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κ-Opioid receptor agonist U50,488H modulates cocaine and morphine self-administration in drug-naive rats and mice

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Abstract

Modulation of the reinforcing effects of cocaine and morphine by the κ-opioid receptor agonist U50,488H (*trans*-3,4-dichloro-*N*-methyl-*N*-(2-1-pyrrolidinyl)-cyclohexyl-benzeacetamide) was studied by using the method of intravenous (i.v.) self-administration in drug-naive Wistar rats and DBA/2 mice. Self-administration of cocaine (by rats) and morphine (by mice) was readily initiated and showed an inverted U-shaped unit dose–response curve. Treatment with the κ-opioid receptor agonist U50,488H dose dependently decreased the intake of both cocaine and morphine when offered in doses that readily initiated and sustained self-administration behavior. Interestingly, treatment with U50,488H induced self-administration behavior with lower sub-threshold doses of cocaine and morphine. With regard to the inverted U-shaped relation between the dose of the drug and the number of self-infusions, it seems that activation of the κ-opioid receptor with U50,488H procuced an almost parallel shift to the left, indicating an increased sensitivity of the animals for the reinforcing effects of cocaine and morphine. These data demonstrate an involvement of κ-opioid systems in the neurobiological mechanisms underlying drug addiction in general, and sensitivity for drug reward in particular. Furthermore, the dual effect of κ-opioid receptor agonists on drug self-administration may prompt further research into the mechanisms underlying the role of endogenous opioids in drug self-administration.

Keywords: Drug self-administration; Cocaine; Morphine; (Rat); (Mouse); κ-Opioid receptor; U50,488H

1. Introduction

The effects of opioid drugs are thought to be mediated by the three major types of opioid receptors, the μ-, δ- and κ-opioid receptors. The physiological action of a specific opioid drug depends on, among others, the particular population of receptor types that is activated by the drug. Stimulation of μ- and δ-opioid receptors by specific agonists has been found to have reinforcing effects in several paradigms (Devine and Wise, 1994; Shippenberg et al., 1987), whereas aversive effects have been associated with the stimulation of the κ-opioid receptor. For example, the κ-opioid receptor agonist U50,488H was reported to induce conditioned place and taste aversion in animals (Shippenberg and Herz, 1987). The aversive properties of κ-opioid receptor agonists, including U50,488H, are probably mediated at both a peripheral and a central level (Bals-Kubic et al., 1989, 1993). Neurochemically, the effects of κ-opioid receptor agonists are proposed to be mediated through an action on dopamine activity in the nucleus accumbens. In several studies it was demonstrated that both systemic and intra-accumbal administration of κ-agonists decreases dopamine levels in the nucleus accumbens and inhibits the firing of dopamine neurons in, among others, the nucleus accumbens (Di Chiara and Imperato, 1988; Spanagel et al., 1990, 1992; Devine et al., 1993).

The results of behavioral studies are consistent with the antagonistic relationship between κ-opioid receptor agonists and dopamine functioning. For instance, Narita et al. (1993) showed that treatment with U50,488H blocked the increased dopamine turnover in the limbic forebrain in response to morphine treatment and concomitantly prevented morphine-induced behavioral sensitization. In addition, it is reported that treatment with the κ-opioid receptor agonists U69593 and U50,488H abolishes cocaine-induced

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behavioral sensitization (Heidbreder et al., 1995), probably by normalizing the cocaine-induced increases in basal levels of dopamine overflow in the nucleus accumbens (Maisonneuve et al., 1994).

There is also evidence that κ-opioid receptors play a role in the mediation of drug-induced reward. It has been reported that κ-opioid receptor agonists attenuate the preference for both morphine (Funada et al., 1993; Narita et al., 1993) and cocaine (Crawford et al., 1995; Suzuki et al., 1992) in a conditioned place preference paradigm. Shippenberg et al. (1996) demonstrated additionally that treatment with κ-opioid receptor agonists prevented the development of sensitization towards cocaine-induced conditioned effects in this paradigm. Furthermore, κ-opioid receptor agonists blocked the discriminative stimulus effect of morphine in rats (Spanagel and Shoaib, 1994) and of cocaine in monkeys (Spealman and Bergman, 1994). Finally, Glick et al. (1995) recently reported that treatment with the κ-opioid receptor agonists U50,488H and spiradoline decreases both morphine and cocaine self-administration in rats during the maintenance phase.

