reinforcing effect of cocaine in drug-naive mice

Cocaine concentration (mg/ml)	R	$N+/N$
0 (saline)	-0.03 ± 0.17	1/18
0.125	0.20 ± 0.03	0/6
0.25	1.87 ± 0.44 [a]	6/6 [b]
0.5	1.04 ± 0.25 [a]	4/6
1.0	-0.38 ± 0.06	0/6

An intravenous injection of 1.6 μl cocaine at the indicated concentration was made contingent upon each nose poke response of the active mouse. R: the ratio between the cumulative number of the nose poke responses of the active and passive mice during a 30-min period of intravenous self-infusions, minus one. Each value is the mean $\pm$ S.E.M. of the number of pairs of mice indicated in column N. $N+$: represents the number of pairs (left value) in the whole group (right value) with $R > 0.4$. [a,b] $P < 0.05$ as compared to the animals self-administering saline (Newman-Keuls test and Fishers exact test, respectively).

performed, which was followed by analysis of each cocaine dose or saline per treatment.

2.4. Drugs

Nimodipine and BayK 8644 (1,4-dihydropyridine-2,6-dimethyl-3-nitro-4-(2-trifluoromethylphenyl)-pyridine-5-carboxylate) were kindly donated by Bayer AG (Germany). Cocaine HCl was obtained from Sigma

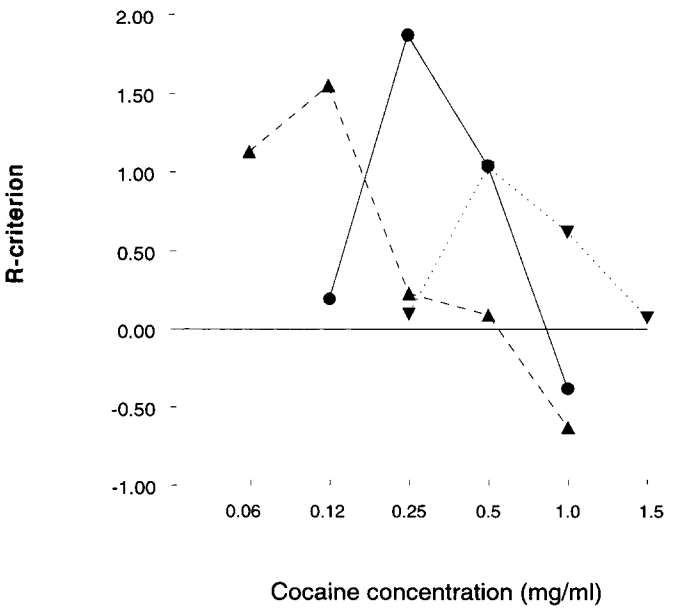

Fig. 1. Influence of nimodipine (▼; 10 mg/kg SC), BayK 8644 (▲; 0.2 mg/kg s.c.) and vehicle (●) on the concentration-dependent reinforcing effect of cocaine in the self-administration test with mice. Data points represent means (R criterion); error bars are not shown to improve the clarity of the figure. For statistics see text.

Table 2
Influence of nimodipine and BayK 8644 on the reinforcing effect of cocaine (0.25 mg/ml) in drug-naive mice

Pretreatment (mg/kg)	R	$N+/N$
Vehicle	1.78 ± 0.17	6/6
Nimodipine		
5.0	1.40 ± 0.50	4/6
10.0	0.60 ± 0.20 [a]	1/6
20.0	-0.20 ± 0.08 [a]	0/6 [b]
Bay K 8644		
0.1	0.77 ± 0.25	4/6
0.2	0.23 ± 0.20 [a]	2/6
0.4	-0.08 ± 0.20 [a]	1/6

For legends see Table 1. [a,b] $P < 0.05$ as compared to the vehicle-treated group (Newman-Keuls test and Fishers exact test, respectively).

