ELSEVIER

Pharmacology Biochemistry & Behavior, Vol. 55, No. 1, pp. 87–91, 1996

0091-3057/96 $15.00 + .00

PII S0091-3057(96)00073-1

Low-Dose Apomorphine Attenuates Morphine-Induced Enhancement of Brain Stimulation Reward

CLIFFORD M. KNAPP[1] AND CONAN KORNETSKY[2]

Boston University School of Medicine, Laboratory of Behavioral Pharmacology, 80 East Concord St., L-602, Boston, MA 02118

Received 7 July 1995; Revised 3 January 1996; Accepted 9 January 1996

KNAPP, C. M. AND C. KORNETSKY. *Low-dose apomorphine attenuates morphine-induced enhancement of brain stimulation reward.* PHARMACOL BIOCHEM BEHAV **55**(1) 87–91, 1996.—Thresholds for brain stimulation reward (BSR) delivered to the medial forebrain bundle-lateral hypothalamus were determined by means of a rate free psychophysical method. Lower doses of apomorphine (0.5 to 0.2 mg/kg) produced modest elevations in BSR thresholds. A 0.4 mg/kg dose of apomorphine resulted in emergence of stereotypic behaviors and the loss of stimulus control. Morphine's BSR threshold lowering effects were significantly blocked by the concurrent administration of a 0.1 mg/kg dose of apomorphine. These results support the hypothesis that presynaptic dopamine neurons are involved in the mediation of morphine's reinforcing effects and that dopamine autoreceptor agonists may be of some use in the pharmacotherapy of opiate abuse.

ICSS Self-stimulation Dopamine Reward

THE administration of morphine (8) and other opiates including buprenorphine (19), nalbuphine (42), pentazocine (41), heroin, and 6-acetylmorphine (20) all produce a lowering in the threshold for brain stimulation reward (BSR). These actions are similar to those of the indirect dopamine agonists amfonelic acid (22,26), *d*-amphetamine (9), cocaine (1), and the direct dopamine agonist bromocriptine (27). The threshold-lowering effects of morphine are potentiated by the coadministration of either amfonelic acid (22) or *d*-amphetamine (18). These findings are consistent with a dopaminergic-opioid system interactions in the reinforcement pathways activated by brain stimulation. The finding that depletion of dopamine from the VTA attenuates morphine-induced enhancement of BSR suggests that the mesolimbic dopamine system is involved in the mediation of morphine's reinforcing effects (17). This notion is also supported by evidence that infusion of morphine into the VTA enhances the effects of BSR (3,43). The interaction of opioid and dopaminergic systems within the mesolimbic system has become increasingly well characterized. Both the electrophysiologic (16,33) and metabolic activity (24) of mesolimbic dopaminergic neurons can be markedly increased by treatment with opioid agents such as morphine. Dopamine release in the terminal areas of the mesolimbic dopamine systems is also enhanced by morphine (6). Notably, infusion of morphine into the VTA results in an increase in dopamine levels in the nucleus accumbens (31). Secondary cells in the VTA that may contain GABA are hyperpolarized by m-opioid receptor agonists (23). Microdialysis infusion of morphine into the VTA reduces extracellular concentrations of gamma aminobutyric acid (GABA) (25). Opioid-induced increases in the activity of VTA dopaminergic neurons may result from inhibition of interneurons that release GABA to tonically suppress dopamine cell firing (23).

In contrast to the effects of opiates, administration of the direct dopamine agonist, apomorphine, causes a decrease in the firing activity of dopaminergic neurons located in the VTA (13,44) and the evoked release of dopamine in the olfactory tubercle (40). Also, apomorphine (0.1 mg/kg) reduces responding for rewarding brain stimulation (39). These actions may result from the effects of apomorphine at dopamine autoreceptors. Administration of a 0.1 mg/kg dose of apomorphine can attenuate morphine-induced increases in locomotor activity (21). These inhibitory effects of apomorphine are antagonized by the administration of a very low dose of the dopamine

[1] Present address: Psychiatry Service, Boston Veterans Affairs Medical Center, Outpatient Clinic, 251 Causeway Street, Boston, MA 02114-2119.
[2] To whom requests for reprints should be addressed.