In view of these findings, it was of interest to further evaluate the involvement of κ-opioid receptors in the reinforcing effects of cocaine and morphine. In the present studies, we examined the effect of graded doses of the specific κ-opioid receptor agonist U50,488H on the reinforcing effects of graded doses of cocaine (in rats) and morphine (in mice), using the paradigm of initiation of intravenous self-administration. During the initation phase of self-administration, drug-taking behavior is thought to be mainly determined by the positive reinforcing effects of the drugs and less by other effects of the drug that contribute to drug intake during maintenance.

2. Materials and methods

2.1. Animals

Animals were male Wistar rats bred from our own stock (Utrecht, Netherlands) weighing 180–220 g and male DBA/2 mice (Rappolova State Breading Farm, St. Petersburg, Russian Federation) weighing 20–22 g. Before the experiments animals were housed in groups, received food and water ad libitum, and were kept under standard laboratory conditions (i.e., temperature 20–21°C, 60–65% relative humidity and 12/12 h light regimen with lights on at 7.00 a.m.).

2.2. Intravenous cocaine self-administration in rats

Details of the experimental set-up and procedure have been published previously (see Van Ree et al., 1978; Gerrits et al., 1994). Rats were equipped with a silicone intravenous (i.v.) cannula into 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 (lights on between 7.00 p.m. and 7.00 a.m.). At this time point the food supply was restricted in order to reduce the body weight by 20%, which has been shown to facilitate the initation of cocaine self-administration (De Vry et al., 1989). Testing and treatment started 3 days later. Testing was done in standard operant chambers with two levers protruding from one wall, one of which was marked by a red light placed just above the lever. The i.v. cannula was connected to an infusion pump. Depression of the lever marked with the red light (reinforcement lever) triggered a 13-s i.v. infusion (0.25 ml, fixed ratio 1). The red light went off during the infusion and pressing the lever during this time did not result in an infusion. Depression of the other lever had no programmed consequences (dummy lever). Drug and lever press-naive animals were placed in the test cages and were allowed to i.v. self-administer a drug solution for 3 h a day or until a maximum of 60 infusions had been reached. Testing took place in five consecutive daily sessions. After the fifth and last session, proper placement and functioning of the i.v. cannulas was verified.

For the first experiments separate groups of animals were allowed to i.v. self-administer saline, or graded doses of cocaine (7.5 (extra low), 15 (low), 30 (medium) or 60 (high) μg per infusion). Animals in each cocaine unit-dose group were treated i.p. daily 5 min prior to testing with placebo (saline) or U50,488H (2.5 mg/kg). For the subsequent experiments, separate groups of animals were allowed to i.v. self-administer a cocaine dose of 15 or 30 μg per infusion. Animals from each dose group were treated i.p. daily 5 min prior to testing with placebo (saline) or graded doses of U50,488H (0.625, 1.25 and 2.5 mg/kg). Each rat was tested only once. The number of animals per treatment group ranged between 6 and 14.

For the first series of experiments, the number of self-infusions obtained in sessions 2–5 was statistically analyzed using a two-way analysis of variance with repeated measurements, in which cocaine dose (0, 7.5, 15, 30 and 60 μg per infusion), treatment (placebo vs. U50,488H) and time (four sessions) were the variables. The data of day 1 were not included in the analysis because some rats did not show regular responding over time on that day. Following the overall analysis of the data, separate analyses were performed per cocaine dose. The differences in average number of self-infusions (mean of four sessions) between cocaine doses per treatment group were analyzed using a one-way analysis of variance with Student-Newman-Keuls test. For the second series of experiments the number of self-infusions (sessions 2–5) was statistically analyzed per cocaine dose group (15 or 30 μg per infusion) using a two-way analysis of variance with repeated measurements, in which treatment (placebo or graded doses of U50,488H) and time (four sessions) were the variables. A one-way analysis of variance with Student-Newman-Keuls test was used to analyze the differ-

ences in average number of self-infusions over the sessions between the different treatment groups. The number of responses on the dummy lever in either series of experiments was analyzed using two-way analysis of variance with repeated measurements.