(USA) or OPG (The Netherlands). Nimodipine and BayK 8644 were freshly dissolved in pure ethanol and the stock solutions were diluted to the required concentration with distilled water (20% ethanol solution at the end). Both stock and final solutions were carefully protected from light. The drugs were injected s.c. in a volume 1 ml/kg in mice and 0.5 ml/kg in rats 30 min before the self-administration session. Cocaine HCl was dissolved in saline and the pH of the solution was adjusted to 7.3 by 0.01 N NaOH.

3. Results

3.1. Intravenous self-administration in mice

There was no statistically significant difference in the mean number of nose poke responses of the active and passive mice when saline injections were made contingent upon nose pokes; R was not different from zero (Table 1). Cocaine in all the concentrations tested increased nose poke responses in both active and passive mice, but modified R in a different way depending on the dose. The R criterion was highest at the concentration of 0.25 mg/ml. Thus, this concentration was

Table 3
Theoretical equations for concentration-response curves for cocaine self-administration in mice and calculated potency and efficacy.

Pretreatment (mg/kg)	Equation	Optimal concentration (mg/ml)	R in optimal concentration
Vehicle	$R = 6.3x - 6.7x^2 - 0.1$	0.47	1.43
Nimodipine (20)	$R = 3.2x - 1.9x^2 - 0.4$	0.84	0.95
BayK 8644 (0.2)	$R = 2.2x^2 - 0.4x + 1.6$	0.10	1.58

Optimal points were calculated after construction of theoretical concentration-response equations by using the multifactor regression method.

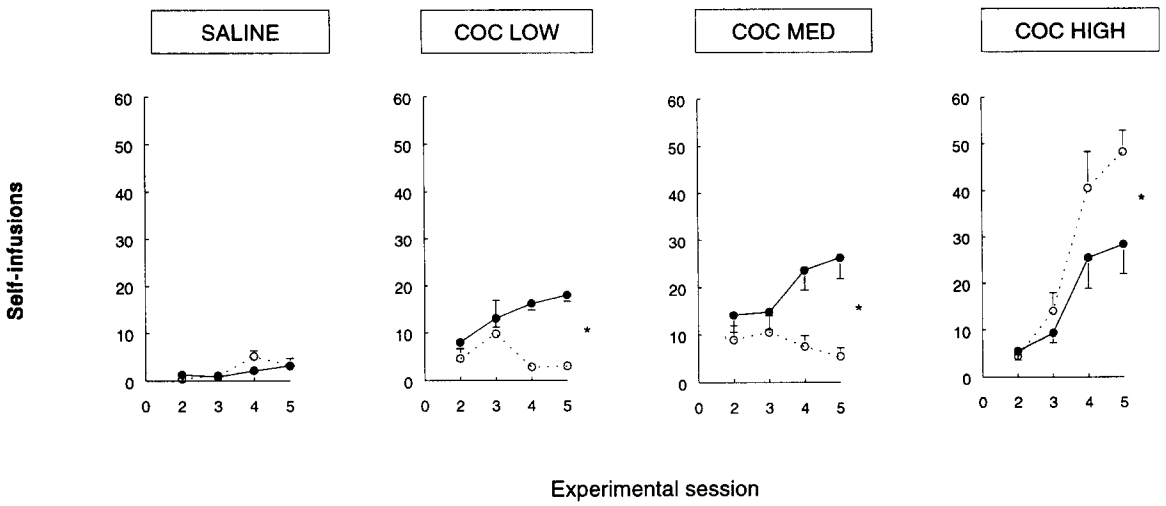

Fig. 2. Effect of nimodipine (20 mg/kg s.c.) on self-administration of saline or one of three doses of cocaine (low dose 15 μg; medium dose 30 μg; high dose 60 μg per infusion). Shown are mean numbers of self-infusions (with S.E.M.) for nimodipine (○)- and vehicle (●)-treated rats. * Significant treatment and/or treatment × time effect. See text for details.

considered to be optimal for cocaine self-administration. The calculated theoretical value for the optimal concentration of cocaine was 0.47 mg/ml (Table 3).

