Pharmacology Biochemistry & Behavior, Vol. 32, pp. 977–982. © Maxwell Pergamon Macmillan plc, 1989. Printed in the U.S.A. 0091-3057/89 $3.00 + .00

The Effects of Amfonelic Acid Alone and in Combination With Naloxone on Brain-Stimulation Reward

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

Laboratory of Behavioral Pharmacology, Boston University School of Medicine
80 East Concord Street, Boston, MA 02118

Received 8 October 1987

KNAPP, C. M. AND C. KORNETSKY. *The effects of amfonelic acid alone and in combination with naloxone on brain-stimulation reward.* PHARMACOL BIOCHEM BEHAV **32**(4) 977–982, 1989.—Thresholds for rewarding brain stimulation delivered to the medial forebrain bundle-lateral hypothalamus were determined by means of a rate-free psychophysical method. Amfonelic acid (AFA), an indirect dopamine agonist, alone caused a significant dose-dependent lowering of the rewarding threshold. Although naloxone treatment by itself did not significantly alter the reward threshold, it blocked AFA's threshold lowering effect in every animal at one or more of the dose combinations of the two drugs tested. Naloxone was found to be more effective in blocking the threshold lowering actions of a higher (1 mg/kg) dose as opposed to a lower (0.25 mg/kg) dose of AFA. Since a lowering of threshold for rewarding intracranial stimulation is a model for drug-induced euphoria, the findings presented here indicate that AFA may have abuse potential. Furthermore, these results suggest that endogenous opioid systems may begin to modulate the effects of AFA on the reward system only when a certain level of activation of dopaminergic systems is reached.

Amfonelic acid Brain-stimulation reward Dopamine Naloxone

THIS study and the following report present findings concerning the effects of amfonelic acid, an indirect dopamine agonist, on the neuronal substrates associated with central reinforcement systems. In this paper the effects of administration of amfonelic acid alone and in combination with naloxone on the threshold for brain-stimulation reward are described while the following report discusses how brain-stimulation reward is affected by the interaction of morphine with either amfonelic acid or nisoxetine, a noradrenergic reuptake blocker.

The indirect catecholamine agonists, cocaine and d-amphetamine, have been found to lower the threshold and to increase rates of responding for rewarding brain stimulation (4, 11, 15, 23). These findings indicate that cocaine and d-amphetamine may enhance the sensitivity of the brain to the effect that rewarding brain stimulation has on central reward processes. The effects of rewarding brain stimulation have been shown to be attenuated by either selective lesioning of dopaminergic neurons or by administration of dopamine blocking agents (8, 10, 14, 27). Thus, there is substantial evidence that dopamine plays a crucial role in the neuronal systems involved in the mediation of the effects of rewarding brain stimulation. Furthermore, selective lesion studies suggest that d-amphetamine acts via dopaminergic neurons to facilitate the effects of brain-stimulation reward (8,9). Therefore, there is reason to believe that as a class, psychomotor stimulants like cocaine and d-amphetamine influence the effects of rewarding brain stimulation through their direct actions on dopaminergic systems. There is, on the other hand, little evidence which indicates that psychomotor stimulants can enhance the effects of rewarding intracranial stimulation through their actions on noradrenergic systems. Neither selective lesioning of noradrenergic neurons nor inhibition of norepinephrine synthesis has been shown to attenuate the increases in rates of responding for rewarding brain stimulation produced by administration of d-amphetamine (8,9).

While psychomotor stimulants may alter the effects of rewarding brain stimulation via their direct actions on dopaminergic neurons, it has also been found that the opioid antagonist naloxone can either reverse or attenuate the lowering of reward thresholds which results from treatment with either cocaine or d-amphetamine (4,11). Increased response rates for rewarding stimulation produced by d-amphetamine administration have also been significantly decreased by concurrent treatment with naloxone (15,23). These results suggest that endogenous opioid systems may be involved in the regulation of the actions of agents like cocaine and

[1]Present address: Clifford M. Knapp, Albert Einstein College of Medicine, Department of Neuroscience, Rose Kennedy Center, Room 603, 1410 Pelham Parkway South, Bronx, NY 10461.