antagonist spiperone. Apomorphine's inhibition of morphine's effects on locomotor activity may reflect apomorphine-induced functional antagonism of morphine's excitatory effects on dopaminergic systems. Pretreatment with apomorphine has been shown to block morphine from producing increases in the dopamine metabolite, dihdroxyphenylacetic acid, in both the nucleus accumbens and the olfactory tubercle (34,35). However, it must be noted in animals treated with the monoamine oxidase inhibitor, pargyline, administration of a 0.5 mg/kg dose of apomorphine did not affect increases in the dopamine metabolite 3-methoxytyramine in the nucleus accumbens produced by treatment with a 3.3 mg/kg dose of morphine (35). This result is not consistent with the notion that apomorphine antagonizes morphine-induced dopamine release. The effects of apomorphine on opiate-induced reinforcement have not been extensively examined. A low dose of apomorphine has been found to greatly increase the intake of self-administered morphine (14). It is not clear if this is the result of the apomorphine's enhancement or attenuation of morphine's reinforcing effects. To further examine the interaction of morphine and apomorphine in central reinforcement systems the effects of morphine and apomorphine, alone and in combination, on the threshold for rewarding brain stimulation were determined.

METHOD

Bipolar stainless steel electrodes (0.13 mm in diameter and insulated at the tips) were stereotactically implanted bilaterally in the lateral hypothalamic region of the medial forebrain bundle (MFB-LH) of 5 male F-344 albino rats (300 g), (Charles River Laboratories, Wilmington, MA). Surgical anesthesia was produced by systemic administration of xylazine (13 mg/kg) and ketamine (87 mg/kg). MFB-LH coordinates were 4.0 mm posterior to bregma, 1.4 mm lateral to the midline suture, and 8.5 mm ventral to the skull surface. Behavioral testing was begun approximately 1 week after surgery. Animals were maintained on a 12 L:12 D cycle, tested during the light cycle, housed individually in stainless steel cages, and had ad lib access to food and water.

The electrode that produced appetitive behavior at the lowest current intensity and had the least or no motor artifact was used in this experiment. Rats were trained and tested in a plastic chamber (20 × 20 × 35 cm). A wheel manipulandum was located within one wall of the test chamber. Immediate delivery of a stimulation occurred when the wheel was rotated one-quarter of a turn. A constant current stimulator (Sunrise Systems, Pembroke MA) was used to deliver the biphasic symmetrical pulses. Each stimulus consisted of a 500-ms train with a pulse width of 0.2 ms and a delay of 0.2 ms between the positive and negative pulses at a frequency of 160 Hz.

Thresholds were determined by a rate-independent, discrete trial procedure using a modification of the psychophysical method of limits (7,28,29,32).

Rats required approximately six 1-h training sessions to learn the task and approximately four additional sessions for establishment of a stable threshold level, whereupon BSR thresholds were determined after saline injections for 5 days before drug treatments were initiated. At least 72 h was allowed to elapse between drug treatment days.

Drug Preparation and Administration

All injections were administered subcutaneously in volumes of 1 ml/kg. Morphine sulfate and apomorphine (Sigma Chemical Company, St. Louis, MO) both were dissolved in normal saline. Sodium metabisulfate was added to apomorphine solutions in sufficient amounts to produce solutions with a 0.1% concentration of this antioxidant. Apomorphine solutions were discarded 72 h after their preparation.

In the first experiment animals were injected with either apomorphine or saline. The postsessions were started 5 min after drug and saline injections. The doses of apomorphine tested ranged between 0.05 and 0.4 mg/kg and the sequence of doses was balanced among animals.

In the second set of trials, four of the animals used in the first experiment received injections of either morphine sulfate or saline and 5 min later were injected with either apomorphine or saline. Animals in this experiment were treated with only the following treatment combinations: morphine-saline, morphine-apomorphine, and saline-saline. The postsession was started 5 min after administration of the second agent. The doses of morphine administered were 0.5, 1.0, 2.0, and 4.0 mg/kg. These doses of morphine were administered both alone and in combination with a 0.1 mg/kg dose of apomorphine.

