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Potentiating Effect of Morphine Upon *d*-Methamphetamine-Induced Hyperthermia in Mice. Effects of Naloxone and Haloperidol

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FUNAHASHI, M., H. KOHDA, O. HORI, H. HAYASHIDA AND H. KIMURA. *Potentiating effect of morphine upon d-methamphetamine-induced hyperthermia in mice. Effects of naloxone and haloperidol.* PHARMACOL BIOCHEM BEHAV **36**(2) 345–350, 1990.—We have examined changes in rectal temperature of mice after subcutaneous administrations of *d*-methamphetamine alone or methamphetamine plus morphine. Methamphetamine 5 mg/kg produced slight hyperthermia, while simultaneous administration of morphine (25–100 mg/kg), which alone produces hypothermia, potentiated markedly the increase in body temperature by methamphetamine. Methamphetamine showed a hyperthermic effect in a dose-dependent manner in the presence of morphine. The hyperthermia due to methamphetamine plus morphine was avoided by pretreatment with 10 mg/kg naloxone. When animals were pretreated with 2.5 mg/kg haloperidol, hyperthermia due to methamphetamine alone was completely abolished, while that due to methamphetamine plus morphine was still observed. These results showed that dopamine may be implicated in methamphetamine hyperthermia and a haloperidol-nonsensitive mechanism may be involved in the methamphetamine-morphine hyperthermia.

Methamphetamine Morphine Hyperthermia Naloxone Haloperidol

MANY studies have been presented concerning the role of neurotransmitters in the thermoregulation of animals since Feldberg and Myers (11) reported involvement of epinephrine, norepinephrine and serotonin in the regulation of body temperature. Now, regulation of body temperature is known to be very complex and to be mediated by numerous agents, such as neurotransmitters, neuromodulators, prostaglandins and interleukin (1, 5, 7–9, 28, 30, 33). During experiments on the interaction of *d*-methamphetamine and morphine, we have found that simultaneous systemic administration of methamphetamine and morphine produces marked hyperthermia and increased toxicity in mice (13). Both morphine and amphetamines are known to have pronounced and complex effects on body temperature in animals. Both hyperthermia and hypothermia are produced by such drugs, depending on the individual species, the dose, the route of administration and the environmental temperature (1, 7–9, 16). However, the hyperthermic effect of amphetamines and the hypothermic effect of morphine, when administered systemically at environmental temperature close to room temperature, are prominent in rodents and man (6, 22, 23, 29).

Recently, a number of studies on morphine-amphetamine interactions concerning locomotion, food intake and analgesia have been reported (2, 12, 15, 19, 25, 32, 41). However, such studies concerning the thermoregulation of animals are few and a distinct result has not been obtained. Richards (35) observed that amphetamine antagonizes morphine-induced hypothermia in man for clinical purposes, while Holtzman (19) and Quock (34) reported no effect of naloxone on hypothermia and hyperthermia produced by amphetamine in rats and in rabbits. Evidences have been accumulating that amphetamine is not a simple dopaminergic agonist (20,34).

In this report, we have examined the effect of the dopamine antagonist haloperidol, since much attention has been focused on dopamine-mediated amphetamine effects (15, 38–40, 43), and the morphine antagonist naloxone on hyperthermia induced by methamphetamine alone and by methamphetamine plus morphine