[2]Requests for reprints should be addressed to Conan Kornetsky, Boston University School of Medicine, 80 East Concord Street, L-602, Boston, MA 02118

d-amphetamine on reward systems. The precise nature of the neuronal mechanism involved in this regulatory process has yet to be determined. It has been shown that opioid receptors exist in association with dopaminergic neurons in both the mesolimbic and nigrostriatal systems (34,35). There is also evidence that opioid agents can increase dopamine synthesis and metabolism in both mesolimbic and nigrostriatal systems (47). Both systemic and local administration of morphine have been found to increase the firing rates of dopaminergic neurons in the ventral tegmental area (32). Opioid systems, then, appear to exist which may, if activated, act synergistically with psychomotor stimulants to increase the activity of dopaminergic systems.

The present study was undertaken to assess the effects of amfonelic acid, an indirect dopamine agonist, on brain-stimulation reward thresholds when administered alone and in combination with naloxone. In vitro, amfonelic acid, when compared to either d-amphetamine or cocaine, appears to be more selective as an inhibitor of dopamine reuptake as opposed to norepinephrine reuptake (20,46). Unlike d-amphetamine, pretreatment with alpha-methyltyrosine does not antagonize amfonelic acid's central actions, suggesting that these actions are not dependent on dopamine derived from newly synthesized pools (40). Instead, amfonelic acid appears to mobilize granular dopamine stores for impulse-dependent release. This has been shown to occur at doses which do not affect norepinephrine turnover (31). Norepinephrine reuptake may be inhibited in vivo by relatively small doses of amfonelic acid, but this appears to result in reduced noradrenergic impulse flow with no net increase in norepinephrine turnover (16).

METHOD

Bipolar stainless steel electrodes (0.13 mm in diameter and insulated except at the tips) were stereotaxically implanted bilaterally in the lateral hypothalamic region of the medial forebrain bundle (MFB-LH) of 4 male F-344 albino rats (300 g, Charles River Laboratories). 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 from the midline suture, and 8.5 mm ventral to the skull surface. The electrodes were placed through small burr holes in the skull and attached permanently to the surface with an acrylic platform. After surgery, animals received 60,000 units of penicillin (Bicillin) IM and were given at least one week for postoperative recovery before behavioral testing was begun. Animals were maintained on a 12-hour light/dark cycle,housed individually in stainless steel cages and had ad lib access to food and water.

During the initial phase of animal training each of the two electrodes was tested to determine the current intensity needed to produce appetitive behavior and to determine the presence or absence of motor artifact. The electrode which produced appetitive behavior at the lowest current intensity and had the least or no motor artifact was used in the subsequent study. Animals were trained and tested in a plastic chamber ($20 \times 20 \times 35$ cm). A wheel manipulandum was located within one wall of the test chamber. Four equally spaced cams on one endplate of the wheel manipulandum operated a microswitch which resulted in the immediate delivery of a stimulation 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-msec train with a pulse width of 0.2 msec and a delay of 0.2 msec between the positive and negative pulses at a frequency of 160 Hz.

Thresholds were determined by a rate-independent procedure involving the use of discrete trials systematically presented over a range of stimulus intensities. A trial began with the delivery of noncontingent intracranial stimulus. A response of one-quarter wheel turn within 7.5 sec of this stimulus resulted in the delivery of contingent stimulus, identical in all parameters to the noncontingent stimulus, and terminated the trial. Failure to respond had no scheduled consequences and the trial was terminated after 7.5 sec. The interval between trials were randomly varied around an average of 15 sec (7.5 to 21.5 sec) and responses made during the intertrial interval (error responses) resulted in a 15-sec delay before the start of the next trial.