Data Analysis

Threshold values were calculated for both the preinjection and the postinjection sessions, with the difference between the two scores taken as the dependent measure (post-pre). These difference scores were transformed to standard scores (z-scores) based on the mean and standard deviation of the difference scores for all saline days. A minimum of 20 control scores for each animal were used for determining each z-score value. For an individual animal a z-score of ± 1.96 or greater (95% confidence limits) was preselected as the level of significance.

Histology

At the completion of the experiments, the animals were killed with an overdose of pentobarbital and perfused intracardially with saline followed by formalin. The brains were then removed from the skull, fixed, embedded, and sliced at 40 μ. Mounted sections were stained with cresyl violet and luxol fast blue and examined under a light microscope to determine the placement of electrode tips.

RESULTS

For the trials when apomorphine alone was administered the mean of the mean presaline thresholds for each animal was 55.0 μa. The mean of the mean post minus presaline difference was 4.3 μa and the mean of the individual standard deviations used to compute z-scores was 5.6 μa. For morphine and morphine-apomorphine combination trials the mean presaline threshold was 53.7 μa, the mean difference value was 5.3 μa, and the mean of individual standard deviation was also 5.3 μa.

Figure 1 summarizes the effects of 0.05, 0.1, and 0.2 mg/kg of apomorphine in the five animals. As shown, all the doses tested decreased the sensitivity (raised the threshold) of the rats to rewarding intracranial stimulation with statistical significance found at the 0.05 and 0.2 mg/kg doses.

Although 0.4 mg/kg of apomorphine was administered to all of the animals, none of the rats were able to maintain the experimental schedule at this dose. Four animals stayed in one area of the test chamber where they continuously sniffed and gnawed at the bars on the floor of the test chamber. The

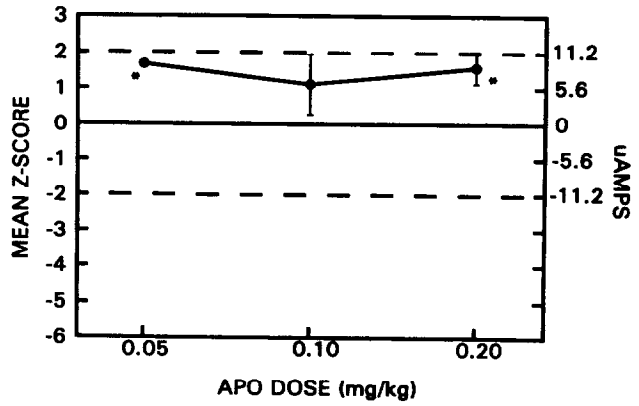

FIG. 1. Mean z-score changes in the threshold for brain stimulation reward after the administration of apomorphine (APO) to five animals. A z-score change of one is equivalent to a 5.6 μa change in current level. Saline treatment z-scores = 0. *$p < 0.05$, saline vs. APO.

fifth animal rapidly spun the wheel manipulandum before and after the start of the test session.

The effects of morphine (0.5, 1.0, 2.0, and 4.0 mg/kg) alone and in combination with 0.1 mg/kg apomorphine was determined in four of the five animals used in the apomorphine alone experiment. The mean z-scores for animals treated with morphine and morphine in combination with apomorphine are shown in Fig. 2. As indicated, the mean BSR thresholds were significantly less than those obtained after saline treatment following the administration of 1.0 mg/kg, $t(3) = 12.8$, $p = 0.001$, and 4.0 mg/kg, $t(3) = 10.2$, $p = 0.002$, of morphine to animals. The threshold change after 2.0 mg/kg of morphine compared to the threshold after saline treatment approached the significance range, $t(3) = 3.13$, $p = 0.052$.