2.3. Intravenous morphine self-administration in mice

Mice were tested in pairs (active and yoked control) in identical test cages ($8 \times 8 \times 8$ cm) made from non-transparent material. Each cage had a frontal hole for nose-poking supported with infrared sensors interfaced to a computer. Mice were partially immobilized by fixing their tails, which protruded through the vertical slot in the back wall, by Scotch tape to the horizontal surface. Pairs of animals were selected on the basis of approximately equal levels of nose-poking assessed before testing ('pretest'). During testing, each nose-poke of the active mouse resulted in a contingent injection of 1.6 μl of a drug solution to the lateral tail vein of both the active mouse and the yoked passive mouse. The duration of injection was constant and lasted 0.5 s. Nose-pokes of the yoked control were counted but had no programmed consequences.

The active mice were treated with placebo (saline) or graded doses of U50,488H (2.5, 5.0 or 10.0 mg/kg, i.p.) 15 min before they were placed in the test cage. During testing an i.v. injection of saline or graded doses of morphine (0.2, 0.4, 0.8, 1.6 or 2.4 μg per infusion) was made contingent upon each nose-poke of the active animal. This (self)administration phase lasted 30 min. The number of animals per treatment group ranged between 6 and 15. The reinforcement criterion of a drug, a measure of a drug's reinforcing effect, was calculated as the logarithm of the ratio of the cumulative number of the nose-poke responses between the active and passive mice during the 30-min period minus the logarithm of the ratio of nose-poke responses during the period without drug injections ('pretest') (Kuzmin et al., 1994). Logarithms were used in order to normalize the distribution of the data.

Differences between saline and morphine self-injection per treatment group were statistically analyzed using a one-way analysis of variance followed by a Student-Newman-Keuls test, in which the reinforcement criterion was the grouping variable. Additionally, treatment effects per dose of morphine were analyzed using a one-way analysis of variance with Student-Newman-Keuls test.

2.4. Drugs

U50,488H (*trans*-3,4-dichloro-*N*-methyl-*N*-(2-1-pyrrolidinyl)-cyclohexyl-benzeacetamide) (gift of Upjohn, Kalamazoo, MI, USA) was dissolved in saline and was administered intraperitoneally (i.p.) in a volume of 1 ml/kg in rats and 10 ml/kg in mice. Cocaine (cocaine-HCl, OPG, Utrecht, Netherlands) and morphine (morphine-HCl, Sigma, St. Louis, MO, USA) were dissolved in saline and the pH of the drug solutions were adjusted to 7.35 ± 0.05.

3. Results

3.1. Intravenous cocaine self-administration in rats

The overall analysis of variance of all data of the first series of experiments with treatment (U50,488H vs. placebo) and cocaine dose (0, 7.5, 15, 30 and 60 μg per infusion) as between-group factors and time (four sessions) as within-subject factor revealed a main time effect with respect to the number of self-infusions with cocaine ($F(3,222) = 5.8,\ P < 0.001$) due to an increase in the number of self-infusions over sessions 2–5 and a main dose effect ($F(4,74) = 3.0,\ P < 0.05$) (Fig. 1). The main effect of treatment was not significant. Besides the interaction of treatment with dose ($F(4,74) = 4.5,\ P < 0.01$) the