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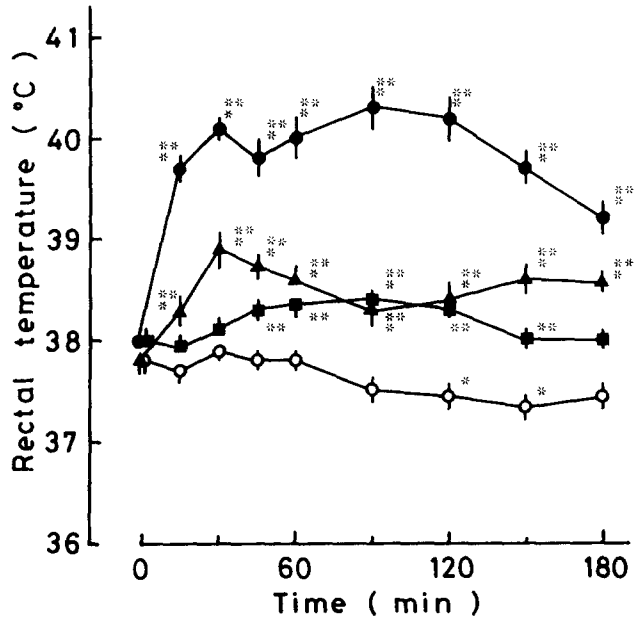

FIG. 1. Changes in rectal temperature after subcutaneous injections of methamphetamine in mice. Each point is the mean ± SE. Doses of methamphetamine injected were 1 mg/kg (■) (n = 6), 5 mg/kg (▲) (n = 10) and 40 mg/kg (●) (n = 11). Control mice received saline (○) (n = 10). Values of * and ** ($p<0.05$) were significantly different from those before injection and of control mice, respectively.

to determine how morphine and dopamine participate in methamphetamine hyperthermia. We found that haloperidol abolished the hyperthermia induced by methamphetamine alone but not by methamphetamine plus morphine, while naloxone blocked the hyperthermia produced by methamphetamine-morphine but not by methamphetamine alone. Administration of morphine to mice pretreated with naloxone or haloperidol showed profound hypothermia. A role of morphine in the potentiation of methamphetamine-induced hyperthermia was discussed in terms of a two-receptor theory proposed by Geller *et al.* (14).

METHOD

Male mice of *ddY* strain (28–32 g) (Japan SLC Inc.) were housed in groups of 5 animals per cage in a temperature-controlled room (23 ± 1°C) maintained on a 12-hr light-dark cycle. All animals were well habituated to handling for a week and to measuring rectal temperature for the day before the experiments. All drugs (as the respective salts) were dissolved in 0.9% NaCl and were administered subcutaneously in a volume of 0.05 ml/10 g body weight, except for haloperidol which was used from preprepared injection ampules. Control mice were given the same volume of saline. Methamphetamine and morphine were injected simultaneously when they were used in combination. Naloxone and haloperidol were given subcutaneously 15 min and 30 min before experiments, respectively. Using a digital thermistor (D925, Takara thermistor, Yokohama), rectal temperature was measured immediately before and at 15- or 30-min intervals after drug injection. The probe was inserted into the rectum to a constant