Stimulus intensities were varied using a modification of the classical psychophysical method of limits. Stimuli were presented in alternating descending and ascending series with five trials presented at each intensity level before the next lower or higher intensity was presented. The step size was adjusted to either 5 or 10 μA depending on the sensitivity of the individual animal. A step size that is too large would result in an abrupt change from responding to all stimuli at a particular intensity to failure to respond at the next lowest intensity. Subjects completed 4 series (i.e., descending, ascending, descending, and ascending) prior to injection and 8 series postinjection. The duration of the preinjection and the postinjection testing sessions was approximately 45 minutes and 90 minutes respectively. All experimental data were collected and stored by an on-line microcomputer. Each series' threshold value was defined in microamperes as the midpoint between the level at which the animal responded to three or more of the 5 stimulus presentations (a plus score) within the 7.5 sec available response time and the level where less than 3 correct responses (a minus score) were made. The pre- and postinjection thresholds were based on the means of their respective series thresholds. Thresholds determined in this manner are a close approximation to the intensity level at which an animal will respond 50 percent of the time. In correct responses, those responses during the intertrial interval and extra responses within the 7.5 sec available response time are not used to determine threshold levels, but provide additional information as to whether or not the animals are under stimulus control. We have found that after training, a response during the intertrial interval is a rare occurrence.

Animals required approximately 6 one-hour training sessions to learn the task and approximately 4 additional sessions for the establishment of a stable threshold level, whereupon saline injections were begun. Animals were tested with saline injections for 5 days before drug administration was initiated. Also, saline days were interspersed with drug treatment days so that animals received drug only twice weekly.

Experiment I—Amfonelic Acid Alone

Four animals were injected intraperitoneally with either saline or amfonelic acid. All injections were in volumes of 1 ml/kg body weight. Postinjection testing sessions were begun 1 minute after either drug or saline administration. The doses of amfonelic tested ranged between 0.063 mg/kg to 1 mg/kg and the sequence of doses was balanced amongst animals.

Experiment II—Naloxone Alone and in Combination With Amfonelic Acid

The four animals used in Experiment I were used in Experiment II. On drug days animals received intraperitoneal injections of naloxone followed five minutes later by an injection of either saline or amfonelic acid. On control days animals received isotonic saline intraperitoneally. The doses of naloxone used were

TABLE 1

THE MEAN PRE-SALINE THRESHOLD AND POST MINUS PRE-SALINE THRESHOLD DIFFERENCE ±SD FOR EACH ANIMAL IN μA

Animal	Pre-saline Threshold	Post Minus Pre-saline Difference ±SD*
242	85.1	10.3 ± 8.1*
245	72.7	7.4 ± 8.3
255	56.2	12.9 ± 8.6
260	77.5	14.3 ± 7.1

*z-Scores after drug treatment for each animal are based on these difference scores.

2.5, 5 and 10 mg/kg. Either 0.25 or 1 mg/kg doses of amfonelic acid were used.

Drugs

Naloxone was dissolved in isotonic saline. Amfonelic acid was prepared by first dissolving the drug in 1 N NaOH and a few milliliters of normal saline. This solution was then brought to pH 8 with 1 N HCl. Saline was then added to bring this solution up to volume. Aliquots of this solution were added to saline to obtain solutions of the desired concentrations. Amfonelic acid solutions were prepared weekly.

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 in determining each z-score value. A z-score of ±2.0 or greater (95% confidence limits) was preselected as the level of significance.

Dose-response curves were generated for amfonelic acid alone in Experiment I. In Experiment II, dose-response curves for naloxone and combinations of amfonelic acid and naloxone were obtained.

Histology

Following testing, the animals were sacrificed with an overdose of nembutal and perfused intracardially with saline followed by formalin. The brains were subsequently 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 the electrode tips.

RESULTS

Table 1 shows the mean pre-saline threshold in μA plus the post minus pre-saline threshold difference and its standard deviation for each animal. z-Scores after drug treatment were based on these difference scores.