With the exception of the 4 mg/kg dose of morphine in one animal, the coadministration of apomorphine blocked the threshold lowering effects of morphine in all four test animals at every effective dose. Repeated measures ANOVA indicates

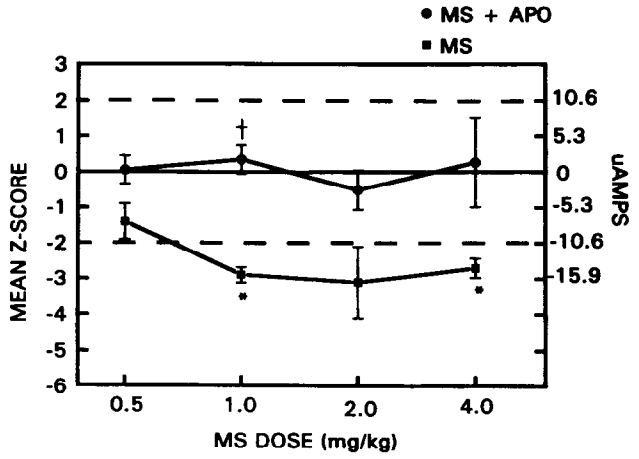

FIG. 2. Mean z-scores changes in BSR thresholds after the administration of morphine (MS) alone and in combination with apomorphine (APO) 0.1 mg/kg. A z-score change of one is equivalent to 5.3 μa change in current levels. Saline treatment z-score = 0. *$p < 0.05$, saline vs. MS $^{+}p < 0.05$, MS vs. MS + APO.

that there was a significant difference in the effects of morphine treatment alone as compared to those of morphine-apomorphine combinations, $F(1) = 16.49$, $p = 0.027$. Significant dose treatment interaction effects were not found, $F(3) = 0.76$, $p = 0.54$. When results for specific doses of morphine were compared the mean threshold obtained for the 1.0 mg/kg dose of morphine was significantly lower than was the one determined for the combination of this dose of morphine with apomorphine, $t(3) = 8.16$, $p = 0.004$.

Histological examination showed that all electrode tips were placed in the caudal aspect of the lateral hypothalamus.

DISCUSSION

Studies of the effects of apomorphine on rates of responding for rewarding brain stimulation do not provide a clear picture of the nature of apomorphine's effects on reward processes. Rates of responding for BSR have been both decreased and increased following apomorphine administration or shown to increase or decrease depending on the current intensity and drug dose (4,5,30). At high current intensities rates of responding for rewarding stimulation have been reduced by treatment with a 0.2 mg/kg dose of apomorphine while response rates were increased by this treatment at low current intensities. These results may be related to a loss of stimulus control that results in the flattening of the response–current intensity curve. Alternatively, they may reflect apomorphine-induced enhancement of the reinforcing effects of low currents and simultaneous reduction in the high current reinforcement.

Administration of a 0.1 mg/kg dose of apomorphine increases rates of responding for BSR to above those observed after saline treatment in animals with 6-hydroxydopamine lesions of the nucleus accumbens (39). This result suggests that apomorphine, at this dose, can activate reward pathways in which presynaptic dopamine neurons have been destroyed.

Some researchers have found that animals treated with apomorphine will continue pressing on levers even after the delivery of rewarding stimulation has been discontinued (4). These findings might be attributable to the development of stereotypic behaviors in animals treated with apomorphine or to some other drug-induced disruption of behavioral regulation. In this investigation all animals exhibited some form of stereotypic behavior at the highest apomorphine dose tested (0.4 mg/kg), a dose that may be acting at both pre- and postsynaptic dopamine receptor sites. With the loss of stimulus control it is no longer possible to assess the effects of a drug on reward processes. In the present experiment, BSR thresholds were either elevated or remained unchanged after the administration of apomorphine at doses (0.2 mg/kg and lower) that did not cause a loss of stimulus control. In another study in which pulse frequencies at 50% of maximal response rates were used as threshold values, the intraperitoneal administration of apomorphine at doses of 0.3 and 1 mg/kg produced a drop in thresholds to below levels obtained with vehicle injection (12). Administration of bromocriptine, which like apomorphine is a direct dopamine agonist, also has been found to lower BSR thresholds at doses at which stimulus control was maintained (27).

There was trend in this investigation for low doses of apomorphine to produce modest elevations in the BSR threshold. Low doses of apomorphine have also been shown to produce small increases in pulse frequency thresholds (12). Other reports indicate that treatment with low doses of apomorphine and selective dopamine autoreceptor agonists 3-PPP and TL-

99 to reduce rates of responding for rewarding stimulation delivered to the medial septal areas (15) and the lateral hypothalamus (11,30). These results suggest that stimulation of dopamine autoreceptors can antagonize the reinforcing effects of intracranial self-stimulation.

