Pharmacology Biochemistry and Behavior, Vol. 58, No. 1, pp. 153–158, 1997

0091-3057/97 $17.00 + .00

ELSEVIER

PII S0091-3057(96)00403-0

Interaction of Morphine and Haloperidol on Agonistic and Motor Behaviors of Male Mice

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Received 25 April 1996; Revised 3 October 1996; Accepted 3 October 1996

RODRÍGUEZ-ARIAS, M., J. MIÑARRO AND V. M. SIMÓN. *Interaction of morphine and haloperidol on agonistic and motor behaviors of male mice.* PHARMACOL BIOCHEM BEHAV **58**(1) 153–158, 1997.—To further clarify the interaction between opioid and dopaminergic systems, the effects of simultaneous administration of morphine hydrochloride (1.25 or 2.5 mg/kg) and haloperidol (0.1 mg/kg) on aggressive behavior of male mice were explored. Isolated male mice (experimental animals) were confronted in a neutral area with anosmic, group-housed conspecifics (standard opponents) 30 min after injection of both compounds, and aggression was evaluated by estimation of times allocated to 11 different behavioral categories. In the first experiment (which functioned as a pilot study), the two doses of morphine were explored. In the second one, incorporating a more complete experimental design, only the lowest morphine dose was used and the animals were preselected by a previous aggression test. In attack behavior, morphine added to haloperidol counteracted, at least partially, the antiaggressive effect of the neuroleptic. In contrast, the impairing effects of haloperidol on motor activity were increased by the addition of morphine. These results show that the behavioral effects of dopaminergic antagonists are modulated by opioid influences and that opiates and dopaminergic agents interact in a different manner on motor and on aggressive behaviors. © 1997 Elsevier Science Inc.

Aggression Morphine Haloperidol Motor activity Reward Mice Dopamine Opiates

THE functional interaction of dopaminergic and opioid systems has become a subject of great interest for many researchers, and a substantial number of revealing experiments have been designed with the purpose of understanding the nature of such interaction. The majority of available results suggest that the dopaminergic system mediates several effects of opioids (5,6,10,36,41,48), especially their reinforcing and psychomotor actions. The strategy most frequently used is to interfere with dopaminergic functioning and observe any changes that appear in the behavioral effects of the opioid compounds.

Opiate agonists (like morphine, heroin, or β-endorphin) locally placed in dopaminergic regions (such as the ventral tegmental area or the nucleus accumbens) generally stimulate motor activity as well as reinforced behaviors. These effects are blocked not only by opiate antagonists (like naloxone) but also by dopaminergic antagonists such as haloperidol (16,19,36), suggesting that, at least partially, these effects of opiates must be mediated by dopaminergic neurons. Moreover, it has been shown that lesions in the ventral tegmental area (VTA) or in the nucleus accumbens (NA) abolish motivational and motor effects of opiates (38,41).

Spyraki et al. (40), using the conditioning place preference (CPP) paradigm, observed that the rewarding effects of the μ agonist heroin were attenuated by pretreatment with haloperidol and that lesions of the mesolimbic dopaminergic pathway at the level of the NA also attenuated the heroin-induced CPP. These data provided direct support for the mesolimbic pathway as a substrate for opiate reward. In 1988, Shippenberg and Herz (36), using selective antagonists for D1 and D2 receptors in a CPP situation, postulated that aversive as well

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as reinforcing motivational states were more related to D1 than to D2 receptors. Furthermore, Acquas et al. (1) showed that SCH 23390, a selective D1 antagonist, blocked the CPP induced by morphine. More recently, Shippenberg et al. (35) confirmed the intervention of the NA in mediating opiate reward, but they could verify only the involvement of D1 receptors. Gerrits et al. (16), using systemic self-administration of heroin, also found that the selective D1 antagonist SCH 23390 decreased heroin intake, although only at doses that also affect motor behavior. If these results are considered together, it could be proposed that the stimulation of D1 but not D2 receptors mediates the rewarding effects of opioids.

