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The Role of Histaminergic–Noradrenergic Axis in Naloxone-Induced Withdrawal Symptoms in Mice

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EL-KADI, A. O. S. AND S. I. SHARIF. *The role of histaminergic–noradrenergic axis in naloxone-induced withdrawal symptoms in mice.* PHARMACOL BIOCHEM BEHAV **55**(1) 49–54, 1996.—The effects of histamine antagonists on naloxone-precipitated withdrawal symptoms were studied in morphine-dependent mice. Chlorpheniramine (0.5–10 mg/kg), a H_1-blocker, given IP 30 min before naloxone challenge produced a dose-dependent potentiation of withdrawal body weight loss, burrowing, and hypothermia, but did not influence either jumping or wet-dog shakes. On the other hand, cimetidine (10–100 mg/kg), a H_2-blocker, produced dose-dependent potentiation of withdrawal hypothermia and jumping. Cimetidine was without effect on wet-dog shakes, burrowing, and body weight loss. The effect of chlorpheniramine was investigated in mice injected with 6-hydroxydopamine (6-OHDA) intracerebrally to examine whether histamine-mediated effects are somehow linked to noradrenergic pathways. Intracerebral injection of 6-OHDA in 5-day-old mice pups resulted in hyperlocomotion by the end of 30 days before initiation of morphine dependence. Mice pretreated with 6-OHDA developed a higher degree of naloxone-induced withdrawal jumping than nontreated mice. 6-OHDA (50 μg) lesions completely blocked the potentiating effect of chlorpheniramine on burrowing, hypothermia, and even reversed the effect on body weight loss. These findings suggest that both histamine H_1- and H_2-receptors may be involved in the expression of precipitated withdrawal in morphine-dependent mice and histamine receptors function as modulators of noradrenergic neurotransmission.

Chlorpheniramine Cimetidine 6-Hydroxydopamine Morphine Naloxone Withdrawal symptoms

EXTENSIVE work has been carried out in attempts to define the mechanisms involved in the development of physical dependence to opiates. Several neurotransmitters (NT), including noradrenaline (18), dopamine (17,18), acetylcholine (12), GABA (38), and serotonin (5), have been implicated in such a phenomena.

Morphine is known to release histamine, both in peripheral (11) and in brain tissue (40), and there could be some functional relationship between central morphine action and the release of histamine in the CNS. The evidence in favour of the involvement of central histaminergic mechanisms in some effects of acute and chronic morphine treatment has been a subject of controversy. Chronic but not acute morphine treatment results in a significant decrease in the histamine concentration in the rat hypothalamus, while a slight decrease is noted in the brainstem and cortex. In addition, morphine withdrawal causes a significant decrease in histamine concentration in all three brain regions (30). Moreover, it has been shown that acute morphine treatment enhances the turnover of neuronal histamine via opioid receptors, and that morphine also releases histamine from a nonneuronal pool(s) in the mouse brain (31). On the other hand, Oishi et al. (33), found that in mice the brain histamine level is highly stable, irrespective of the development of morphine-dependence or the induction of withdrawal symptoms. In contrast with these results, earlier work found no changes in the brain histamine level in mice rendered morphine dependent (22). Moreover, morphine was shown to produce a biphasic effect on the brain histamine level of the mouse: low doses increase the concentration of histamine while reduced concentrations are seen at higher doses (28). These discrepancies may be explained by differences in the species, the technique used to establish dependence, the degree of dependence attained, and the doses of morphine used.

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Despite extensive studies on the involvement of histamine in morphine-induced antinociception (15,16,19,39) there is very little information available on the possible role of histamine in morphine dependence. It has been reported that injections of histamine into specific brain sites produced signs and symptoms strikingly similar to those seen during opiate withdrawal, and that the effects of histamine appear mediated by both histamine H_1- and H_2-receptors (14).