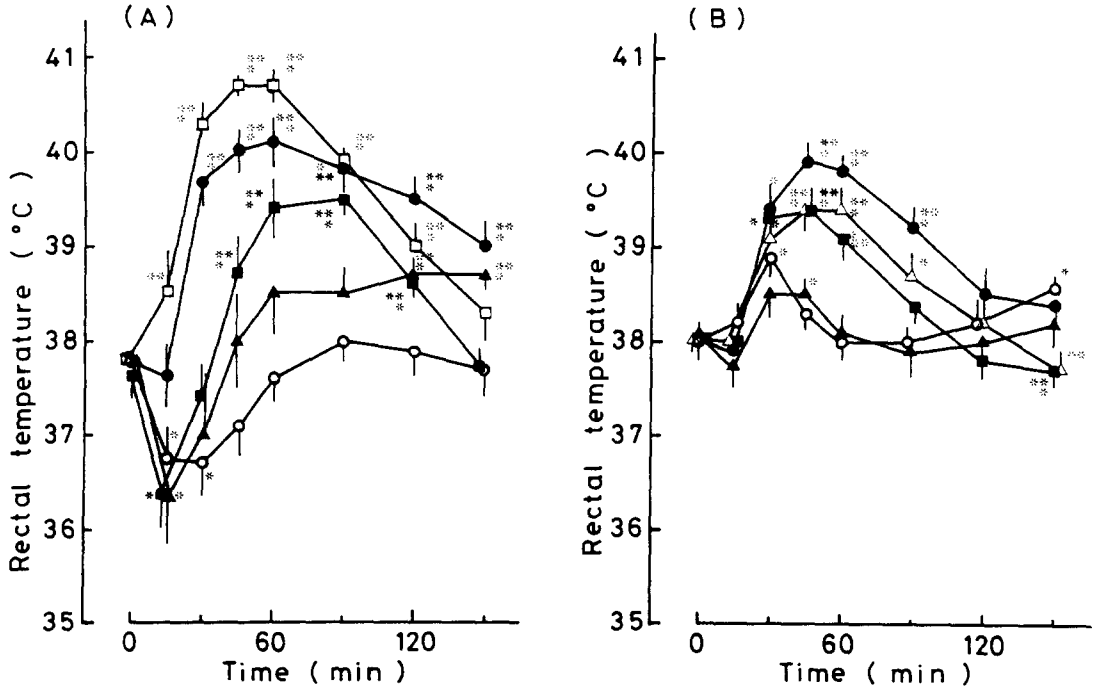

FIG. 2. Dose-dependency of methamphetamine (A) and morphine (B) in changes in rectal temperature with fixed amounts of morphine (100 mg/kg) (A) and methamphetamine (5 mg/kg) (B), respectively. Each point represents the mean ± SE. (A) Morphine (100 mg/kg) and different amounts of methamphetamine were subcutaneously injected simultaneously at time zero. Methamphetamine injections were (▲) 1 mg/kg (n = 6), (■) 2.5 mg/kg (n = 6), (●) 5 mg/kg (n = 8) and (□) 7.5 mg/kg (n = 8). Control mice were given morphine alone (○) (n = 8). (B) Methamphetamine (5 mg/kg) and various doses of morphine [(▲) 10 mg/kg (n = 14), (■) 25 mg/kg (n = 16), (△) 50 mg/kg (n = 15) and (●) 100 mg/kg (n = 12)] were administered subcutaneously at time zero. Control mice received methamphetamine alone (5 mg/kg) (○) (n = 8). Values of * and ** ($p<0.05$) were significantly different from those before injection and of control mice, respectively.