On the other hand, Stinus et al. (43) observed that chronic neuroleptic treatment increased the reinforcing properties of opiates administered in the NA, but these effects were completely abolished when the opiates were administered in the VTA. Likewise, the threshold dose of heroin required to induce CPP was lower in rats chronically treated with neuroleptics. This phenomenon was also demonstrated by using other paradigms, such as heroin-induced intravenous self-administration (43). Stinus et al. (43) suggested that chronic neuroleptic treatment increases the synaptic biodisponibility of endogenous opiates within the NA and that the reinforcing effects of opiates are mediated by the activation of mesolimbic DA10 neurons in the VTA whereas these effects do not seem to be dopamine (DA)-dependent in the NA.

Recently, Da Silva Planeta et al. (12), studying the increase of motor activity and the reinforcing properties of fecanfamine (an indirect dopaminergic agonist), found that these effects were blocked by D1 dopaminergic antagonists and by naloxone but not by D2 dopaminergic antagonists. These results also assign an important role to D1 receptors in mediating the rewarding and psychomotor effects of opiates.

The hypothesis that morphine administration activates the dopaminergic pathways enhancing locomotor activity is sustained by numerous results. Morphine-induced locomotion is depressed after pretreatment with the dopaminergic antagonist spiperone or with the agonist apomorphine, which inhibits presynaptically dopaminergic neurons (17). Morphine injected in the VTA increases locomotion, an action that is blocked by systemic administration of either naloxone or haloperidol (19). Moreover, the increase in motor activity induced by injection of morphine in the NA is blocked by pretreatment with a D1 antagonist (SCH 23390) or with a predominantly D2 dopaminergic antagonist like haloperidol (26,27) or by lesions of the NA with 6-OHDA (42). Nevertheless, some authors have failed to confirm this result. Kalivas et al. (21) found that microinjection of DALA (an enkephalin analogue) into the VTA produced an increase in locomotion that was antagonized by neuroleptic administration (fluphenazine) in the NA, but when DALA and fluphenazine were both injected into the NA, the neuroleptic compound failed to block this behavioral response. Likewise, Vaccarino et al. (45) found that heroin-induced locomotion was not blocked by the dopaminergic antagonist α-flupenthixol or by 6-OHDA lesions of the NA.

All of these results illustrate that dopaminergic activity seems instrumental in mediating the effects of opioid compounds, but this interaction also functions the other way around. Layer et al. (25) applied two DA agonists (*d*-amphetamine and dopamine) in the NA and obtained an increase in locomotor activity. The response was cancelled when the drugs were coadministered with morphine.

The interaction between dopaminergic and opioid systems has been little explored in behaviors other than reinforcement and motility. Few experiments have been carried out in the field of aggression. Gianutsos and Lal, in 1978 (15), observed that apomorphine-induced aggression was blocked by morphine. In morphine withdrawal studies, dopaminergic antagonists decreased aggression (15,24) whereas dopaminergic agonists increased it (22). On the other hand, Tidey and Miczek (44) did not find this increase in aggression produced by morphine withdrawal when selective dopaminergic agonists were administered. Winslow and Miczek (47), using the resident–intruder paradigm in male mice, studied the interaction between an opiate antagonist (naltrexone) and a dopaminergic agonist (amphetamine). Naltrexone increased the disruptive effect of amphetamine on aggressive behavior but also blocked its stimulant effects on locomotor activity.

It seems clear that opiates and the dopaminergic system interact in a different way on aggressive and motor behaviors. With the purpose of looking into this interaction further, we administered an opiate agonist (morphine) and a dopaminergic antagonist (haloperidol) and studied their effects on aggressive behavior and motor activity. Numerous researchers have used a wide range of doses of haloperidol in aggression experiments with mice (2,29,30), the results of which show an unmistakably antiaggressive action of this neuroleptic. In the present study, a relatively low dose of the butyrophenone (0.1 mg/kg), which had previously shown clear antiaggressive effects but a moderate depressing action on motor activity (29,33), was used after carrying out a pilot experiment that confirmed these expectations.