The interaction between several NT has been suggested in the pharmacological effects of morphine. This hypothesis is further supported by numerous reports, including but not limited to cholinergic–dopaminergic interactions (23), GABA–benzodiazepine interactions (38), and serotonergic–noradrenergic interactions (10). Moreover, catecholaminergic–histaminergic interactions have long been recognized (26,34,41) and there is evidence for the inhibition of histamine release through α_2-adrenoceptors (3). This suggests a possible interaction between noradrenaline and histamine in the expression of morphine withdrawal.

The present study was conducted to investigate the effects of the H_1-antagonist chlorpheniramine and H_2-antagonist cimetidine on several parameters of withdrawal symptoms induced by naloxone in morphine-dependent mice. In addition, the effects of chlorpheniramine were examined after removal of adrenergic influence by 6-hydroxydopamine (6-OHDA) to determine the extent of the adrenergic component involved in the expression of effects mediated by histamine receptors.

METHOD

Animals

Male albino mice (15–20 g) were housed in groups of six, and maintained at 18–20°C on a 12 L:12 D cycle in a room. They were provided with tap water and standard mice pelleted diet ad lib.

Induction of Dependence

Mice were injected subcutaneously (SC) in the scruff of the neck with three doses of morphine given at 8-h intervals. The initial dose was 5 mg/kg and was doubled every day to reach 160 mg/kg on the sixth day. On the seventh day, the final dose of morphine (160 mg/kg) was given at 0800 h and withdrawal was induced 3 h later.

Withdrawal

Each mouse was pretreated with the drug or vehicle (0.9% w/v NaCl, saline) given IP. For each dose of the drug or vehicle 8–10 animals were used. Abrupt withdrawal was then precipitated 30 min later by naloxone (1 mg/kg) given IP, a dose producing maximal withdrawal symptoms (9).

Body Weight Loss and Hypothermia

The body weight and rectal temperature of each mouse were measured before administration of vehicle or test drug, before the injection of naloxone, and finally 30 min after naloxone. Body temperature was measured with a thermistor probe inserted into the rectum and connected to a telethermometer.

Behaviour

Following the injection of naloxone, mice were placed individually into a circular glass observation chamber (6 × 25 cm), with sawdust bedding and perforated perspex lid and closely observed for 15 min. The withdrawal signs selected for quantification were jumping (all feet off the floor), body shakes (wet-dog shakes), and burrows (escape digging). The frequency of these behaviours (score/15 min) was recorded for each animal and results are compared to the frequency in the appropriate control group.

Injection of 6-Hydroxydopamine

Chemical sympathectomy was achieved by intracerebral injections of 6-OHDA as described by Schanberg et al. (37). It selectively destroys adrenergic nerve terminals and permits investigation of the role of histamine receptors in the absence of adrenergic component. The intracerebral injections of 6-OHDA 50 μg in 1 μl were made in 5-day-old unanaethetized mice pups, with a Hamilton syringe using a 26 G 9 mm long needle. The needle was pushed vertically into the brain to a depth of 2 mm previously scratch marked on the needle, at a point 1 mm lateral to the midline and 4 mm in front of the ears. Preliminary experiments with dye indicated that the injected dye filled both ventricular and subarachnoid spaces. The dose of 50 μg of 6-OHDA has been reported to destroy the adrenergic nerve terminals completely (1,37). Higher doses proved lethal. After 1 month all mice were rendered morphine dependent as previously described. On the day of challenge with naloxone, the animals (in groups of six each) were pretreated with an IP injection of saline (control) or chlorpheniramine (5 mg/kg, IP), and 30 min later both groups received naloxone (1 mg/kg, IP). Withdrawal symptoms were recorded, and the mice of each group were used only once.

Drugs

Chlorpheniramine maleate (Weimer Pharma), cimetidine (Smith-Kline and French labs), and morphine HCl (MacFarlane Smith) were dissolved in saline. 6-Hydroxydopamine (Sigma) was dissolved in saline containing 1% ascorbic acid.