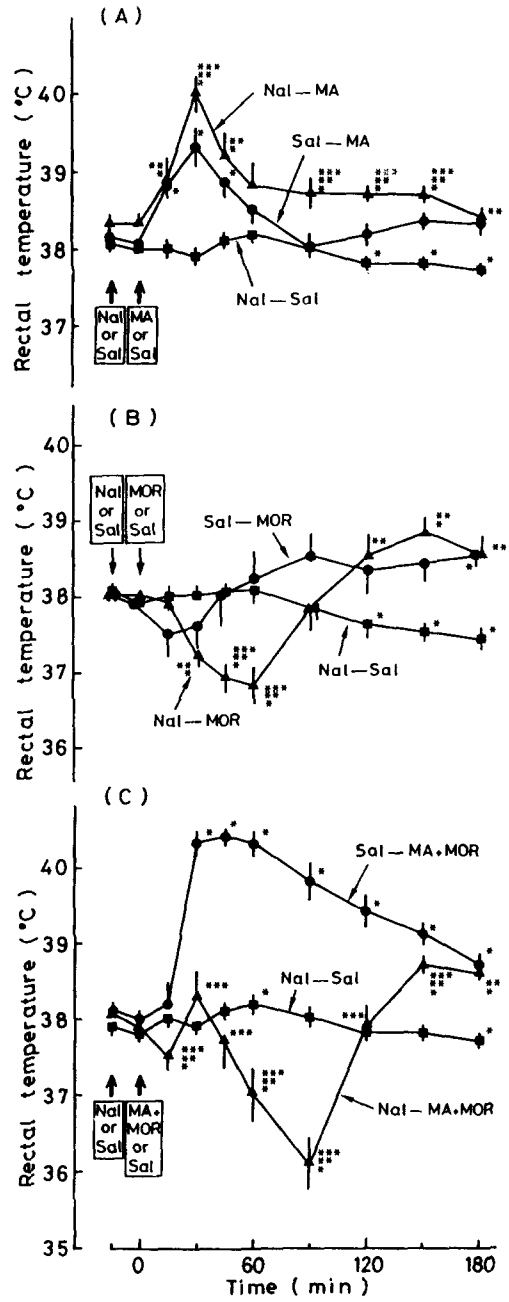

FIG. 3. Effect of naloxone on methamphetamine- and methamphetamine-morphine-induced hyperthermia. Naloxone or saline was administered 15 min before injection of methamphetamine, morphine or methamphetamine plus morphine. In (A), mice pretreated with saline were given methamphetamine (●) (n = 10) (Sal-MA), and those pretreated with naloxone received saline (control group) (■) (n = 12) (Nal-Sal) or methamphetamine (▲) (n = 10) (Nal-MA) at time zero. In (B), mice pretreated with saline were given morphine (●) (n = 11) (Sal-MOR), and those pretreated with naloxone were given saline (n = 10) (Nal-Sal) (■) or morphine (n = 16) (Nal-MOR) (▲). In (C), mice pretreated with saline were given methamphetamine plus morphine (●) (n = 9) (Sal-MA+MOR), and those pretreated with naloxone also received saline (control mice) (■) (n = 12) (Nal-Sal) or methamphetamine plus morphine (▲) (n = 10) (Nal-MA+MOR). The doses used were: 10 mg/kg naloxone, 5 mg/kg methamphetamine and 100 mg/kg morphine. Each point represents the mean ± SE. The value of * ($p<0.05$) was significantly different from that before injection of naloxone or saline in each group. Values of ** and *** ($p<0.05$) were significantly different from those of mice given naloxone alone (A, B and C) and of mice treated with methamphetamine (A), morphine (B) and methamphetamine plus morphine (C), respectively. Abbreviations used in the figure are as follows: Sal, physiological saline; Nal, naloxone; MA, methamphetamine; MOR, morphine.

depth of 2.5 cm and was removed after each reading (13). Behavior of the mice was also observed, as described previously (27). Experiments were carried out between 1200 and 1700 hour. The mice were unrestrained, and drug-naive mice were used only once. Statistical analysis was performed with the student *t*-test.

Drugs used were as follows: *d*-methamphetamine hydrochloride, morphine hydrochloride and haloperidol (Serenase Injection) were purchased from Dainippon Pharm. Osaka and naloxone hydrochloride from Sigma Chemical, St. Louis, MO.

RESULTS

Figure 1 shows changes in rectal temperature after injections of methamphetamine. The body temperature of mice receiving saline showed no change or decreased slightly but significantly, compared to that before injection. Body temperature of mice given 1 mg/kg methamphetamine rose gradually by 0.4°C for 90 min after injection. Mice treated with 5 mg/kg methamphetamine developed a rapid increase in body temperature (1°C at 30 min), and mice that received 40 mg/kg methamphetamine showed marked hyperthermia (2.1°C at 30 min) that lasted 3 hours (Fig. 1). At doses of 1 and 5 mg/kg, a marked increase in locomotor activity was observed, whereas administration of 40 mg/kg produced stereotypy, such as biting and sniffing, and marked salivation (27).