The two morphine doses used (1.25 and 2.5 mg/kg) were initially selected because in a previous study they had been found to reduce aggression (14). Although in this experiment they did not show a clear antiaggressive action, the results proved them to be of great help in the task of exploring the nature of the opioid–dopaminergic interaction.

METHODS

Subjects

First experiment. Forty-eight OF.1 albino male mice (Laboratorios IFFA CREDO, Barcelona) 42 days old were housed under standard laboratory conditions: constant temperature (21°C), a reverse light schedule (white lights on 0730–1930 h), and food and water available ad lib, except during behavioral testing. All animals underwent an adaptation period of 30 days before experimental treatments were applied. Half were individually housed in transparent plastic cages (24 × 13.5 × 13 cm) and employed as experimental animals. The remainder were housed in groups of five to be used as standard opponents and were made temporarily anosmic by intranasal lavage with a 4% zinc sulphate solution on the day before testing (37). Such animals provoke aggressive behavior in isolated aggressive mice (7) but do not initiate attack.

Second experiment. One hundred twenty OF.1 albino male mice (Laboratorios IFFA CREDO) 21 days old were used. The housing conditions and preexperimental treatment were similar to those described above.

Drug Treatments and Experimental Design

First experiment. Morphine hydrochloride (Laboratorios Alcaliber, Toledo, Spain), haloperidol® (Laboratorios Latino), and physiological saline (0.9% NaCl) were used in this experiment. Drugs were diluted in physiological saline (0.1 mg/ml) and administered intraperitoneally.

Animals were allocated to one of three groups ($n = 8$): one

control and two experimental. Experimental groups received simultaneously morphine plus haloperidol in two separate injections. One experimental group received 1.25 mg/kg of morphine plus 0.1 mg/kg of haloperidol (M1 + H). The other experimental group received 2.5 mg/kg of morphine plus 0.1 mg/kg of haloperidol (M2 + H). The control group received two injections of physiological saline (V + V).

Second experiment. Four groups of animals were used: one control and three experimental. The control group received two doses of physiological saline (V + V). The first experimental group received 1.25 mg/kg of morphine plus physiological saline (V + M1). The second experimental group received 0.1 mg/kg of haloperidol plus physiological saline (V + H), and the third group received 1.25 mg/kg of morphine plus 0.1 mg/kg of haloperidol (M1 + H). All animals were injected only once, although the syringe was changed to administer the two different compounds.

In this experiment, animals underwent a previous aggression test with an anosmic opponent; subjects not showing any aggressive behavior were excluded.

Social Encounters

Behaviors were evaluated 30 min after the last injection. After treatment, an experimental animal and a standard opponent confronted each other in a neutral cage for 10 min. All tests were carried out under white illumination between the second and fifth hour of the dark phase of the light/dark cycle. The animals were allowed 1 min of adaptation to the neutral cage before the encounter, during which time they were separated by means of a plastic barrier. Encounters were videotaped with a Panasonic VHS camera.

Behavioral Analysis

The videotapes were analyzed using a microprocessor (Commodore 64 computer) and a custom-developed program (8) that facilitated estimation of times allocated to 11 broad functional categories of behavior. Each category included a collection of different postures and elements. The names of categories are the following: body care, digging, nonsocial exploration, explore from a distance, social investigation, threat (aggressive groom, sideways offensive, upright offensive, tail rattle), attack (charge, lunge, attack, chase), avoidance/flee, defensive/submissive, sexual, and immobility. A detailed description of all elements can be found in Brain et al. (8) and Martínez et al. (28).

Statistical Analysis

Data were initially analyzed using the Kruskal–Wallis test. For the behavioral categories in which this test was significant, differences between control and experimental groups in accumulated times were then examined by the two-tailed Mann–Whitney *U*-test.