Statistics

Values reported are mean ± SEM. Data were analyzed using one-way analysis of variance (ANOVA) procedures followed by Newman–Keuls post hoc tests. The results were considered significant when the probability level was less than 0.05.

RESULTS

Naloxone-Precipitated Withdrawal in the Absence and Presence of 6-OHDA

The administration of naloxone (1 mg/kg, IP) to mice chronically treated with morphine produced characteristic withdrawal symptoms. The symptoms observed included jumping, wet-dog shakes, burrowing, body weight loss, and hypothermia.

Mice pretreated in the neonatal period with 6-OHDA (50 μg) produced marked enhancement of naloxone precipitated withdrawal jumping, $F(1, 18) = 78.177$, $p < 0.0001$, without significant modification of other signs as compared to their corresponding control group that received the vehicle (Fig. 1c).

Effect of Chlorpheniramine

In morphine-dependent mice, chlorpheniramine (0.5–10 mg/kg, IP) given 30 min before naloxone, produced dose dependent potentiation of withdrawal burrowing, $F(4, 35) =$

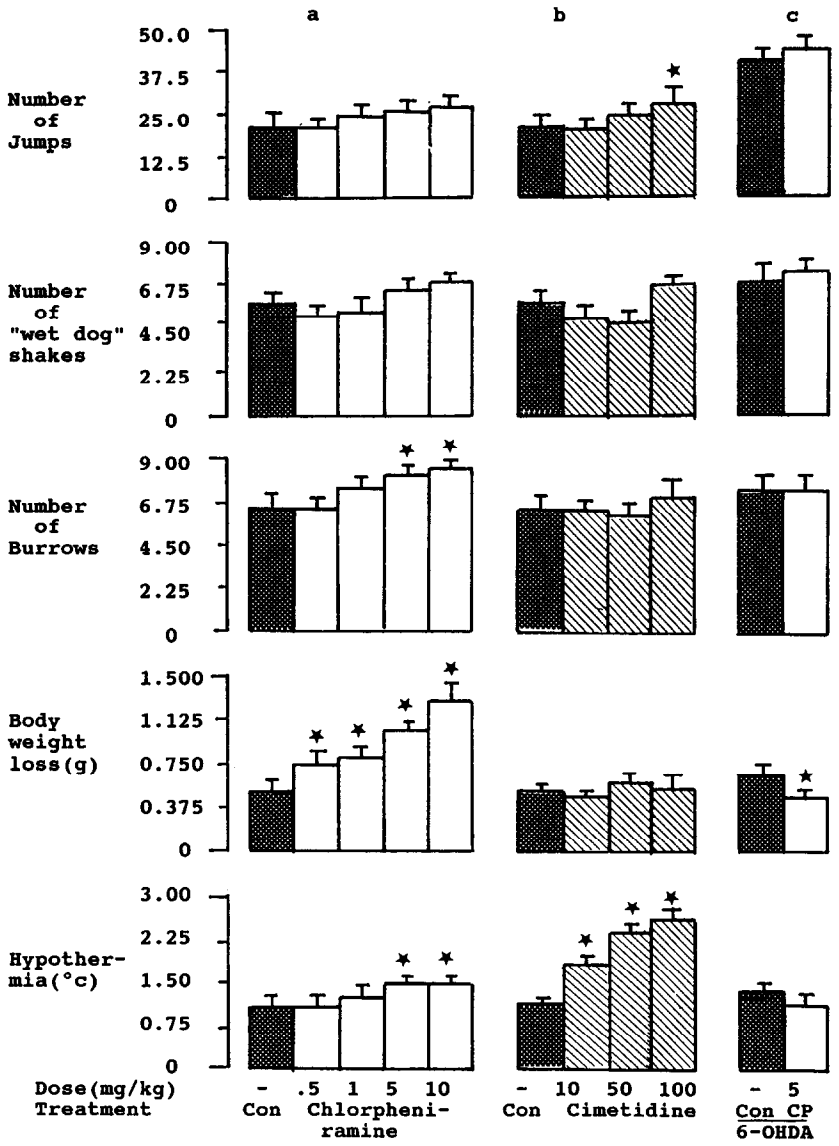

FIG. 1. Effect of chlorpheniramine and cimetidine on naloxone-induced withdrawal symptoms in morphine-dependent mice. Morphine dependent mice were injected IP with saline (control, con, dark columns), (a) chlorpheniramine (CP, 0.5–10 mg/kg, open columns), and (b) cimetidine (10–100 mg/kg, hatched columns). In c, chlorpheniramine (5 mg/kg, open columns) was also tested in mice pretreated with 6-OHDA (50 μg) injected intracerebrally. Saline or test drugs were always given 30 min before induction of withdrawal by naloxone (1 mg/kg, IP). Jumping, wet-dog shakes and burrows were counted within 15 min while body weight loss and hypothermia were measured 30 min following naloxone. Results are expressed as mean ± SEM (n = 8–10 mice/group). *Indicates significant difference from corresponding control ($p < 0.05$).

11.212, $p < 0.0001$, body weight loss, $F(4, 35) = 73.337$, $p < 0.0001$, and hypothermia, $F(4, 35) = 16.01$, $p < 0.0001$. In contrast, withdrawal jumping, $F(4, 35) = 2.592$, $p < 0.06$, and wet-dog shakes, $F(4, 35) = 2.384$, $p < 0.07$, were not significantly modified by chlorpheniramine (Fig. 1a).

Pretreatment of mice with 6-OHDA completely prevented the potentiation by chlorpheniramine of naloxone-induced withdrawal burrowing and hypothermia, while withdrawal jumping and wet-dog shakes were not significantly modified by pretreatment of mice with 6-OHDA. In addition, chlorpheniramine reversed the withdrawal body weight loss, $F(1, 18) = 179.499$, $p < 0.0001$, induced by naloxone in morphine-dependent mice (Fig. 1c).