Because 5 mg/kg of methamphetamine and 300 mg/kg of morphine produced marked hyperthermia in mice in the previous study (13), we examined the dose-dependency of each drug in the presence of a fixed amount of other (Fig. 2). Morphine, at a dose of 10 mg/kg, did not potentiate hyperthermia due to 5 mg/kg of methamphetamine (Fig. 2B). Although larger doses of morphine enhanced methamphetamine-induced hyperthermia, the differences in the extent of potentiation by 25, 50 and 100 mg/kg of morphine were small: the difference was significant only between 25 and 100 mg/kg morphine 60–150 min after injection. Although the dose-dependency of morphine to an increase in body temperature is not clear, that of methamphetamine is clear (Fig. 2A). When morphine (100 mg/kg) alone was injected, rectal temperature decreased during 30 min after injection and then gradually returned to baseline level or increased slightly. However, when methamphetamine (1 and 2.5 mg/kg) and morphine (100 mg/kg) were used concomitantly, the lowest point of body temperature shifted to 15 min after injection, after which the body temperature increased rapidly. At 5 and 7.5 mg/kg of methamphetamine, the hyperthermic effect of methamphetamine prevented the hypothermic effect of morphine. The magnitude of hyperthermia is greater than that of respective doses of methamphetamine alone (Fig. 1). The hyperthermic effect of methamphetamine in the presence of morphine was clearly dose-dependent. A dose of 5 mg/kg of methamphetamine and 100 mg/kg of morphine were chosen for the following experiments in which we assessed the effects of antagonists on methamphetamine-morphine hyperthermia.

Naloxone (10 mg/kg) alone caused no significant change in rectal temperature compared to saline alone (Figs. 1 and 3). As shown in Fig. 3C, pretreatment with naloxone (10 mg/kg) reversed the hyperthermic response to methamphetamine plus morphine to cause rather marked hypothermia. Animals pretreated with saline or naloxone and then given methamphetamine plus morphine