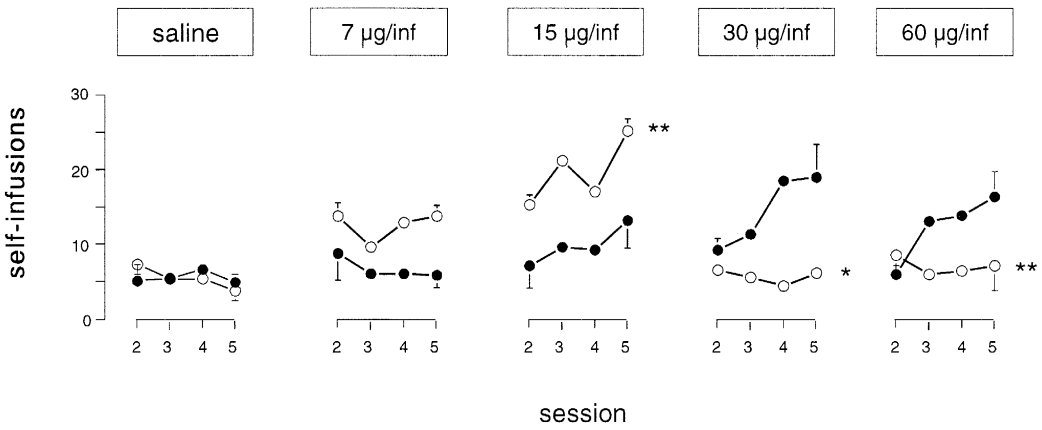

Fig. 1. Effect of U50,488H on i.v. self-administration of graded doses of cocaine in rats. Animals were treated (i.p.) with placebo (●) or U50,488H (2.5 mg/kg) (○) and were allowed to i.v. self-administer saline or one of four doses of cocaine (7 (extra low); 15 (low); 30 (medium) or 60 μg per infusion (high)). Animals were tested in five consecutive daily 3-h sessions. The mean number of self-infusions (±S.E.M.) is plotted versus the day of testing. The number of animals per treatment group ranged between 7 and 14. * Significant treatment and/or treatment × time effect (see text for statistics).

following interactions were significant: time × treatment, time × dose and time × treatment × dose ($F(3,222) = 4.1$, $P < 0.01$, $F(12,222) = 3.0$, $P < 0.001$ and $F(12,222) = 2.8$, $P < 0.01$, respectively). Analysis of data from placebo-treated animals revealed a main time effect ($F(3,117) = 6.5$, $P < 0.001$) and a signifcant time × dose interaction ($F(12,117) = 2.75$, $P < 0.01$), indicating that in the placebo-treated groups the animals increased their cocaine intake over time but this increase depended on the cocaine dose.

In addition to an overall analysis, separate analyses of the number of self-infusions per cocaine dose were performed. In the saline self-administration group, treatment with U50,488H (2.5 mg/kg) did not affect the self-infusion rate, in that a time effect, a treatment effect or a significant treatment × time interaction was not found. Similarly, no effects of U50,488H were found on the number of self-infusions with the extra-low cocaine dose (7 μg per infusion), although there was a tendency to a significant treatment and time effect ($F(1,12) = 4.1$, $P = 0.07$, $F(3,36) = 2.6$, $P < 0.07$, respectively). Self-administration of the low cocaine dose was stimulated by U50,488H treatment. Time ($F(3,36) = 9.6$, $P < 0.001$) and treatment effects ($F(1,12) = 10.4$, $P < 0.01$) were significant, but the treatment × time interaction was not. U50,488H significantly decreased self-administration at the medium cocaine dose in that the treatment effect was significant ($F(1,12) = 5.1$, $P < 0.05$). No significant time effect or treatment × time interaction was found. Finally, the self-infusion rate with the high cocaine dose was decreased by U50,488H treatment. The time effect ($F(3,78) = 6.0$, $P < 0.001$) and the treatment × time interaction ($F(3,78) = 12.5$, $P < 0.001$) were significant, but the treatment effect was not significant ($F(1,26) = 2.4$, n.s.).

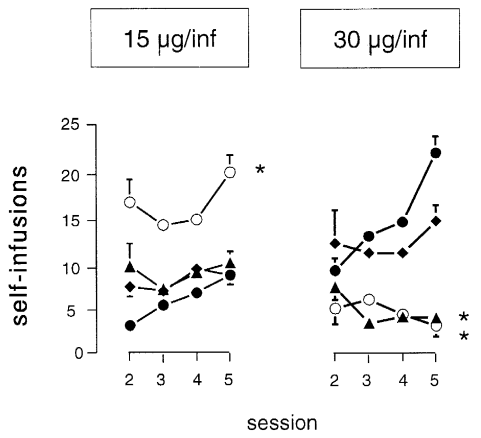

Fig. 2. Effect of graded doses of U50,488H on initiation of i.v. cocaine self-administration in rats. Animals were treated (i.p.) with placebo (●) or graded doses of U50,488H (0.6 mg/kg (♦), 1.2 mg/kg (▲) or 2.5 mg/kg (○) and were allowed to i.v. self-administer a low (15 μg per infusion) or medium (30 μg per infusion) cocaine unit-dose. Animals were tested in five consecutive daily 3-h sessions. The mean number of self-infusions (±S.E.M.) is plotted versus the day of testing. The number of animals per treatment group ranged between 5 and 7. * Significant treatment and/or treatment × time effect (see text for statistics).