Figure 1 shows the mean z-score for all animals after the administration of amfonelic acid. As shown, the dose response curve is characteristic of the effects of drugs that increase an animal's sensitivity to a drug. If higher doses are tested the curve turns up even more with the animals eventually unable to complete the task if the dose is sufficiently high. Each of the animals

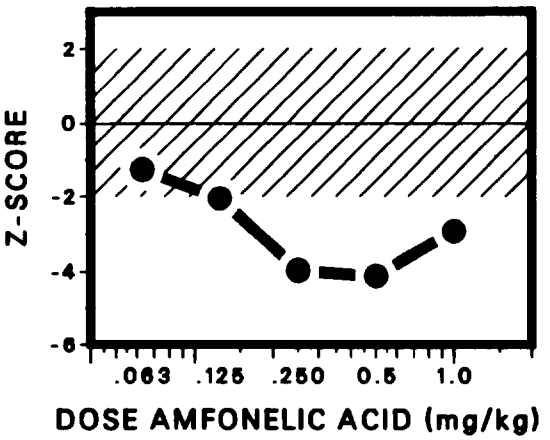

FIG. 1. Mean z-score changes in the threshold for rewarding brain stimulation after various doses of amfonelic acid for four animals. A z-score of ±2 (shaded area) indicates the 95% confidence limits.

showed this U-shape curve with maximum lowering for an individual animal occurring at 0.125 mg/kg for one animal, 0.25 mg/kg for 2 animals, and 0.5 mg/kg for one animal. The lowest dose at which all animals had significant lowering of the threshold was 0.25 mg/kg with all subsequent doses significantly lowered for each of the animals.

Figure 2 shows the mean z-score for all animals after naloxone alone and naloxone in combination with 0.25 and 1.0 mg/kg of amfonelic acid. As shown, naloxone blocked the threshold effect of 1.0 mg/kg of amfonelic acid. In all four of the animals naloxone blocked the threshold lowering effect of 1.0 mg/kg of amfonelic acid.

A *t*-test comparison at the 5 mg/kg dose of naloxone gave a value of 2.99 ($p<0.05$ single tail) between 1.0 mg/kg of amfonelic acid alone and the amfonelic acid plus the naloxone. (Since there was no expectation that naloxone would potentiate the effect of amfonelic acid, single-tail test was appropriate.) Two animals receiving 1.0 mg/kg of amfonelic acid plus naloxone, 5 mg/kg in one case and 10 mg/kg in another case, were not able to complete the task. In order to group this data a z-score of 0.0 was assigned to these animals. It should be noted that amfonelic acid or

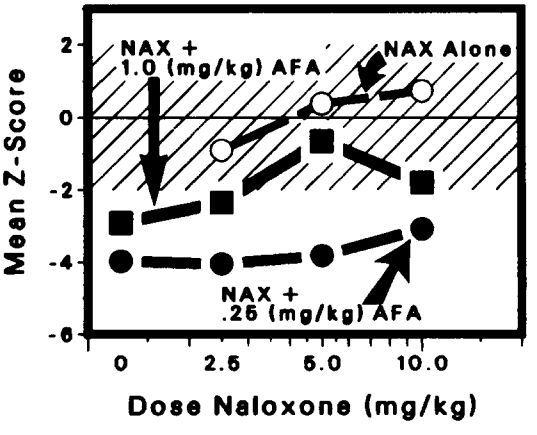

FIG. 2. Mean z-score changes in the threshold for rewarding brain stimulation for naloxone alone, and naloxone plus 0.25 mg/kg or 1.0 mg/kg of amfonelic acid (AFA). A z-score of ±2 (shaded area) indicates the 95% confidence limits.

naloxone alone never resulted in the inability of the animal to complete the task. Also shown is the failure of the threshold lowering effect of 0.25 mg/kg of amfonelic acid to be blocked by any dose of naloxone.

Histological verification showed that electrode tips in all the subjects were located in the caudal aspect of the lateral hypothalamus, one placement being superior to the MFB (#242), one lateral to the MFB (#245) and two inferior to the MFB (#255 and #260).