Effect of Cimetidine

In morphine-dependent mice, cimetidine (10–100 mg/kg, IP) given 30 min before naloxone, produced dose-dependent potentiation of withdrawal hypothermia, $F(3, 28) = 66.662$, $p < 0.0001$, but did not influence wet-dog shakes, $F(3, 28) = 2.4$,

$p < 0.07$, burrowing, $F(3, 28) = 0.397$, $p < 0.8$, or body weight loss, $F(3, 28) = 0.889$, $p < 0.6$. Only the highest dose tested (100 mg/kg) significantly potentiated withdrawal jumping, $F(3, 28) = 8.328$, $p < 0.0006$ (Fig. 1b).

DISCUSSION

The central effects of histamine antagonists have been explained on the basis of their ability to antagonize the actions of endogenous brain histamine (8). In the present study, the histamine H_1-receptor antagonist chlorpheniramine produced dose-dependent exacerbation of naloxone-induced withdrawal burrowing, body weight loss, and hypothermia. However, withdrawal jumping and wet-dog shakes were not significantly modified by chlorpheniramine. This suggests that any further reduction in the activity of the transmitter by H_1-antagonists will worsen the withdrawal syndrome. Our results are consistent with earlier reports showing that the H_1-antagonist mepyramine injected before precipitation of withdrawal by naloxone produces no significant effect on jumping behaviour and significantly increase body weight loss in mice (43). These results were substantiated by a more recent report showing that L-histidine, α-fluoromethylhistidine, or metoprine injected to mice did not produce any significant effect on naloxone-precipitated withdrawal jumping and body shakes (33). In contrast to our results, it has been previously demonstrated that the H_1-antagonists tripelennamine, diphenhydramine, or cyclizine, when administered 30 min before naloxone, enhance the number of jumps and decrease the number of wet-dog shakes in morphine-dependent mice (29). This discrepancy can be explained by antiserotonergic properties of these agents or by an occupation of nonspecific receptors. This hypothesis is strengthened by the fact that the administration of ritanserine (35) or methysergide (10), specific serotonergic antagonists, produce a significant decrease of wet-dog shakes in rats and mice, respectively, while serotonergic agonists increase wet-dog shakes and decrease jumping in morphine-dependent rats (36).