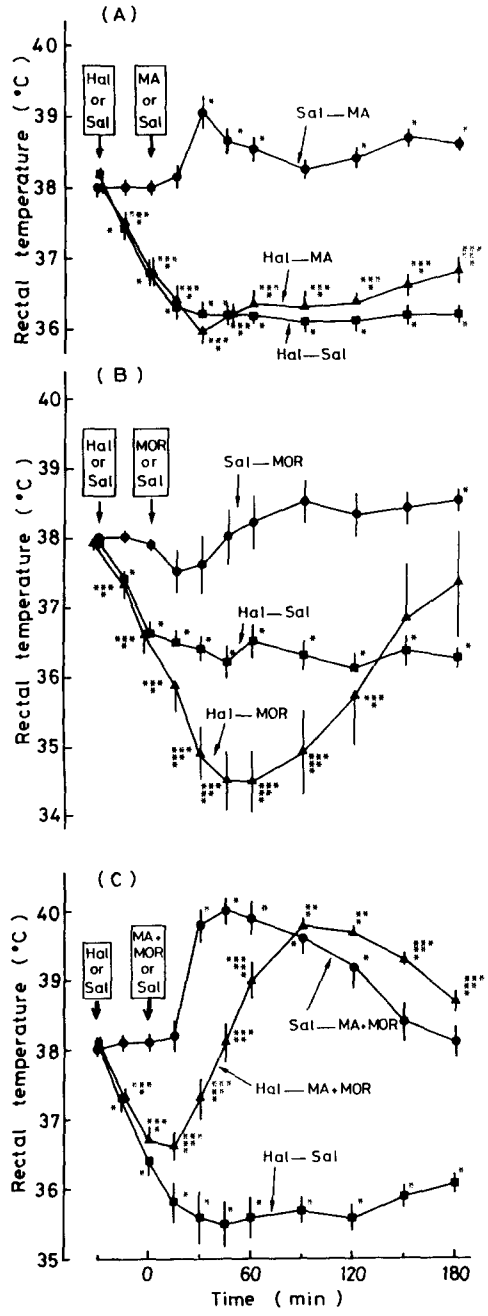

FIG. 4. Effect of haloperidol on methamphetamine- and methamphetamine-morphine-induced hyperthermia. Each point is the mean ± SE. All experimental conditions were the same as described in the legend for Fig. 3 except that haloperidol (2.5 mg/kg) instead of naloxone was injected 30 minutes before administration of methamphetamine (A), morphine (B) or methamphetamine plus morphine (C). (A): (■) haloperidol-saline (n = 12) (Hal-Sal), (●) saline-methamphetamine (n = 9) (Sal-MA) and (▲) haloperidol-methamphetamine (n = 10) (Hal-MA). (B): (■) haloperidol-saline (n = 12) (Hal-Sal), (●) saline-morphine (n = 11) (Sal-MOR) and (▲) haloperidol-morphine (n = 12) (Hal-MOR). (C): (■) haloperidol-saline (n = 12) (Hal-Sal), (●) saline-methamphetamine plus morphine (n = 9) (Sal-MA+MOR) and (▲) haloperidol-methamphetamine plus morphine (n = 11) (Hal-MA+MOR). The value of * ($p<0.05$) was significantly different from that before injection of haloperidol or saline in each group. Values of ** and *** ($p<0.05$) were significantly different from those of mice given naloxone alone (A, B and C) and of mice treated with methamphetamine (A), morphine (B) or methamphetamine plus morphine (C), respectively. Abbreviations used in the figure are the same as in Fig. 3 except for Hal which indicates haloperidol.

exhibited hypermotility with or without the Straub tail phenomenon, respectively, during the first 90 min. After this, saline-pretreated mice began to calm down, whereas mice pretreated with naloxone still showed hypermotility with the Straub tail phenomenon, suggesting that an effect of naloxone disappeared at 90 min. Mice pretreated with naloxone and then given methamphetamine showed greater hyperthermia than those receiving methamphetamine alone (Fig. 3A). Injection of morphine to mice pretreated with naloxone produced hypothermia than that of morphine alone (Fig. 3B), that is, pretreatment with naloxone did not antagonize hypothermia due to morphine, although hypermotility and the Straub tail phenomenon produced by morphine were blocked by naloxone. The decreases in body temperature of mice pretreated with naloxone followed by morphine alone or morphine plus methamphetamine in the first 60–90 min (Fig. 3B and C) are similar. After that a late hyperthermic effect of morphine and/or a hyperthermic effect of methamphetamine appeared to be prominent in each case.

Since dopaminergic mediation of the effects of amphetamines on thermoregulation, locomotion and food intake has been reported (10, 15, 38–40), an effect of the dopamine antagonist haloperidol was examined. When methamphetamine (5 mg/kg) was administered to mice pretreated with haloperidol (2.5 mg/kg), the change in rectal temperature was the same as that of mice received haloperidol alone, i.e., marked hypothermia (Fig. 4A). Haloperidol also blocked the hyperthermic response to 40 mg/kg of methamphetamine (not shown). However, as shown in Fig. 4C, haloperidol did not antagonize methamphetamine-morphine hyperthermia, suggesting that methamphetamine-morphine hyperthermia is haloperidol-independent. Coadministration of methamphetamine and morphine 30 min after haloperidol prevented further lowering of rectal temperature by haloperidol; the temperature began to rise 15 min after injection and reached maximum 75 min later (Fig. 4C). Mice exhibited a characteristic posture; that is, they rested against the wall with the Straub tail phenomenon. Thus, the hypermotility due to methamphetamine plus morphine was blocked by haloperidol whereas the increase in body temperature was not abolished. Administration of morphine to mice pretreated with haloperidol showed profound hypothermia which is more than that produced by haloperidol alone, possibly due to a synergistic effect of morphine and haloperidol, followed by an increase in body temperature (Fig. 4B).

DISCUSSION

We have demonstrated here that the hyperthermic effect of methamphetamine in mice was markedly potentiated by administration of morphine, which by itself produces a small decrease in the body temperature. Methamphetamine increased the body temperature in a dose-dependent manner in methamphetamine-morphine hyperthermia, while the dose-dependency of morphine was not clear (Fig. 2). There may be a threshold for the action of morphine or a possible permissible role of morphine in methamphetamine-morphine hyperthermia.