RESULTS

First Experiment

Table 1 illustrates medians (with ranges) of accumulated times allocated to the 11 broad categories described above. Both groups of animals treated with haloperidol showed a significant (U = 1.0 and 0.0 for M1 + H and M2 + H, respectively, $p < 0.001$) increase in the time allocated to immobility behaviors with respect to the control animals. The group treated with haloperidol plus the higher dose of morphine showed a significant ($U = 11$, $p < 0.02$) decrease in the time allocated to nonsocial exploration with respect to the other two groups. No changes were observed in offensive behaviors (threat and attack) in either experimental group with respect to controls.

TABLE 1

FIRST EXPERIMENT: MEDIANS ALLOCATED TO 11 CATEGORIES OF BEHAVIOR

Behavioral Category	V + V	M1 + H	M2 + H
Body care	8 (1–11)	5 (0–13)	2 (0–35)
Digging*	8 (1–25)	5 (2–14)	1† (0–11)
Nonsocial exploration*	325 (270–440)	318 (246–354)	221† (70–346)
Explore from a distance	49 (12–65)	54 (6–86)	27 (11–92)
Social investigation	77 (22–203)	35 (13–94)	27 (5–211)
Threat	46 (10–134)	48 (6–154)	37 (0–101)
Attack	29 (1–103)	17 (0–57)	14 (0–31)
Avoidance/flee	0 (0–6)	0 (0–2)	0 (0–4)
Defensive/submissive	0 (0–0)	0 (0–0)	0 (0–0)
Sexual	0 (0–0)	0 (0–0)	0 (0–0)
Immobility**	4 (1–15)	106†† (13–225)	212†† (61–469)

Medians of accumulated times (in s) with ranges allocated to 11 categories of behavior. Kruskal–Wallis test shows significant variance at $*p < 0.05$ or $**p < 0.001$. Differs from controls on two-tailed Mann–Whitney U-test at $\dagger p < 0.02$ or $\dagger\dagger p < 0.001$.

Second Experiment

Table 2 illustrates medians (with ranges) of accumulated times allocated to the 11 behavioral categories. Animals treated with haloperidol plus saline showed a significant ($U = 9.5$, $p < 0.002$) decrease in the time allocated to attack behaviors with respect to the other three groups. Immobility was significantly ($U = 0.0$, $p < 0.002$) increased in the two groups treated with haloperidol plus saline. Nonsocial exploration significantly ($U = 26$, $p < 0.02$) decreased in the group treated simultaneously with haloperidol and morphine. Neither morphine with saline nor morphine with haloperidol decreased attack behavior. Threat behavior was not significantly modified in any of the four groups studied.

DISCUSSION

The most obvious finding of this study is that opiates and dopaminergic agents interact in a different way on motor and aggressive behaviors. In aggressive behavior, morphine administered with haloperidol counteracts, at least partially, the clear antiaggressive effect of the neuroleptic. On the contrary, the impairing effects of haloperidol on motor activity are increased by the addition of morphine.

In agreement with our findings, a number of papers have pointed out this dissociation between antiaggressive and mo-

TABLE 2
SECOND EXPERIMENT: MEDIANS ALLOCATED TO 11 CATEGORIES OF BEHAVIOR

Behavioral Category	V + V	V + H	V + M1	M1 + H
Body care	5	12	6	10
	(0–121)	(0–26)	(0–41)	(0–25)
Digging*	0	3	1	1
	(0–2)	(0–16)	(0–22)	(0–19)
Nonsocial exploration*	372	329	387	282†
	(100–467)	(58–439)	(249–446)	(108–424)
Explore from a distance	18	19	22	27
	(7–119)	(2–67)	(6–34)	(1–63)
Social investigation	15	30	18	16
	(0–345)	(0–109)	(0–48)	(0–69)
Threat	58	16	47	50
	(17–93)	(0–72)	(18–105)	(1–122)
Attack**	95	9††	71	38
	(2–159)	(0–26)	(27–151)	(0–106)
Avoidance/flee	0	0	0	0
	(0–0)	(0–0)	(0–0)	(0–0)
Defensive/submissive	0	0	0	0
	(0–0)	(0–0)	(0–0)	(0–0)
Sexual	0	0	0	0
	(0–0)	(0–0)	(0–0)	(0–0)
Immobility**	0	80††	0	143††
	(0–9)	(18–534)	(0–95)	(32–264)