There is some evidence showing that the catecholaminergic system could also play an important role in the origin of withdrawal jumping and wet-dog shakes, because the intracerebral administration of dopamine and noradrenaline or the peripheral administration of L-dopa significantly reduces withdrawal wet-dog shakes (42). Moreover, noradrenaline and dopamine depletion produces significant decreases in jumping behaviour (18). In addition, it has been reported that L-dopa can by itself induce a jumping response, even in animals not exposed to treatment with narcotic or narcotic antagonists (27).

Pretreatment with cimetidine show that the H_2-antagonist, produce dose-dependent exacerbation of withdrawal hypothermia, but did not influence wet-dog shakes, burrowing, or body weight loss, while at the highest dose tested it significantly exacerbated jumping. This is probably due to poor penetration of the drug into the CNS (16) or due to its locomotor effects, because it has been reported that peripheral administration of cimetidine induces an increase in opiate-induced hyperactivity (29). This hypothesis is further supported by other findings demonstrating that cimetidine administration into the third ventricle in fowls induces a strong behavioural stimulation, cortical desynchronization, tachypnea, escape responses, and stereotyped movement (32). Our results with cimetidine are consistent with a report showing that cimetidine given 30 min before naloxone significantly potentiated jumping, while the number of wet-dog shakes remains unchanged in morphine-dependent mice (29). Moreover, metiamide, a H_2-antagonist given intracerebrally before naloxone, produces a biphasic effect on withdrawal jumping; that is, low doses exacerbate and high doses attenuate withdrawal jumping in morphine-dependent mice (43). The attenuation of jumping may be related to the sedative effect of high doses of the drug.

Frederickson (12), classified withdrawal jumping, wet-dog shakes, and burrowing as central effects, whereas body weight loss and hypothermia might be peripheral effects. It appears that blockade of either type of histamine receptors would influence the expression of both peripherally and centrally mediated withdrawal symptoms-induced by naloxone in morphine-dependent mice. Our results suggest that blockade of both types of histamine receptors might potentiate the severity of withdrawal symptoms.

In the present study, pretreatment of mice with 6-OHDA, given in the neonatal period 1 month before the initiation of morphine dependence, produced marked enhancement of naloxone-precipitated withdrawal jumping without significant modification of other signs.

The effects of 6-OHDA on jumping may indicate that either the dependent mice were rendered more sensitive to naloxone and/or that the development of dependence was accelerated by 6-OHDA. A similar conclusion was advanced by earlier workers (13). This group observed that the enhanced jumping response to naloxone was evident in mice injected with 6-OHDA prior to but not after morphine pellet implantation. An alternative explanation for the enhanced jumping response induced by 6-OHDA can be offered in terms of denervation supersensitivity. Analogously, it has been pointed out that physical dependence might be a manifestation of a central denervation supersensitivity, and as a consequence, the withdrawal phenomenon would reflect a state of rebound hyperexcitability (24). Sympathectomy on the counter-adaptive responses occurring during the withdrawal state could explain the enhanced withdrawal jumping response that was observed.