Nimodipine and BayK 8644 were tested in graded doses, using the optimal concentration of cocaine. Both drugs decreased R in a dose-related manner (Table 2). The ED_{50} (and confidence limits) of nimodipine and BayK 8644 were 6.2 (3.8–10.1) and 0.15 (0.07–0.32) mg/kg, respectively (calculated with the aid of the Litchfield and Wilcoxon method).

Next, nimodipine (20 mg/kg) and BayK 8644 (0.2 mg/kg) were tested with graded concentrations of cocaine. The doses of dihydropyridines were selected on the basis that they caused an approximately identical inhibition of R (see Table 2). Nimodipine produced a shift of the concentration-response cocaine curve to the right, with the theoretical optimal concentration of cocaine being 0.84 mg/ml (Fig. 1, Table 3). BayK 8644 exhibited the opposite effect, producing a shift of the curve to the left, with the optimal concentration of cocaine being 0.10 mg/ml (Fig. 1, Table 3). As compared to vehicle-treated animals, nimodipine significantly decreased and increased the R criterion at cocaine concentrations of 0.25 and 1.0 mg/ml, respectively ($t = 3.8$, $P < 0.01$ and $t = 5.5$, $P < 0.01$), while BayK 8644 significantly increased the R criterion at

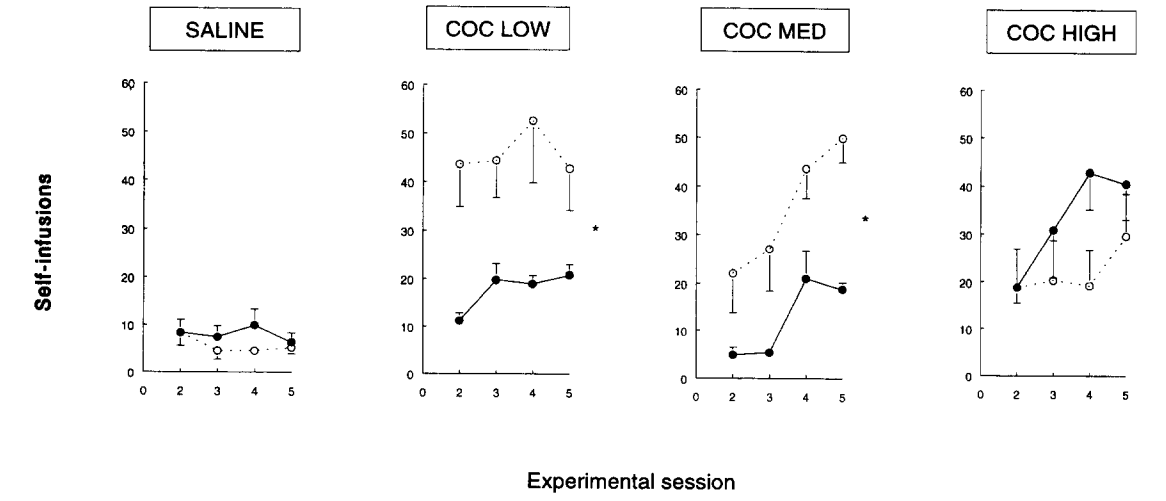

Fig. 3. Effect of BayK 8644 (0.5 mg/kg s.c.) on self-administration of saline or one of three doses of cocaine (low dose 15 μg; medium dose 30 μg; high dose 60 μg per infusion). Shown are mean numbers of self-infusions (with S.E.M.) for BayK 8644 (○)- and vehicle (●)-treated rats. * Significant treatment and/or treatment × time effect. See text for details.

cocaine concentrations of 0.125 ($t = 5.4$, $P < 0.01$) and decreased the R criterion at cocaine concentrations of 0.25, 0.50 and 1.0 mg/ml ($t = 3.4$, $P < 0.01$; $t = 3.6$, $P < 0.01$ and $t = 3.6$, $P < 0.01$, respectively).