Medians of accumulated times (in s) with ranges allocated to 11 categories of behavior. Kruskal–Wallis test shows significant variance at $*p < 0.05$ or $**p < 0.001$. Differs from controls on two-tailed Mann–Whitney U-test at $\dagger p < 0.02$ or $\dagger\dagger p < 0.002$.

tor effects. Winslow and Miczek (47) found that, when given to mice, the opioid antagonist naloxone increased the antiaggressive action of amphetamine (a dopaminergic agonist) but blocked its stimulant effects on motor activity. In a similar direction, Cunningham and Kelley (11) found that opiates stimulated activity when infused into the NA (which is a major target of dopaminergic neurons) but did not affect response for conditioning reward. For these authors, the data demonstrate an important dissociation of the effects of opiates on motor activity and on reward.

Studying morphine withdrawal, Tidey and Miczeck (44) found a clear dissociation between the time course of changes in motor activities and in aggressive behaviors. In withdrawal, frequency of attack was increased, and this effect persisted at least 4 days. In contrast, increase in motor activities was greatly diminished within the first 24 h. Moreover, *d*-amphetamine maintained the elevated level of aggressive behavior but increased locomotion in morphine-withdrawn mice. A similar dissociation, affecting only haloperidol, was found by Navarro et al. (30). They observed that the motor but not the antiagressive effects of haloperidol developed tolerance to repeated daily injections of the drug (0.4 mg/kg).

The underlying question in the interpretation of all these experiments is, of course, the relationship between the dopaminergic and the opioid systems. Given the complexity of their anatomical and functional connections and our deficient knowledge of them, the scope of the conclusions obtained by studying the overall effects of neurochemical compounds on behavior must be necessarily quite limited. Nevertheless, some interesting comments can be made on the peculiarities of this relationship in aggressive as well as in motor behaviors.

With regard to aggressive behavior, it is believed that specific activation of dopaminergic transmission in the mesolimbic system is a common mechanism for the reinforcing properties of drugs of abuse (34,39). Aggression, considered as a reinforcing process (32), like eating or sexual behavior, would stimulate brain areas related to the reward system, most probably dopaminergic pathways, which could sufficiently explain why a dopaminergic antagonist like haloperidol exerts powerful antiaggressive effects (29). In the conditions of our experiment, when morphine was administered in addition to haloperidol, it partially antagonized the antiaggressive effects of the neuroleptic. (In contrast, morphine alone did not show any effect on aggressive behavior.) This antagonistic action of morphine on the effects of haloperidol can be explained through its facilitatory role in DA transmission. It is known that morphine increases DA release and turnover in many cerebral areas (5,13,36), such as the VTA or substantia nigra, probably using intermediate GABAergic neurons (18). Thus, morphine (at these low doses) would stimulate the reinforcing system, enough at least to counteract the inhibiting effects of haloperidol on aggression.

The classical impairing effects of haloperidol on motor activity (9) are reflected in our results by the increased immobility of the group treated only with haloperidol. On the other hand, morphine at low doses does not impair motor behavior but even increases it (31), although at high doses it has been described to decrease motility. In our results, as could be expected, the animals treated with morphine showed no increase in immobility.

These effects of morphine on motor activity are generally related to its action on the dopaminergic system, especially on