DISCUSSION

The ability of amfonelic acid to lower the threshold for rewarding brain stimulation, an effect that is similar to that seen with abuse substances including cocaine, d-amphetamine, and heroin, strongly suggests that amfonelic acid has potential for abuse in humans. In accord with this idea is the recent finding that rats will readily self administer amfonelic acid (17). It has also been shown that both cocaine and d-amphetamine will generalize to amfonelic acid and that amfonelic acid will generalize to d-amphetamine in a drug discrimination test (1,39).

The finding that amfonelic acid can lower threshold for rewarding brain stimulation adds support to the view that enhanced activation of dopaminergic systems can have a facilitory effect on central reward processes. Nomifensine and bupropion which act as indirect dopamine agonists also appear to facilitate the effects of rewarding brain stimulation (18,30). Direct dopamine agonists such as 3-PPP, and Tl-99, which may act selectively on dopamine autoreceptors to decrease dopamine release, on the other hand, have been reported to decrease rates of responding for rewarding intracranial stimulation (13,18).

Many reports have shown that the opioid antagonists naloxone and naltrexone can markedly decrease response rates for rewarding brain stimulation (5, 15, 24, 36, 38, 42). Other reports indicate that naloxone does not significantly affect rates of responding for intracranial self-stimulation (23,44). As demonstrated here and in previous work, treatment with naloxone alone does not alter the threshold for brain stimulation reward (4,11). The reason for the discrepancy between these studies is not at present clear. There is a difference in the number of stimulations received per unit of time in case of animals performing in response rate studies as compared to the number of stimulations received by animals in threshold studies of the type described here. Electrical stimulation of the medial forebrain bundle has been shown to result in the release of dopamine in the neostriatum and biochemical evidence indicates that dopamine turnover is increased in the neostriatum and mesolimbic areas (28, 33, 41). Consequently, high rates of stimulation may place excessive demands on presynaptic dopamine neurons. Thus, when the demand becomes great enough, endogenous opioid systems may come into play. Some support for this view is provided by the finding that there appears a direct relationship between the rates at which animals will work for rewarding brain stimulation and the levels of beta-endorphin in the hypothalamus and whole brain (43). Endogenous opioids may act on dopaminergic neurons so as to allow them to function efficiently under taxing conditions. Thus naloxone's inhibitory actions may become manifest only when dopaminergic systems reach a certain level of activation. Dopamine metabolism in the striatum does not appear to be altered under basal conditions by treatment with either naloxone or the opioid antagonist WIN 44,441-3 (47). This suggests that dopaminergic neurons are not affected tonically by endogenous opioids. Similarly, treatment with naloxone alone has been shown to have no effect on the release of dopamine from either caudate nucleus or nucleus accumbens tissue slices (21). Naloxone, however, has been found to attenuate the increase in dopamine release seen in caudate nucleus and nucleus accumbens tissues treated with d-amphetamine.

The hypothesis that opioid peptide systems will influence the system activated by rewarding brain stimulation only when activation of dopaminergic systems reaches a certain critical level may explain why naloxone has been found to reverse or attenuate the threshold lowering effects of cocaine and d-amphetamine while having no effect on the threshold when administered alone. Furthermore, it may provide an explanation as to why naloxone, as shown here, more effectively blocks the effects of a high as opposed to a lower dose of amfonelic acid.

In two instances the combination of naloxone and amfonelic acid completely disrupted responding for rewarding brain stimulation. The reason for this disruption is not at present clear. Naloxone's blockade of amfonelic acid's threshold lowering effects in most cases resulted in thresholds which did not deviate significantly from thresholds obtained with administration of saline alone suggesting that performance of the task was not itself impaired. Some additional factors may be coming into play in those instances when responding is impaired. It was also observed that administration of a higher dose of naloxone sometimes failed to block the effects of a dose of amfonelic acid which had been reversed by a lower dose of the opioid antagonist. It is not clear why this occurred. A similar pattern, however, was observed in studies of the effects of concurrent administration of either cocaine (4) or d-amphetamine (11) with naloxone on the brain-stimulation reward threshold.