The profile of the effects of chlorpheniramine with respect to withdrawal burrowing, body weight loss, and hypothermia changed dramatically in animals receiving neonatal 6-OHDA. Chlorpheniramine in these experiments produced attenuation of body weight loss instead of exacerbation of naloxone-induced withdrawal body weight loss, and its exacerbating effect on burrowing and hypothermia was completely abolished. Intracerebral injection of 6-OHDA has been reported to destroy noradrenergic and dopaminergic neuronal systems in adult animals (4,25), while in newborn animals the neurotoxin has been reported to selectively destroy noradrenergic nerve terminals (1). In addition, newborn mice and rats are more susceptible to the destructive effects of 6-OHDA than mature animals, whereas the ganglia are fairly resistant to the effects of 6-OHDA (2,6). It is possible that chlorpheniramine may modify naloxone-precipitated withdrawal symptoms by acting on histamine H_1-receptors that modulate central adrenergic transmission.

Although there are few studies to clarify the role of brain histamine in the establishment and expression of morphine dependence and withdrawal, conflicting results have been reported in the literature. It has been reported that decreases in brain histamine levels by the histidine decarboxylase inhibitor, thiazol-4-ylmethoxyamine (20), or an increase of brain histamine by a histamine precursor, L-histidine (21), inhibited the development of physical dependence when injected during the induction phase of physical dependence in mice. However, no significant changes in the development of physical dependence on morphine were observed when these agents were

injected to mice during the withdrawal phase (33). Moreover, the H_1-antagonist mepyramine, when injected to mice during the induction phase of physical dependence, was found to inhibit the development of physical dependence (22). However, using the same experimental condition and the same doses, mepyramine did not produce significant changes in the development of physical dependence when injected during the withdrawal phase of physical dependence (43). An explanation of these conflicting results was given by Collier et al. (7), who have pointed out that the development of tolerance and physical dependence can be divided into two phases. The induction phase occurs during the period of administration of morphine, whereas the withdrawal phase begins with the termination of morphine administration or injection of an opiate antagonist. The later phase is associated with the appearance of the withdrawal symptoms. These authors also suggested that a given neurotransmitter may play quite different roles in these two phases.

Interestingly, these observations suggest that the integrity of the histamine neuronal stores is not a necessary prerequisite for the action of histamine agonists and antagonists, and now it is evident that histamine receptors that modulate the expression of morphine withdrawal are dependent in their functional responsiveness on intact noradrenergic pathways.