In the second series of experiments, the effect of treatment with placebo and graded doses of U50,488H (0.6, 1.2 and 2.5 mg/kg) on i.v. self-administration with the low and medium cocaine doses was tested (Fig. 2). Analysis of the number of self-infusions in the low cocaine dose group revealed a time effect ($F(3,63) = 7.1$, $P < 0.001$), a treatment effect ($F(3,21) = 7.8$, $P < 0.001$) but no significant between dose × time interaction ($F(9,63) = 1.7$, n.s.). Analyses of the average number of self-infusions over the sessions revealed a significant increase in the self-infusion rate after treatment with the highest dose of U50,488H (2.5 mg/kg) ($P < 0.05$). Results obtained with the medium dose of cocaine showed a significant treatment effect ($F(3,23) = 15.4$, $P < 0.001$) and a treatment × time interaction ($F(9,63) = 4.0$, $P < 0.001$), but no significant time effect ($F(3,69) = 2.6$, n.s.). The average number of self-infusions over sessions in the medium cocaine dose group was significantly lower after treatment with either 1.2 or 2.5 mg/kg U50,488H than that of placebo-treated animals ($P < 0.05$).

Two-way analysis per series of experiments revealed no main effects with respect to the number of responses on the dummy lever. That is, in none of the experiments was there a significant time or treatment effect, nor was there a significant time × treatment interaction.

Taken together, these data indicate that animals readily self-administer cocaine when cocaine is offered in a medium (30 μg per infusion) or a high (60 μg per infusion) dose. Treatment with U50,488H (1.2 and/or 2.5 mg/kg) significantly blocked cocaine intake in these dose groups. Administration of 2.5 mg/kg U50,488H induced cocaine self-administration in the extra-low (7.5 μg per infusion) and low (15 μg per infusion) cocaine dose groups. With regard to the dose–response curve of cocaine self-administration, it was found that treatment with U50,488H caused a leftward shift, indicating increased sensitivity for the reinforcing effects of cocaine. Finally, treatment with U50,488H did not significantly affect responding on the dummy lever.

3.2. Intravenous morphine self-administration in mice

The baseline number of nose-pokes assessed in the 'pretest' was similar in all groups of animals, i.e., about 25–30 in 10 min.

The effect of graded doses of U50,488H on the reinforcement criteria of animals allowed to self-administer graded doses of morphine is shown in Fig. 3. One-way analysis of variance of data from placebo-treated animals revealed a significant difference between morphine doses ($F(4,48) = 6.1$, $P < 0.001$). Further analysis revealed that animals self-injecting morphine in doses of 1.6 and 2.4 μg per infusion had a significantly higher reinforcement criterion than animals self-injecting saline (reinforcement crite-

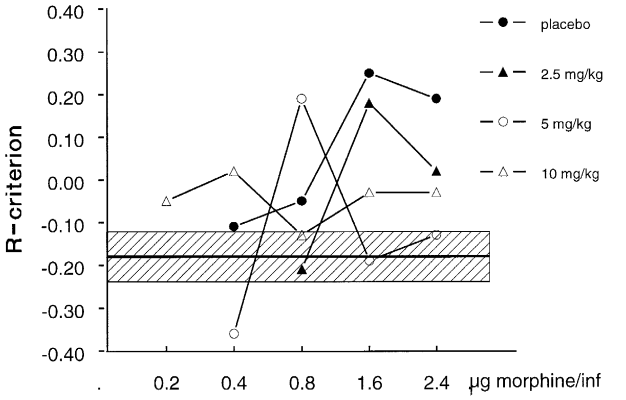

Fig. 3. Effect of U50,488H on i.v morphine self-administration in mice. Animals were treated (i.p.) with placebo or graded doses of U50,488H (2.5, 5 or 5 mg/kg) and were allowed to i.v. self-administer saline or one of five doses of morphine (0.2, 0.4, 0.8, 1.6 or 2.4 μg per injection). Data are represented as mean reinforcement criterion (±S.E.M.) per treatment group versus dose of morphine. The horizontal line represents the mean reinforcement criterion (±S.E.M.) of animals offered saline during self-administration. The number of animals per treatment group ranged between 6 and 15. * Significantly different from saline self-administration (see text for statistics).

rion -0.18 ± 0.06, mean ± S.E.M., $n = 15$), indicating significant self-administration with these morphine doses.