its mesolimbic and nigrostriatal portions. Microinjections of morphine in the VTA produce an increase in locomotor activity similar to that observed following systemic administration of DA agonists (20). Moreover, in the experiments of Iwamoto (17), opioid-induced locomotion was disrupted by both presynaptic (apomorphine) and postsynaptic (spiperone) dopaminergic inhibitors. Both D_1 and D_2 DA receptors seem to be involved in this mediation (3), although some researchers accept only the participation of the D_1 receptor (46). From these experimental results it could be expected that coadministration of morphine with haloperidol would counteract the haloperidol-induced immobility. However, this was not the case. Morphine not only failed to decrease immobility but, on the contrary, it increased it, although not significantly. Our results are in agreement with those of Kiritsy-Roy, Standish, and Cass Tery (23), who found that DA D_1 as well as D_2 antagonists administered in combination with morphine produced a powerful catalepsy. Neither of these two types of receptor antagonist alone nor morphine alone (12 mg/kg) produced a remarkable catalepsy. It is thought that opioid circuits in the striatum reduce nigrostriatal DA neurotransmission by presynaptic inhibition of DA release (4), thus inhibiting motor behavior. The mutual potentiation of morphine and haloperidol in the inhibition of motility is corroborated by the decrease found in nonsocial exploration, a typical motor behavior that occurred only when the two drugs were administered together.

In conclusion, the relationship between dopaminergic and opioid systems could be explained through a triangular interaction involving opioids, the dopaminergic system, and behavior. Opiates could produce their effects on behavior either directly or with the intervention of the dopaminergic system. On the other hand, the behavioral effects of dopamine could also be influenced (in a positive or negative way, depending on each particular behavior) by the existing opioid tone, which is the main conclusion of our experiment.