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REFERENCES

1. Angeletti, P. U. Chemical sympathectomy in newborn animals. Neuropharmacology 10:55–59; 1971.
2. Angeletti, P. U.; Levimontalcini, R. Specific cytotoxic effect of 6-hydroxydopamine on sympathetic neuroblasts. Arch. Ital. Biol. 108:213–221; 1970.
3. Arrigoreina, R.; Chiechio, S. Histaminergic mechanisms in clonidine induced analgesia in rat tail-flick test. Inflamm. Res. 44: 21–23; 1995.
4. Barone, P.; Morelli, M.; Popoli, M.; Cicarelli, G.; Campanella, G.; Di Chiara, G. Behavioural sensitization in 6-hydroxydopamine lesioned rats involves the dopamine signal transduction: Changes in DARPP-32 phosphorylation. Neuroscience 61:867–873; 1994.
5. Berthold, H.; Fozard, J. R.; Engel, G. 5-HT_1 receptor agonists attenuate the naloxone-induced jumping behaviour in morphine-dependent mice. Eur. J. Pharmacol. 162:19–27; 1989.
6. Breese, G. R.; Traylor, T. D. Developmental characteristics of brain catecholamines and tyrosine hydroxylase in the rat: Effects of hydroxydopamine. Br. J. Pharmacol. 44:210–222; 1972.
7. Collier, H. O. J.; Francis, D. L.; Schneider, C. Modification of morphine withdrawal by drugs interacting with neuronal mechanisms. Some contradictions and their interpretations. Nature 237:220–223; 1972.
8. Crossland, J. Chemical transmission in the central nervous system. Pharm. Pharmacol. 12:1–36; 1960.
9. El-kadi, A. O. S.; Sharif, S. I. The influence of various experimental conditions on the expression of naloxone-induced withdrawal symptoms in mice. Gen. Pharmacol. 25:1505–1510; 1994.
10. El-kadi, A. O. S.; Sharif, S. I. The role of 5-HT in the expression of morphine withdrawal in mice. Life Sci. 57:511–516; 1995.
11. Feldberg, W.; Paton, W. D. M. Release of histamine from skin and muscle in the cat by opium alkaloids and other histamine liberators. J. Physiol. 114:490–509; 1951.
12. Frederickson, R. C. A. Morphine withdrawal response and central cholinergic activity. Nature 257:131–132; 1975.
13. Friedler, G.; Bhargava, H. N.; Quock, R.; Way, E. L. The effect of 6-hydroxydopamine on morphine tolerance and physical dependence. J. Pharmacol. Exp. Ther. 183:49–55; 1972.
14. Glick, S. D.; Crane, L. A. Opiate-like and abstinence-like effect of intracerebral histamine administration in rats. Nature 237:547–549; 1978.
15. Gogas, K. R.; Hough, L. B.; Eberle, N. B.; Lyon, R. A.; Glick, S. D.; Ward, S. J.; Young, R. C.; Parsons, M. E. A role for histamine and H_2-receptors in opioid antinociception. J. Pharmacol. Exp. Ther. 250:476–484; 1989.
16. Gogas, K. R.; Hough, L. B.; Glick, S. D.; Su, K. Opposing action of cimetidine on naloxone-sensitive and naloxone-insensitive forms of foot shock-induced analgesia. Brain Res. 370:370–374; 1986.
17. Harris, G. C.; Aston-Jones, G. Involvement of D_2 dopamine receptors in the nucleus accumbens in the opiate withdrawal syndrome. Nature 371:155–157; 1994.
18. Herz, A.; Blasig, J.; Papeschi, R. Role of catecholaminergic mechanisms in the expression of the morphine abstinence syndrome in rats. Psychopharmacology (Berlin) 39:121–143; 1974.
19. Hough, L. B.; Nalwalk, J. W.; Battles, A. H. Zolanitidine-induced attenuation of morphine antinociception in rhesus monkeys. Brain Res. 526:153–155; 1990.
20. Hui, K. S. The effect of thiazol-4-ylmethoxyamine, a histamine decarboxylase inhibitor, on the development of morphine tolerance and physical dependence in mice. Eperientia 32:1313–1315; 1976.
21. Hui, K. S.; Roberts, M. B. L-Histidine: Effect on the development of morphine dependence in mice. IRCS 2:1688; 1974.
22. Hui, K. S.; Roberts, M. B. The effect of mepyramine on the development of morphine tolerance and physical dependence in mice. Life Sci. 17:891–900; 1975.
23. Iwamoto, E. I.; Ho, I. K.; Way, E. L. Elevation of brain dopamine during naloxone-precipitated withdrawal in morphine-dependent mice and rats. J. Pharmacol. Exp. Ther. 187:558–563; 1973.
24. Jaffe, J. H.; Sharpless, S. K. Pharmacological denervation supersensitivity in the central nervous system: A theory of physical dependence. Proc. Assoc. Res. Nerv. Ment. Dis. 46:226–246; 1968.
25. Johnsson, G.; Malmfors, T.; Sachs, C. 6-Hydroxydopamine as a denervation tool in catecholamine research. Amsterdam: North Holland Publishing Co.; New York: Oxford University Press; 1975.
26. Karachentsev, A. N.; Baranov, A. G. The role of peripheral cholinergic and adrenergic receptor systems in the action of histamine on the isolated coronary arteries. Fiziologicheskii Zhurnal. 35: 92–95; 1989.
27. Lal, H.; Colpaert, F. C.; Laduron, P. Narcotic withdrawal like mouse jumping produced by amphetamine and *l*-dopa. Eur. J. Pharmacol. 30:113–116; 1975.
28. Lee, J. R.; Fennessy, M. R. Effects of morphine on brain histamine, antinociception and activity in mice. Clin. Exp. Physiol. Pharmacol. 3:179–189; 1976.
29. Leza, J. C.; Lizasoain, I; Lorenzo, P. Effects of antihistaminics on naloxone-induced withdrawal in morphine-dependent mice. Psychopharmacology (Berlin) 102:106–111; 1990.
30. Mazurkiewicz-Kwilecki, I.; Henwood, R. W. Alterations in brain endogenous histamine levels in rats after chronic morphine treatment and morphine withdrawal. Agent Actions 6:402–408; 1976.
31. Nishibori, M.; Oishi, R.; Loh, Y.; Saeki, K. Morphine-induced changes in histamine dynamics in mouse brain. J. Neurochem. 45:719–724; 1985.
32. Nistico, G.; Rotiroti, D.; De Sarro, A.; Naccari, F.; Stephenson, J. D. Central effects of histamine and H_1 and H_2 receptor agonists and antagonists after intraventricular infusion in fowls. Res. Commun. Chem. Pathol. Pharmacol. 27:431–450; 1980.
33. Oishi, R.; Nishibori, M.; Itoh, Y.; Saeki, K.; Fukuda, T.; Araki,