3.2. Intravenous self-administration in rats

Self-administration behavior was readily acquired and increased during the first days reaching a ceiling on the fourth and fifth days. As shown in the Figs. 2 and 3 (influence of nimodipine 20 mg/kg and BayK 8644 0.5 mg/kg, respectively), rats treated with vehicle developed self-administration of cocaine at all concentrations tested. Overall analysis with treatment (nimodipine/BayK 8644 versus vehicle) and cocaine dose (0, 15, 30 and 60 μg) as between group factors and 'time' (four sessions) as within subject factor revealed that the main effect of cocaine dose was significant ($F(3,55) = 13.8$, $P < 0.01$), as was the interaction between cocaine dose and treatment ($F(3,55) = 5.62$, $P < 0.01$). There was no main effect of treatment. In addition, the overall time effect was significant ($F(3,165) = 23.76$, $P < 0.01$), as was interaction between time and cocaine dose ($F(9,165) = 12.69$, $P < 0.01$) and between time, cocaine dose and treatment ($F(9,165) = 4.33$, $P < 0.01$). Time and treatment did not interact. A multiple comparison test (Newman-Keuls test) on the average self-infusion rate over sessions revealed that only six groups of rats had higher self-infusion rates than the saline self-injecting groups, these being the BayK-cocaine low-dose group ($P < 0.01$), the vehicle-cocaine medium-dose group, BayK-cocaine medium-dose group ($P < 0.01$), the vehicle-cocaine high-dose group ($P < 0.05$) and the nimodipine-cocaine high-dose group ($P < 0.01$).

Subsequently the data were analyzed for each cocaine dose separately. In the saline experiment, nimodipine treatment did not affect the self-infusion rate (no main effect or interaction with time) (Fig. 2). Overall, the time effect was significant ($F(3,33) = 6.51$, $P < 0.01$). Self-administration of the low cocaine dose was affected by nimodipine treatment (main effect $F(1,8) = 8.07$, $P < 0.05$), treatment × time interaction $F(3,24) = 4.28$, $P < 0.05$). The main time effect was not significant. Similar results were obtained with the medium cocaine dose: there was a main treatment effect and an interaction between treatment and time ($F(1,23) = 7.96$, $P < 0.05$, and $F(3,39) = 5.48$, $P < 0.05$, respectively), without there being a main time effect. Finally, the self-infusion rate with the high cocaine dose was also affected by nimodipine treatment. There was an interaction between treatment and time ($F(3,39) = 3.12$, $P < 0.05$), but no main effect of treatment, and there was a main time effect ($F(3,39) = 32.88$, $P < 0.01$).

BayK 8644 treatment did not affect the self-infusion rate of saline infusions (no main effect or interaction with time) (Fig. 3). The main time effect was not significant. Self-administration of the low cocaine unit dose was affected by BayK 8644 treatment (main treatment effect $F(1,39) = 17.9$, $P < 0.01$), without there being a treatment × time interaction. The main time effect was not significant. Similar results were obtained with the medium cocaine dose: there was a main

Table 4
Influence of nimodipine (20 mg/kg s.c.) and BayK 8644 (0.5 mg/kg s.c.) on the number of presses on the non-reinforced lever during the 4 consecutive days of acquisition of self-administration of cocaine by rats