Opioid antagonists have been reported to interact with cocaine or d-amphetamine in several studies which have focused on behaviors other than responding for rewarding brain stimulation. Increased avoidance responding and locomotor activity produced by administration of low doses of d-amphetamine have been found to be antagonized by naloxone administration as has d-amphetamine induced increases in rates of responding for food on a DRL schedule (2,22). Chronic naltrexone treatment has been shown to potentiate the effects of both d-amphetamine and apomorphine on locomotor activity (3).

Despite the attenuation or blocking of psychomotor stimulant effects on brain-stimulation reward by opioid antagonists, these antagonists have not altered, with one exception, the self administration of psychomotor stimulants. A recent report indicates that treatment with naltrexone increased the number of cocaine infusions self administered over a twenty-four-hour period (6). This interaction was not observed, however, when the effects of naltrexone on the self administration of cocaine over a three-hour period were studied (12). Naloxone and naltrexone have also been reported to have no effect on the self administration of either cocaine or methamphetamine, respectively, in rhesus monkeys (19,25). Periods of access to psychomotor stimulants were all much shorter in the studies in which opioid antagonists had no effect on stimulant self administration compared to the study in which an effect was observed. This difference may explain why a disparity exists between the results reported in the one study as opposed to the other reports.

In summary, the results presented here show that amfonelic acid can lower the threshold for rewarding brain stimulation which, in turn, indicates that this agent may have abuse potential. It has been demonstrated that the opioid antagonist naloxone can block amfonelic acid's threshold lowering effects and that naloxone is more effective at blocking the effects of higher as opposed to lower doses of this psychomotor stimulant. This suggests that naloxone's inhibitory actions may become apparent only when dopaminergic systems reach a sufficiently high level of activation.

ACKNOWLEDGEMENTS

Supported by NIDA Grant DA 02326 and NIDA Research Scientist Award DA 00099 to C.K.