REFERENCES

1. Acquas, E.; Carboni, E.; Leone, P.; Di Chiara, G.: SCH23390 blocks drug-conditioned place-preference and place-aversion: Anhedonia (lack of reward) or apathy (lack of motivation) after dopamine-receptor blockade. Psychopharmacology 99:151–155; 1989.
2. Aguilar, M. A.; Miñarro, J.; Pérez-Iranzo, N.; Simón, V. M.: Behavioral profile of raclopride in agonistic encounters between male mice. Pharmacol. Biochem. Behav. 47:753–756; 1994.
3. Axon, D. I. R.; Fletcher, G. H.; Starr, M. S.: In morphinised rats SKF 38393 converts dopamine D2 receptor-mediated forward locomotion into backward walking. Pharmacol. Biochem. Behav. 26:45–47; 1987.
4. Balsara, J. J.; Nandal, N. V.; Burte, N. P.; Jadhav, J. H.; Chandorkar, A. G.: Effects of naloxone on methamphetamine and apomorphine stereotypy and on haloperidol catalepsy in rats. Psychopharmacology 82:237–240; 1984.
5. Bozarth, M. A.: Opioid reinforcement processes. In: Rodgers, R. J.; Cooper, S. J., eds. Endorphins, opiates and behavioural processes. London: John Wiley and Sons Ltd.; 1988:53–75.
6. Bozarth, M. A.; Wise, R. A.: Neural substrates of opiate reinforcement. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 7:569–575; 1983.
7. Brain, P. F.; Benton, D.; Childs, G.; Parmigiani, S.: The effect of the opponent in test of murine aggression. Behav. Processes 6:319–328; 1981.
8. Brain, P. F.; McAllister, K. H.; Wamsley, S. V.: Drug effects on social behaviour. Methods in ethopharmacology. In: Boulton, A. A.; Baker, G. B.; Greenshow, A. J., eds. Neuromethods. Clifton, NJ: The Humana Press Inc.; 1989:687–739.
9. Cambell, A.; Baldessarini, R. J.: Circadian changes in behavioral effects of haloperidol in rats. Psychopharmacology 77:150–155; 1982.
10. Cooper, S. J.: Interactions between endogenous opioids and dopamine: Implications for reward and aversion. In: Willner, P.; Scheel-Kruger, J., eds. The mesolimbic dopamine system: From motivation to action. London: John Wiley & Sons Ltd.; 1991:331–366.
11. Cunningham, S. T.; Kelley, A. E.: Opiate infusion into nucleus accumbens: Contrasting effects on motor activity and responding for conditioned reward. Brain Res. 588:104–114; 1992.
12. Da Silva Planeta, C.; Luiz, M.; DeLucia, R.: Reinforcing properties of fencamfamine: Involvement of dopamine and opioid receptors. Pharmacol. Biochem. Behav. 50:35–40; 1994.
13. Di Chiara, G.; Imperato, A.: Opposite effects of mu and kappa opiate agonist on dopamine release in the nucleus accumbens and in the dorsal caudate of freely moving rats. J. Pharmacol. Exp. Ther. 244:1067–1080; 1988.
14. Espert, R.; Navarro, J. F.; Salvador, A.; Simón, V. M.: Effects of morphine hydrochloride on social encounters between male mice. Aggressive Behav. 19:377–383; 1993.
15. Gianutsos, G.; Lal, H.: Narcotic analgesis and aggression. Mod. Probl. Pharmacopsychiatry 13:114–138; 1978.
16. Gerrits, M. A.; Ramsey, N. F.; Wolterink, G.; Van Rees, J. M.: Lack of evidence for an involvement of nucleus accumbens dopamine D1 receptors in the initiation of heroin self-administration in the rat. Psychopharmacology 114:486–494; 1994.
17. Iwamoto, E.: Locomotor activity and antinociception after putative mu, kappa and sigma opioid receptor agonists in the rat: Influence of dopaminergic agonists and antagonists. J. Pharmacol. Exp. Ther. 217:451–460; 1981.
18. Johnson, S. W.; North, R. A.: Opioids excite dopamine neurons by hyperpolarization of local interneurons. J. Neurosci. 12:483–488; 1992.
19. Joyce, E. M.; Iversen, S. D.: The effect of morphine applied locally to mesencephalic dopamine cell bodies on spontaneous motor activity in the rat. Neurosci. Lett. 14:207–212; 1979.
20. Joyce, E. M.; Koob, G. F.; Strecker, R.; Iversen, S. D.; Bloom, F.: The behavioral effects of enkephalin analogues injected into the ventral tegmental area and globus pallidus. Brain Res. 221:359–370; 1981.
21. Kalivas, P. W.; Widerlow, E.; Stanley, D.; Breese, G.; Prange, A. J., Jr.: Enkephalin action on the mesolimbic system: A dopamine-dependent and a dopamine-independent increase in locomotor activity. J. Pharmacol. Exp. Ther. 227(10):229–237; 1983.
22. Kantak, K. M.; Miczek, K.: Social, motor and autonomic signs of morphine withdrawal: Differential sensitivities to catecholaminergic drugs. Psychopharmacology 96:468–476; 1988.
23. Kiritsy-Roy, J. A.; Standish, S. M.; Cass Tery, L.: Dopamine D1 and D2 receptor antagonists potentiate analgesic and motor effects of morphine. Pharmacol. Biochem. Behav. 32:717–721; 1989.
24. Lal, H.; Gianutsos, G.; Puri, S. K.: A comparison of narcotic analgesics with neuroleptics on behavioral measures of dopaminergic activity. Life Sci. 17:29–34; 1975.
25. Layer, R. T.; Uretsky, N. J.; Wallace, L. J.: Effects of morphine in the nucleus accumbens on stimulant-induced locomotion. Pharmacol. Biochem. Behav. 40:21–26; 1991.
26. Longoni, R.; Spina, L.; Di Chiara, G.: Dopaminergic D1 receptors: Essential role in morphine-induced hypermotility. Psychopharmacology 93:401–402; 1987.
27. Magnus-Ellenbroek, B.; Haverman-Reinecke, U.: Morphine-induced hyperactivity in rats, a rebound effect? Naunyn-Schmiedeberg's Arch. Pharmacol. 347:635–642; 1993.
28. Martínez, M.; Miñarro, J.; Simón, V. M.: Análisis etoexperimental de la conducta agonística en ratones macho. Psicológica 12:1–22; 1991.
29. Miñarro, J.; Castaño, D.; Brain, P. F.; Simón, V. M.: Haloperidol does not antagonize the effects of stress on aggressive behavior in mice. Physiol. Behav. 47:281–287; 1990.