Treatment with U50,488H in the dose of 2.5 mg/kg decreased the reinforcement criterion in all morphine-treated animals, but this effect was not significant for any of the doses. With respect to differences between morphine and saline self-administration in animals treated with this dose of U50,488H, it was found that the dose of 1.6 μg morphine per infusion had a significantly higher reinforcement criterion than that of saline ($F(3,34) = 4.9$, $P < 0.01$). U50,488H at the dose of 5.0 mg/kg significantly decreased the reinforcement criterion of animals self-injecting morphine in a dose of 1.6 μg per infusion. Furthermore, animals self-injecting morphine at a dose of 0.8 μg per infusion had a significantly higher reinforcement criterion than the saline controls ($F(4,40) = 3.0$, $P < 0.05$). U50,488H at the dose of 10.0 mg/kg significantly decreased the reinforcement criterion at the dose of 1.6 μg per infusion. One-way analysis of variance failed to show significant self-administration of morphine with any of the doses tested ($F(4,44) = 1.5$, n.s.).

Taken together, DBA/2 mice offered morphine in doses of 1.6 or 2.4 μg per infusion showed significant i.v. self-administration as compared to saline self-injecting animals. Treatment with 5.0 and 10 mg/kg U50,488H significantly decreased morphine intake in these animals, whereas treatment with 2.5 mg/kg showed a tendency to decrease morphine intake in these groups. U50,488H (5 mg/kg) induced self-administration behavior in mice offered 0.8 μg per infusion morphine. U50,488H caused a leftward shift of the dose–response curve for morphine self-administration, indicating sensitization towards the reinforcing effects of morphine.

4. Discussion

The present series of studies evaluated the effect of daily treatment with a κ-opioid receptor agonist on i.v. self-administration of different doses of cocaine and morphine. Rats readily self-administered the two higher doses of cocaine (30 and 60 μg per infusion). Similarly, mice self-administered morphine in doses of 1.6 and 2.4 μg per infusion. In the drug self-administration model, the amount of drug taken is linearly related to the dose delivered and is regarded as an index of the reinforcing efficacy of the drug (Van Ree et al., 1978; Weeks and Collins, 1979; Dai et al., 1989; De Vry et al., 1989). Hence, an increase in dose results in an increased total drug intake and, thus, in reinforcing efficacy. Accordingly, a decrease in total drug intake indicates a decrease in the reinforcing efficacy of the drug. Treatment with the κ-opioid receptor agonist U50,488H significantly decreased cocaine as well as morphine intake in animals injecting the higher doses, indicating a decrease in the reinforcing properties of the drugs after activation of the κ-opioid receptor. The decrease in self-administration behavior with the higher dose of the drugs appeared to be dependent on the dose of κ-opioid receptor agonist, in that 1.2 and 2.5 mg/kg U50,488H dose dependently decreased cocaine self-administration, while a dose of 0.6 mg/kg was not effective. With respect to morphine, the daily doses of 5.0 and 10.0 mg/kg U50,488H decreased the intake of morphine, whereas 2.5 mg/kg only tended to decrease morphine intake.

The effect of the κ-agonist on drug intake is thought to be more or less specific for the reinforcing efficacy of the drug, inasmuch as U50,488H by itself did not affect the self-administration behavior of animals offered saline nor did U50,488H in these doses affect responding on the dummy lever, responding which is considered to reflect non-specific behavior (i.e., motor behavior).

The observed decrease of the reinforcing effects of both cocaine and morphine by treatment with a κ-agonist in the present study is in agreement with other recently reported findings. In the conditioned place preference procedure, it was demonstrated that κ-agonists significantly attenuated the preference for cocaine (Crawford et al., 1995; Suzuki et al., 1992; Shippenberg et al., 1996) as well as morphine (Funada et al., 1993; Narita et al., 1993). Moreover, a recent report showed that treatment with the κ-agonists U50,488H and spiradoline decreased morphine and cocaine intake during the maintenance phase of self-administration (Glick et al., 1995).