REFERENCES

1. Aceto, M. D.; Rosecrans, J. A.; Young, R.; Glennon, R. A. Similarity between (+)-amphetamine and amfonelic acid. Pharmacol. Biochem. Behav. 20:635–637; 1984.
2. Adam-Carriere, D.; Merali, Z.; Stretch, R. Effects of morphine, naloxone, d,l-cyclazocine, and d-amphetamine on behavior controlled by a schedule of interresponse time reinforcement. Can. J. Physiol. Pharmacol. 56:707–720; 1978.
3. Amir, S.; Blair, R.; Amit, Z. Increased amphetamine potency following chronic naltrexone administration in rats. Life Sci. 25: 1407–1412; 1979.
4. Bain, G. T.; Kornetsky, C. Naloxone attenuation of the effect of cocaine on rewarding brain stimulation. Life Sci. 40:1119–1125; 1987.
5. Belluzzi, J. D.; Stein, L. Enkephalin may mediate euphoria and drive-reduction reward. Nature 266:556–557; 1987.
6. Carroll, M. E.; Lac, S. T.; Walker, M. J.; Kragh, R.; Newman, T. Effects of naltrexone on intravenous cocaine self-administration in rats during food satiation and deprivation. J. Pharmacol. Exp. Ther. 238:1–7; 1986.
7. Clavier, R. M.; Fibiger, H. C.; Phillips, A. G. Evidence that self-stimulation of the region of the locus coeruleus in rats does not depend upon noradernergic projections to telencephalon. Brain Res. 113:71–81; 1976.
8. Cooper, B. R.; Cott, J. M.; Breese, G. R. Effects of catecholamine-depleting drugs and amphetamine on self-stimulation of brain following various 6-hydroxydopamine treatments. Psychopharmacologia 37:235–248; 1974.
9. Cooper, B. R.; Konkol, R. J.; Breese, G. R. Effects of catecholamine depleting drugs and d-amphetamine on self-stimulation of the substantia nigra and locus coeruleus. J. Pharmacol. Exp. Ther. 204:592–605; 1978.
10. Esposito, R. U.; Faulkner, W.; Kornetsky, C. Specific modulation of brain-stimulation reward by haloperidol. Pharmacol. Biochem. Behav. 10:937–940; 1979.
11. Esposito, R. U.; Perry, W.; Kornetsky, C. Effects of d-amphetamine and naloxone on brain stimulation reward. Psychopharmacology (Berlin) 69:187–191; 1980.
12. Ettenberg, A.; Pettit, H. O.; Bloom, F. E.; Koob, G. F. Heroin and cocaine intravenous self-administration in rats: mediation by separate neural sytems. Psychopharmacology (Berlin) 78:204–209; 1982.
13. Fenton, H. M.; Hall, N. R.; Gerhardt, S.; Noreika, L.; Nale, 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.
14. Fouriezos, G.; Hansson, P.; Wise, R. A. Neuroleptic-induced attenuation of brain stimulation reward in rats. J. Comp. Physiol. Psychol. 92:661–671; 1978.
15. Franklin, K. B. J.; Robertson, A. Effects and interactions of naloxone and amphetamine on self-stimulation of the prefrontal cortex and dorsal tegmentum. Pharmacol. Biochem. Behav. 16:433–436; 1982.
16. German, D. C.; Sanghera, M. K.; Kiser, R. S.; McMillen, B. A.; Shore, P. A. Electrophysiological and biochemical response of noradrenergic neurons to a non-amphetamine CNS stimulant. Brain Res. 166:331–339; 1979.
17. Goodman, N. L.; Porrino, L. J. Intravenous self-administration of the indirect dopamine agonist amfonelic acid. Soc. Neurosci. Abstr. 13:1322; 1987.
18. Gower, A. J.; Broekkamp, C. L. E. Dopaminergic agents including 3-PPP and its enantiomers on medial septal self-stimulation. Pharmacol. Biochem. Behav. 22:309–315; 1985.
19. Harrigan, R. A.; Downs, D. A. Continuous intravenous naltrexone effects on morphine self-administration in rhesus monkeys. J. Pharmacol. Exp. Ther. 204:481–486; 1978.
20. Heikkila, R. E.; Manzino, L. Behavioral properties of GBR 12909, GBR 13069 and GBR 13098: Specific inhibitors of dopamine uptake. Eur. J. Pharmacol. 103:241–248; 1984.
21. Hitzemann, R.; Currell, J.; Hom, D.; Loh, H. Effects of naloxone on d-amphetamine and apomorphine-induced behavior. Neuropharmacology 21:1005–1011; 1982.
22. Holtzman, S. G. Behavioral effects of separate and combined administration of naloxone and d-amphetamine. J. Pharmacol. Exp. Ther. 189:51–60; 1974.
23. Holtzman, S. G. Comparison of the effects of morphine, pentazocine, cyclazocine, and amphetamine on intracranial self-stimulation in the rat. Psychopharmacologia 46:223–227; 1976.
24. Kelsey, J. E.; Belluzzi, J. D.; Stein, L. Does naloxone suppress self-stimulation by decreasing reward or by increasing aversion? Brain Res. 307:55–59; 1984.