Animals will self-administer apomorphine (2,45) and kainic lesions of the nucleus accumbens disrupts apomorphine self-administration, indicating that the mesolimbic system is a major site of this drug's reinforcing actions (46). One report indicates that during initial screening sessions apomorphine self-administration resulted in the emergence of stereotypic behaviors consisting of either bar biting or rapid lever pressing in about 50% of test animals (46). These observations indicate that apomorphine, at higher doses, may not be particularly selective in its effects on reinforcement systems as compared to its actions on systems that regulate motor behaviors.

The finding that low doses of apomorphine blocked morphine's threshold lowering effects is consistent with the hypothesis that morphine's reinforcing actions are mediated by dopaminergic mechanisms. Also compatible with this idea is evidence that morphine, when infused into the VTA, reversed elevations in BSR thresholds produced by administration of the dopamine receptor antagonist pimozide (37). Some self-administration studies, however, provide evidence that dopamine systems are not involved in the mediation of the reinforcing effects of opiates. Treatment with the dopamine-blocking agent alpha-flupenthixol was found to have no effect on heroin self-administration (10). Depletion of dopamine from the nucleus accumbens, in one study, also has been shown to not alter patterns of heroin self-administration (36). In another investigation, however, depletion of dopamine from the nucleus accumbens resulted in a rightward shift in the dose rate of the response curve for morphine (38) suggesting a compensatory increase in rates of morphine self-administration in response to a decrease in the reinforcing effects of this drug.

Because low-dose apomorphine produced elevations in BSR thresholds, apomorphine's attenuation of morphine's threshold lowering effects might simply reflect the additive effects of these agents at two essentially independent sites. The mean elevations in the reward thresholds observed following apomorphine administration, however, were markedly smaller than were the mean reductions in thresholds that were produced by morphine treatments. Thus, a simple additive relationship between the effects of morphine and apomorphine on BSR may not exist.

The results of this experiment indicate that the rewarding effects of opiates, as measured by BSR, can be attenuated by the concurrent administration of a dopamine autoreceptor agonist and, consequently, are consistent with the hypothesis that presynaptic dopamine neurons are involved in the mediation of opiate-induced reinforcement. They also suggest that dopamine autoreceptor agonists may be of some use in the pharmacotherapy of opiate abuse.

ACKNOWLEDGEMENTS

This research was supported in part by NIDA Grant DA02326 and NIDA Research Scientist Award KO5-DA00099 to C.K.