		Day of experiment			
		2	3	4	5
Saline	Vehicle/n	1.7 ± 0.8 [a]	1.4 ± 0.5	1.7 ± 0.5	1.4 ± 0.1
	Nimodipine	2.5 ± 0.8	2.3 ± 1.8	3.8 ± 1.7	2.2 ± 0.9
	Vehicle/b	9.4 ± 3.6	4.8 ± 5.8	3.9 ± 2.8	7.6 ± 6.5
	BayK 8644 [b]	15.7 ± 4.4	13.3 ± 6.5	13.7 ± 5.5	17.3 ± 5.9
Cocaine, low	Vehicle/n	4.0 ± 0.7	2.1 ± 0.4	4.0 ± 1.4	2.4 ± 1.3
	Nimodipine	3.0 ± 0.4	2.8 ± 1.4	0.4 ± 0.5	2.2 ± 1.6
	Vehicle/b	6.2 ± 0.8	2.6 ± 0.6	4.4 ± 1.5	3.8 ± 2.1
	BayK 8644 [c]	4.8 ± 2.0	13.8 ± 5.4	22.6 ± 4.1	23.2 ± 5.9
Cocaine, medium	Vehicle/n	3.6 ± 1.4	2.0 ± 0.9	1.3 ± 0.6	4.4 ± 1.1
	Nimodipine	5.7 ± 2.8	3.8 ± 1.8	5.5 ± 2.5	2.8 ± 1.4
	Vehicle/b	4.6 ± 1.3	2.6 ± 1.0	8.5 ± 3.7	5.4 ± 1.5
	BayK 8644 [c]	8.7 ± 2.3	8.0 ± 2.3	16.6 ± 6.9	15.7 ± 6.9
Cocaine, high	Vehicle/n	2.7 ± 0.4	4.8 ± 1.9	3.1 ± 1.2	8.3 ± 5.5
	Nimodipine	5.3 ± 2.2	3.0 ± 1.4	12.6 ± 9.6	31.6 ± 23.6
	Vehicle/b	17.1 ± 8.1	21.2 ± 7.3	19.2 ± 8.7	16.9 ± 7.1
	BayK 8644	26.4 ± 13.2	27.8 ± 18.4	26.6 ± 9.3	22.0 ± 3.8

[a] Means ± S.E.M.; [b] significant treatment effect versus vehicle; [c] significant main time effect.Vehicle/n and Vehicle/b: results with vehicle treatment for the groups with concurent treatment with nimodipine and BayK 8644, respectively.

treatment effect ($F(1,14) = 19.4$, $P < 0.01$) but no interaction between treatment and time, whereas the main effect of time was significant ($F(3,45) = 6.16$, $P < 0.01$). Finally, the self-infusion rate with the high cocaine unit dose was not affected by BayK 8644 treatment. There was no interaction between treatment and time and no main effect of treatment, but there was a main time effect ($F(3,.33) = 1.74$, $P < 0.05$).

The influence of nimodipine and BayK 8644 on pressing on the non-reinforced lever is presented in Table 4. Nimodipine did not significantly affect pressing on the non-reinforced lever in comparison to vehicle. Analysis of variance did not reveal time and treatment effects nor time × treatment interactions. The same results were obtained when the data were analyzed for each cocaine dose separately. BayK 8644 significantly increased the number of presses on the non-reinforced lever during saline self-administration ($F(3,19) = 3.55$, $P < 0.05$), without there being a time effect and a time × treatment interaction. With respect to the three cocaine doses, BayK 8644 did not influence the rate of responding on the non-reinforced lever (no treatment effect and no treatment × time interaction). There was a main time effect with the low ($F(2,19) = 3.61$, $P < 0.05$) and the medium ($F(3,45) = 2.16$, $P < 0.01$) but not the high dose of cocaine.

Taken together, the data show that nimodipine blocked self-administration of the low and the medium cocaine unit dose, but enhanced self-administration of the high dose, whereas self-administration of saline was not affected. This suggests that nimodipine caused a shift of the self-administration dose-response curve to the right. Whereas for vehicle-treated rats the medium cocaine dose was reinforcing (self-infusion rate exceeded that for saline), for nimodipine-treated rats it was not. With the high cocaine dose, vehicle-treated rats also showed development of self-administration behavior, but now the nimodipine-treated rats had an even higher self-infusion rate, as if the cocaine dose broke through the nimodipine blockade. BayK 8644 enhanced self-administration of the low and the medium cocaine dose, whereas self-administration of the high dose and that of saline was not affected. Thus, BayK 8644 caused a shift of the self-administration dose-response curve to the left. Whereas for vehicle-treated rats the medium cocaine dose was reinforcing (self-infusion rate exceeded that for saline), the low cocaine dose was already reinforcing in BayK 8644-treated rats