30. Navarro, J. F.; Miñarro, J.; Simón, V. M.: Antiaggressive and motor effects of haloperidol show different temporal patterns in the development of tolerance. Physiol. Behav. 53:1055–1059; 1993.
31. Olson, G.; Olson, R.; Kastin, A.: Endogenous opiates: 1990. Peptides 12:1407–1432; 1991.
32. Potegal, M.: The reinforcing value of several types of aggressive behavior: A review. Aggressive Behav. 5:353–373; 1979.
33. Redolat, R.; Miñarro, J.; Simón, V. M.; Brain, P. F.: Influences of haloperidol and sulpiride on social behavior of female mice in interactions with anosmic males. Psicothema 3(1):79–85; 1991.
34. Self, D.; Nestler, E. J.: Molecular mechanisms of drug reinforcement and addiction. Annu. Rev. Neurosci. 18:463–495; 1995.
35. Shippenberg, T. S.; Bals-Kubick, R.; Herz, A.: Examination of the neurochemical substrates mediating the motivational effects of opioids: Role of the mesolimbic dopamine system and D1 versus D2 dopamine receptors. J. Pharmacol. Exp. Ther. 265:53–59; 1993.
36. Shippenberg, T. S.; Herz, A.: Motivational effects of opioids: Influence of D1 versus D2 receptors antagonists. Eur. J. Pharmacol. 151:233–242; 1988.
37. Smoothy, R.; Brain, P. F.; Berry, M. S.; Haug, M.: Alcohol and social behaviour in group-housed female mice. Physiol. Behav. 37:689–694; 1986.
38. Spanagel, R.; Herz, A.; Bals-Kubik, R.; Shippenberg, T.: β-Endorphin induced locomotor stimulation and reinforcement are associated with an increase in dopamine release in the nucleus accumbens. Psychopharmacology 104:51–56; 1991.
39. Spanagel, R.; Shoaib, M.: Involvement of mesolimbic κ-opioid systems in the discriminative stimulus effects of morphine. Neuroscience 63:797–804; 1994.
40. Spyraki, C.; Fibiger, H. C.; Phillips, A. G.: Attenuation of heroin reward in rats by disruption of the mesolimbic dopamine system. Psychopharmacology 79:278–283; 1983.
41. Stinus, L.; Cador, M.; Le Moal, M.: Interaction between endogenous opioids and dopamine within the nucleus accumbens. Ann. N.Y. Acad. Sci. 654:254–273; 1992.
42. Stinus, L.; Koob, G.; Ling, N.; Bloom, F.; LeMoal, M.: Locomotor activation induced by infusion of endorphins into the ventral tegmental area: Evidence for opiate–dopamine interactions. Proc. Natl. Acad. Sci. USA 77:2323–2327; 1980.
43. Stinus, L.; Nadaud, D.; Deminiére, J.; Jauregui, J.; Hand, T.; Le Moal, M.: Chronic flupenthixol treatment potentiates the reinforcing properties of systemic heroin administration. Biol. Psychiatry 26:363–371; 1989.
44. Tidey, J. W.; Miczek, K. A.: Morphine withdrawal aggression: Modifications with D1 and D2 receptor agonists. Psychopharmacology 108:177–184; 1992.
45. Vaccarino, F. J.; Amalric, M.; Swerlow, N. R.; Koob, G.: Blockade of amphetamine but not opiate-induced locomotion following antagonism of dopamine function in the rat. Pharmacol. Biochem. Behav. 24:61–65; 1986.
46. Vermeulen, R. J.; Drukarch, B.; Rob Sahadat, M. C.; Goosen, C.; Schoffelmeer, A. N. M.; Wolters, E. C.; Stoof, J. C.: Morphine and naltrexone modulate D2 but not D1 receptor induced motor behavior in MPTP-lesioned monkeys. Psychopharmacology 118:451–459; 1995.
47. Winslow, J. T.; Miczek, K. A.: Naltrexone blocks amphetamine-induced hyperactivity but not disruption of social and agonistic behavior in mice and squirrel monkeys. Psychopharmacology 96: 493–499; 1988.
48. Wise, R. A.; Rompre, P. P.: Brain dopamine and reward. Annu. Rev. Psychol. 40:191–225; 1989.