REFERENCES

1. Bain, G. T.; Kornetsky, C. Naloxone attenuation of the effect of cocaine on rewarding brain stimulation. Life Sci. 40:1119–1125; 1987.
2. Baxter, B. L.; Gluckman, M. I.; Stein, L.; Scerni, R. Self-injection of apomorphine in the rat: Positive reinforcement by a dopamine receptor stimulant. Pharmacol. Biochem. Behav. 2:387–397; 1974.
3. Broekkamp, C. L.; Phillips, A. G. Facilitation of self-stimulation behavior following intracerebral microinjections of opioids in the ventral tegmental area. Pharmacol. Biochem. Behav. 11:289–295; 1979.
4. Broekkamp, C. L. E.; van Rossum, J. M. Effects of apomorphine on self-stimulation behavior. Psychopharmacology (Berlin) 34: 71–80; 1974.
5. Carey, R. J. Rate dependent inhibition of self-stimulation by apomorphine. Pharmacol. Biochem. Behav. 16:859–861; 1982.
6. Di Chiara, G.; Imperato, A. Drugs abused by humans preferentially increase synaptic dopamine concentrations in the mesolimbic system of freely moving rats. Proc. Natl. Acad. Sci. USA 85: 5274–5278; 1988.
7. Esposito, R.; Kornetsky, C. Morphine lowering of self-stimulation thresholds: Lack of tolerance with long term administration. Science 195:189–191; 1977.
8. Esposito, R. U.; McLean, S.; Kornetsky, C. Effects of morphine on intracranial self-stimulation of various brain stem loci. Brain Res. 168:425–429; 1979.
9. Esposito, R. U.; Perry, W.; Kornetsky, C. Effects of *d*-amphetamine and naloxone on brain stimulation reward. Psychopharmacology (Berlin) 69:187–191; 1980.
10. Ettenberg A.; Petit, H. O.; Bloom, F. E.; Koob, G. Heroin and cocaine intravenous self-administration in rats: Mediation by separate neural systems. Psychopharmacology (Berlin) 78:204–209; 1982.
11. Fenton, H. M.; Hall, N. R.; Gerhardt, S.; Noreika, L.; Neale, R.; Liebman, J. M. Avoidance and ICSS behavioral models dissociate TL-99 and 3-PPP from dopamine receptor antagonists. Eur. J. Pharmacol. 91:421–430; 1983.
12. Fouriezos, G.; Francis, S. Apomorphine and electrical self-stimulation of rat brain. Behav. Brain Res. 52:73–80; 1992.
13. Freeman, A. S.; Bunney, B. S. Activity of A9 and A10 dopaminergic neurons in unrestrained rats, further characterization and effects of apomorphine and cholecystokinin. Brain Res. 405:46–55; 1987.
14. Glick, S. D.; Cox, R. D. Dopaminergic and cholinergic influences on morphine self-administration in rats. Res. Commun. Chem. Pathol. Pharmacol. 12:17–23; 1975.
15. Gower, K.; Broekkamp, C. L. E. Dopaminergic agents including 3-PPP and its enantiomers on medial self-stimulation. Pharmacol. Biochem. Behav. 22:309–315; 1985.
16. Gysling, K.; Wang, R. Morphine-induced activation of A10 dopamine neurons in the rat. Brain Res. 277:119–127; 1983.
17. Hand, T. H.; Franklin, K. B. 6-OHDA lesions of the ventral tegmental area block morphine-induced but not amphetamine-induced facilitation of self-stimulation. Brain Res. 328:233–241; 1985.
18. Hubner, C. B.; Bain, G. T.; Kornetsky, C. The combined effects of morphine and *d*-amphetamine on the threshold for brain stimulation reward. Pharmacol. Biochem. Behav. 28:311–315; 1987.
19. Hubner, C. B.; Kornetsky, C. The reinforcing properties of the mixed agonist-antagonist buprenorphine as assessed by brain stimulation reward. Pharmacol. Biochem. Behav. 30:195–197; 1988.
20. Hubner, C. B.; Kornetsky, C. Heroin, 6-acetylmorphine and morphine effects on the threshold for rewarding and aversive brain stimulation. J. Pharmacol. Exp. Ther. 260:562–567; 1992.
21. Iwamoto, E. T. Locomotor activity and antinociception after putative mu, kappa, and sigma opioid receptor agonists in the rat: Influence of dopaminergic agonists and antagonists. J. Exp. Pharmacol. Ther. 217:451–460; 1981.