Y. Histamine turnover in the brain of morphine-dependent mice. Naunyn Schmiedebergs Arch. Pharmacol. 337:58–63; 1988.
34. Palit, G.; Gupta, M. B.; Bhargava, R.; Dixit, K. S.; Bhargava, K. P. Central histaminoceptor-adrenoceptor interrelations in the release of adrenocorticotrophic hormone. Indian J. Physiol. Pharmacol. 23:372–376; 1979
35. Pranzatelli, M. R. Benzodiazepine-induced shaking behaviour in the rat: Structure–activity and relation to serotonin and benzodiazepine receptors. Exp. Neurol. 104:241–250; 1989.
36. Romandini, S.; Cervo, L.; Samanin, R. Evidence that drugs increasing 5-hydroxytryptamine transmission block jumping but not wet dog shakes in morphine-dependent rats: A comparison with clonidine. J. Pharm. Pharmacol. 36:68–70; 1984.
37. Schanberg, S. M.; Schildkraut, G. R.; Breeze, G. R.; Kopin, I. J. Metabolism of normetanephrine-H_3 in rat brain-identification of conjugated 3-methoxy-4-hydrphenylglycol as the major metabolite. Biochem. Pharmacol. 17:247–254; 1968.
38. Subbiah, P. S.; Ho, I. K. Influence of morphine dependence on GABA-stimulated benzodiazepine binding to mouse brain synaptic membranes. Eur. J. Pharmacol. 79:335–3336; 1982.
39. Suzuki, S.; Takamori, K.; Takahashi, Y.; Narita, M.; Misawa, M.; Onodera, K. The differential effects of histamine receptor antagonists on morphine- and U-50, 488H-induced antinociception in the mouse. Life Sci. 54:203–211; 1994.
40. Tanaka, K.; Lin, Y. Histamine liberation into the cerebrospinal fluid by the drugs applied intraventricularly. Jpn. J. Pharmacol. 19:510–514; 1969.
41. Todorov, S.; Zamfirova, R. Interaction of histamine with adrenergic smooth muscle neurotransmission. III. Significance of magnesium ions for the effects of histamine on contractions induced by endogenous noradrenaline. Acta Physiol. Pharmacol. Bulgarica 8:51–56; 1982.
42. Turski, W.; Czuczwar, S. J.; Turski, L.; Kleinrok, Z. The involvement of catecholaminergic mechanisms in the appearance of wet dog shakes produced by carbachol chloride in rats. Arch. Int. Pharmacodyn. Ther. 255:204–211; 1982.
43. Wong, C. L.; Roberts, M. B. The possible role of brain histamine and H_1 and H_2 receptors in the development of morphine tolerance and physical dependence in mice. Agent Actions 5:476–483; 1975.