4. Discussion

The results show that pretreatment with the Ca^{2+} channel blocker nimodipine decreased the sensitivity of rats and mice to the reinforcing effects of cocaine while the Ca^{2+} channel activator BayK 8644 exhibited the opposite effect. These effects of the drugs could have been influenced by the solvent used (20% ethanol), since interactions between nimodipine and ethanol and BayK 8644 and ethanol have been reported (e.g. Isaacson et al., 1985, Dolin and Little, 1986; Dolin et al., 1988; Kiraç and Eroglu, 1991). However, this is very unlikely, because the amount of ethanol administered (0.16 g/kg in mice and 0.08 g/kg in rats) was far below the dose affecting the behavior of rodents (Rezvani et al., 1993; Scott et al., 1994) and that used in the interaction studies mentioned.

The simplest explanation for the observed effects is that Ca^{2+} modulators, through blockade or activation of Ca^{2+} inward currents in dopaminergic neurons, modify neurotransmitter release and decrease or increase, respectively, the activation of neurons in the nucleus accumbens among others. The modulation of biogenic amine content and metabolism by Ca^{2+} channel blockers and activators has been evaluated, but with contradictory results (Reimann and Kollhofer, 1988). Although the entry of Ca^{2+} into neurons is considered very important for the release of neurotransmitters, it has been difficult to demonstrate the functional role of the L-type channels in the release of catecholamines. In contrast, the dihydropyridine Ca^{2+} channel activator, BayK 8644 has been reported to facilitate directly the release of catecholamines (Middlemiss, 1985, Bechem et al., 1988). In contrast to the effect of BayK 8644 on neurotransmitter release, Ca^{2+} channel antagonists have been shown to be ineffective in this respect (Bourson et al., 1989; Hirning et al., 1988) or to elicit complex changes in the levels of monoamines in the central nervous system (Gaggi and Gianni, 1990). Moreover, direct studies of the influence of nimodipine on dopamine release in mouse brain also resulted in contradictory conclusions. While Nordström et al. (1986) reported that nimodipine enhanced the terminal release of dopamine from striatal slices, it has been also shown that nimodipine reduces dopamine synthesis and under certain conditions also dopamine release (Pielbad and Carlsson, 1986). Previous experiments with brain microdialysis showed that nimodipine failed to affect dopamine release in the ventral striatum of rats (Pani et al., 1990). Thus, Ca^{2+} channel blockers that interact specifically with the L-type channel, such as dihydropyridines (Spedding, 1987), have little effect on catecholamine release in non-drug-treated animals (Reimann and Kollhofer, 1988; Bourson et al., 1989). However, little is known about the influence of dihydropyridines on drug-induced enhanced release of dopamine. In addition, it is possible that L-type Ca^{2+} channels play a more important role in dopamine release in vivo than has been shown in in vitro studies. However, the observed effects of dihydropyridines may also be due to their

interaction with neuronal structures other than L-type channels (Glossman et al., 1989) or due to their modulating influence on the turnover or release of neurotransmitters other than dopamine. In fact, BayK 8644 has been shown to enhance the release of Met-enkephalin (Govoni et al., 1990). Thus, the influence of dihydropyridines on cocaine reward might be due to their action on the synthesis and turnover of endogenous opioids, which have been implicated in cocaine self-administration (De Vry et al., 1989; Sweep et al., 1989; Ramsey and Van Ree, 1991).

Irrespective to the mechanisms involved, the sensitivity of the reinforcing effects of cocaine and morphine (Kuzmin et al., 1992, 1994) to nimodipine and isradipine, dihydropyridine Ca^{2+} channel blockers, may serve as evidence in favor of the existence of a common dihydropypidine-sensitive mechanism for the rewarding action of morphine and cocaine.

Acknowledgements

The authors wish to thank Bayer Pharmaceutical Company (Germany) for the generous gift of Nimodipine and BayK 8644. This work was financially supported by the grant NWO 07-13-87 from Dutch Medical Council.

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