22. Izenwasser, S.; Kornetsky, C. The effect of amfonelic acid or nisoxetine in combination with morphine on brain-stimulation reward. Pharmacol. Biochem. Behav. 32:983–986; 1989.
23. Johnson, S. W.; North, R. A. Opioids excite dopamine neurons by hyperpolarization of local interneurons. J. Neurosci. 12:483–488; 1992.
24. Kim, H. S.; Iyengar, S.; Wood, P. L. Opiate actions on mesocortical dopamine metabolism in the rat. Life Sci. 39:2033–2036; 1986.
25. Knapp, C. M.; Kornetsky, C. The effects of amfonelic acid alone and in combination with naloxone on brain-stimulation reward. Pharmacol. Biochem. Behav. 32:977–982; 1989.
26. Knapp, C. M.; Kornetsky, C. Bromocriptine, a D_2 receptor agonist, lowers the threshold for rewarding brain stimulation. Pharmacol. Biochem. Behav. 49:901–904; 1994.
27. Klitenick, M. A.; DeWitte, P.; Kalivas, P. W. Regulation of somatodendritic dopamine release in the ventral tegmental area by opioids and GABA. J. Neurosci. 12:2623–2632; 1992.
28. Kornetsky, C.; Bain, G. Brain-stimulation reward: A model for drug-induced euphoria. In: Adler, M. W.; Cowan, A., eds. Modern methods in pharmacology testing and evaluation of drugs of abuse. New York: Wiley-Liss, Inc.; 1990:211–231.
29. Kornetsky, C.; Esposito, R. U. Euphorigenic drugs: Effects on the reward pathways of the brain. Fed. Proc. 38(11):2473–2476; 1979.
30. Leith, N. J. Effects of apomorphine on self-stimulation responding: Does the drug mimic the current. Brain Res. 277:129–136; 1983.
31. Leone, P.; Pocock, D.; Wise, R. A. Morphine-dopamine: Ventral tegmental morphine increases nucleus accumbens dopamine release. Pharmacol. Biochem. Behav. 39:469–472; 1991.
32. Markou, A.; Koob, G. F. Intracranial self-stimulation thresholds as a measure of reward. In: Sahgal, A., eds. Behavioural neuroscience: A practical approach. Vol. II. Oxford: Oxford University Press; 1992:93–115.
33. Matthews, R. T.; German, D. C. Electrophysiological evidence for excitation of rat ventral tegmental area dopamine neurons by morphine. Neuroscience 11:617–625; 1984.
34. Moleman, P.; van Valkenburg, C. F. M.; Krogt, J. A. v.d. Effects of morphine on dopamine metabolism in rat striatum and limbic structures in relation to the activity of dopaminergic neurones. Naunyn Schmiedbergs Arch. Pharmacol. 327:208–213; 1984.
35. Moller H.-G.; Kuschinsky, K. Interactions of morphine with apomorphine: Behavioural and biochemical studies. Naunyn Schmiedbergs Arch. Pharmacol. 334:452–457; 1986.
36. Pettit, H. O.; Ettenberg, A.; Bloom, F. E.; Koob, G. F. Destruction of dopamine in the nucleus accumbens selectively attenuates cocaine but not heroin self-administration in rats. Psychopharmacology (Berlin) 84:167–173; 1984.
37. Rompre, P.-P.; Wise, R. A. Opioid-neuroleptic interaction in brainstem self-stimulation. Brain Res. 477:144–151; 1989.
38. Smith, J. E.; Guerin, G. F.; Co, C.; Barr, T. S.; Lane, J. D. Effects of 6-OHDA lesions of the central medial nucleus accumbens. Pharmacol. Biochem. Behav. 23:843–849; 1985.
39. Strecker, R. E.; Roberts, D. C. S.; Koob, G. F. Apomorphine-induced facilitation of intracranial self-stimulation following dopamine denervation of the nucleus accumbens. Pharmacol. Biochem. Behav. 17:1015–1018; 1982.
40. Suaud-Chagny, M. F.; Ponec, J.; Gonon, F. Presynaptic autoinhibition of the electrically evoked dopamine release studied in the rat olfactory tubercle by in vivo electrochemistry. Neuroscience 45:641–652; 1991.
41. Unterwald, E. M.; Kornetsky, C. Effects of concomitant pentazocine and tripelennamine on brain stimulation reward. Pharmacol. Biochem. Behav. 21:961–964; 1984.
42. Unterwald, E. M.; Kornetsky, C. Effects of nalbuphine alone and in combination with tripelennamine on rewarding brain stimulation thresholds in the rat. Pharmacol. Biochem. Behav. 25:629–632; 1986.
43. van Wolfswinkel L.; van Ree, J. M. Site of rewarding action of morphine in the mesolimbic system determined by intracranial electrical self-stimulation. Brain Res. 358:349–353; 1985.
44. White, F. J.; Wang, R. Y. A10 dopamine neurons: role of autoreceptors in determining firing rate and sensitivity to dopamine agonists. Life Sci. 34:1161–1170; 1984.
45. Yokel, R. A.; Wise. R. A. Amphetamine-type reinforcement by dopaminergic agonists in the rat. Psychopharmacology (Berlin) 58:289–296; 1978.
46. Zito, K. A.; Vickers, G.; Roberts, D. C. S. Disruption of cocaine and heroin self-administration following kainic acid lesions of the nucleus accumbens. Pharmacol. Biochem. Behav. 23:1029–1036; 1985.