25. Killian, A. K.; Bonese, K.; Schuster, C. R. The effects of naloxone on behavior maintained by cocaine and heroin injections in the rhesus monkey. Drug Alcohol Depend. 3:243–251; 1978.
26. Kim, H. S.; Iyengar, S.; Wood, P. L. Opiate actions on mesocortical dopamine metabolism in the rat. Life Sci. 39:2033–2036; 1986.
27. Koob, G. F.; Fray, P. J.; Iversen, S. P. Self-stimulation at the lateral hypothalamus and locus coeruleus after specific unilateral lesions of the dopamine system. Brain Res. 146:123–140; 1978.
28. Kornetsky, C.; Esposito, R. U. Euphorigenic drugs: Effects on the reward pathways of the brain. Fed. Proc. 38:2473–2476; 1979.
29. Kuhr, W. G.; Wightman, R. M. Real-time measurement of dopamine release in rat brain. Brain Res. 381:168–171; 1986.
30. Liebman, J. M.; Gerhardt, S.; Prowse, J. Differential effects of d-amphetamine pipradrol and bupropion on shuttle box self-stimulation. Pharmacol. Biochem. Behav. 16:791–794; 1982.
31. McMillen, B. A.; Shore, P. A. Amfonelic acid, a non-amphetamine stimulant, has marked effects on brain dopamine and metabolism but not noradrenaline metabolism: association with differences in neuronal storage systems. J. Pharm. Pharmacol. 30:464–466; 1978.
32. Matthews, R. T.; German, D. C. Electrophysiological evidence for excitation of rat ventral tegmental area dopamine neurons by morphine. Neuroscience 11:617–624; 1984.
33. Murrin, L. C.; Roth, R. H. Dopaminergic neurons: effects of electric stimulation on dopamine biosynthesis. Mol. Pharmacol. 12:463–475; 1976.
34. Pollard, H.; Lorens, C.; Bonnet, J. J.; Costentin, J.; Schwartz, J. L. Opiate receptors on mesolimbic dopaminergic neurons. Neurosci. Lett. 7:295–299; 1977.
35. Pollard, H.; Llorens-Cortes, C.; Swartz, J.C. Enkephalin receptors on dopaminergic neurons in rat striatum. Nature 268:745–747; 1977.
36. Reymann, K. G.; Wulcko, S.; Ott, T.; Matthies, H. Opioid-receptor blockade reduces nose-poke self-stimulation derived from medial entorhinal cortex. Pharmacol. Biochem. Behav. 24:439–443; 1986.
37. Schaeffer, G. J.; Michael, R. P. Effects of opioid antagonists and their quarternary derivatives on locomotor activity and fixed ratio responding for brain self-stimulation in rats. Pharmacol. Biochem. Behav. 23: 797–802; 1985.
38. Schaefer, G. J.; Michael, R. P. Threshold differences for naloxone and naltrexone in the hypothalamus and midbrain using fixed ratio brain self-stimulation in rats. Psychopharmacology (Berlin) 74:17–22; 1981.
39. Schechter, M. D. Amfonelic acid: Similarity to other dopamine agonsits. Pharmacol. Biochem. Behav. 26:413–416; 1987.
40. Shore, P. A.; Actions of amfonelic acid and other non-amphetamine stimulants on the dopamine neuron. J. Pharm. Pharmacol. 28: 855–857; 1976.
41. Stamford, J. A.; Kruk, Z. L.; Millar, J. Sub-second striatal dopamine release measured by in vivo voltammetry. Brain Res. 381:351–355; 1986.
42. Stapleton, J. M.; Merriman, V. J.; Coogle, C. L.; Gelbard, S. D.; Reid, L. D. Naloxone reduces pressing for intracranial stimulation of sites in the periaqueductal gray area, accumbens nucleus, substantia nigra and lateral hypothalamus. Physiol. Psychol. 7:427–436; 1979.
43. Stein, E. A. Effects of intracranial self-stimulation on brain opioid peptides. Peptides 6:67–73; 1985.
44. Van der Kooy, D.; LePaine, F. G.; Phillips, A. G. Apparent independence of opiate reinforcement and electrical self-stimulation systems in rat brain. Life Sci. 20:981–986; 1977.
45. Wauquier, A.; Neimegeers, C. J. E. Intracranial self-stimulation in rats as a function of various stimulus parameters II. Influence of haloperidol, pimozide, and pipamperone on medial forebrain bundle stimulation with monopolar electrodes. Psychopharmacologia 27: 191–202; 1972.

46. Wong, D. T.; Bymaster, F. P. An inhibitor of dopamine uptake, LR5182, CIS-3-(3,4-dichlorophenyl) 2-N, N-dimethylaminomethyl-bicyclo [2,2,2]-octane, hydrochloride. Life Sci. 23:1041–1048; 1978.

47. Wood, P. L. Opioid regulation of CNS dopaminergic pathways: A review of methodology, receptor types, regional variations and species differences. Peptides 4:595–601; 1983.