An interesting finding of the present study is the effect of U50,488H on the self-administration of lower doses of either cocaine and morphine, i.e., doses that do not initiate or support self-administration behavior (sub-threshold doses). Daily treatment with U50,488H induced self-administration behavior with a low dose of cocaine (15 μg per infusion) and tended to stimulate drug-taking behavior with the extra-low cocaine dose (7 μg per infusion). These

findings suggest that U50,488H increases the reinforcing efficacy of lower doses of cocaine and, thereby, facilitates the initiation of self-administration behavior. This facilitating effect was present after treatment with a dose of 2.5 mg/kg U50,488H, but not when lower doses were used. Facilitation of cocaine self-administration behavior seems, therefore, less sensitive to effects of U50,488H than blockade of self-administration of the higher doses of cocaine. The facilitating effect of U50,488H was also present in the experiments with morphine where treatment with U50,488H (5.0 mg/kg) initiated self-administration with a lower sub-threshold dose of morphine.

In agreement with the κ-opioid receptor agonist-induced facilitation of self-administration behavior is the effect of U50,488H on the dose–response curve for drug reward. Drug- and lever press-naive animals readily initiate drug self-administration behavior, there being an inverted U-shaped dose–response curve. In the present study, treatment with the κ-opioid receptor agonist U50,488H caused a leftward shift in the dose–response curves for both cocaine and morphine reward, indicating that activation of the κ-opioid system increases the sensitivity for the reinforcing effects of the drugs.

To date, very few studies have investigated the effect of κ-opioid receptor agonists on drug self-administration (e.g., Glick et al., 1995) and in none of these studies has the effect on the dose–response curve for either cocaine or morphine been assessed. The present observation that the κ-opioid receptor agonist increased the sensitivity for both cocaine and morphine reward does not fit in with the accepted role of κ-opioid receptors in drug reward and is, therefore, difficult to compare and explain. Previous studies with cocaine self-administration have shown that blockade of opioid receptors with naltrexone, an opioid antagonist which blocks different opioid receptors, decreases the sensitivity for cocaine reward (De Vry et al., 1989). Since the present study showed that activation of κ-opioid receptors produces an increase in the sensitivity for drug reward, it might be suggested that κ-opioid systems are selectively involved in drug-taking behavior in general, and in sensitivity in particular. Furthermore, it could be hypothesized that blockade instead of activation of the κ-opioid system might result in a decrease in sensitivity for drug reward, an effect similar to opioid blockade with the non-selective naltrexone.

Interestingly, U50,488H affected cocaine (psychomotor stimulant) and morphine (opiate) self-administration similarly, suggesting a common mechanism underlying the effect of opioid modulation on experimental drug addiction. It has been suggested that the mesolimbic dopamine pathway, originating in the ventral tegmental area and projecting to, e.g., the nucleus accumbens, is of critical importance for the reinforcing effects of several drugs of abuse (e.g., Wise and Bozarth, 1987; Willner and Scheel-Krüger, 1991). In addition, there is evidence that opioids interfere with the activity of mesolimbic dopamine neurons (e.g., Wise and Bozarth, 1982; Wood, 1983; Di Chiara and Imperato, 1988; Spanagel et al., 1992; Devine et al., 1993; Narita et al., 1993), an action which is postulated to underlie, among others, the motivational effects of these agents (Bals-Kubic et al., 1993; Devine and Wise, 1994). As such, modulation of opioid systems might affect the reinforcing effects of drugs of abuse through a common action on the dopamine system at the level of the mesolimbic pathway. Although the present studies did not directly assess the κ-opioid/dopamine interaction in the reinforcing effects of both cocaine and morphine, it can be postulated that U50,488H decreased cocaine and morphine intake by activation of κ-opioid receptors in the nucleus accumbens, thereby depressing cocaine- and morphine-induced dopamine activity in this area (Narita et al., 1993; Shippenberg et al., 1996). Accordingly, since Ramsey (1991) demonstrated that blockade of the opioid systems in the ventral tegmental area, but not in the nucleus acumbens, decreased sensitivity for cocaine reward, probably through interaction with local dopamine activity, the effect of κ-opioid receptor modulation of drug sensitivity might also be mediated by an interaction with dopamine neurons located in this mesolimbic area.

In conclusion, the present findings suggest a role for κ-opioid systems in drug-taking behavior, and in particular in the sensitivity for drug reward. Although the precise mechanism underlying the effect of κ-opioid receptor modulation of drug addiction is yet to be elucidated, the present data may prompt further investigation of the effectiveness of κ-opioid receptor agents as novel pharmacotherapeutic compounds in the treatment of addiction to opiates and stimulant drugs.

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