Effects of the morphine antagonist, naloxone, and the dopamine antagonist, haloperidol, on methamphetamine-morphine hyperthermia were examined. Naloxone, which shows a slight decrease in body temperature similar to that of saline control when administered singly, abolished the hyperthermia induced by

methamphetamine and morphine to produce rather marked hypothermia (Fig. 3C). On the other hand, naloxone potentiated morphine hypothermia (Fig. 3B). Haloperidol, which produced marked hypothermia, completely blocked hyperthermia produced by methamphetamine but not by methamphetamine plus morphine (Fig. 4A and C). When morphine was administered to mice pretreated with haloperidol, marked hypothermia which was more than that produced by haloperidol alone was observed, possibly due to a synergistic effect of morphine and haloperidol (Fig. 4B).

Since we used a considerably high dose of morphine (100 mg/kg), it might be possible to explain methamphetamine-morphine hyperthermia as a result from a poikilothermic state produced by a large dose of morphine (1). However, 25 mg/kg morphine potentiated hyperthermia induced by methamphetamine (Fig. 2B). Administration of methamphetamine plus morphine produced a biphasic response (hypothermia followed by hyperthermia) (Fig. 2A), which was suggested to be not poikilothermic by Rosow *et al.* (36,37). Kapas *et al.* (24) also reported a similar poikilothermic effect of subcutaneous injection of 0.1 mg/kg cholecystokinin octapeptide in rats, suggesting that a poikilothermic state is not specific to a large dose of morphine. Therefore, our results are unlikely to be the result of poikilothermia. Then, we may explain according to the two-receptor theory proposed by Geller *et al.* (14) in that the presence of hyperthermic (+)- and hypothermic (−)-receptors of morphine which are blockable by naloxone is suggested. However, as shown in Fig. 3B, naloxone potentiated morphine hypothermia, suggesting that naloxone blocked only a hyperthermic (+)-receptor of morphine. Therefore, hypothermia due to an effect of a hypothermic (−)-receptor of morphine appeared in the first 60 min followed by late hyperthermia. A similar situation may be happened in mice treated with naloxone and then morphine-methamphetamine (Fig. 3C). Therefore, it seems likely that morphine stimulates a hyperthermic (+)-receptor of morphine which in turn activates a methamphetamine-related hyperthermic mechanism. Although methamphetamine hyperthermia is sensitive to haloperidol (Fig. 4A), it appears that an interaction of a methamphetamine-related hyperthermic mechanism with a hyperthermic (+)-receptor of morphine becomes haloperidol-nonsensitive (Fig. 4C) by unknown reason at present. Yamawaki *et al.* (42) also suggested two opposing dopamine-related thermoregulatory mechanisms with different sensitivities to haloperidol: haloperidol-sensitive hypothermia and haloperidol-nonsensitive hyperthermia mechanisms.

The possibility of the interaction of morphine and possible endogeneous amphetamine mediator, β-phenylethylamine, may also be considered (3, 18, 21). The presence of β-phenylethylamine in animals has been known as one of a number of trace biogenic amines from the beginning of the 1960's (31) and much attention has recently been focused on this amine because its structure is similar to that of amphetamine and it produces amphetamine-like behavioral effects in rodents (4,10). Therefore, we find it necessary to consider the effect of morphine on an amphetamine or β-phenylethylamine receptor (3, 18, 21).

Finally, the methamphetamine-morphine hyperthermia described here may be a useful model to understand the lethal diseases associated with hyperthermia in human, such as malignant hyperthermia (26), neuroleptic malignant syndrome (17) and acute methamphetamine poisoning (22,23).

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REFERENCES

1. Adler, M. W.; Geller, E. B.; Rosow, C. E.; Cochin, J. The opioid system and temperature regulation. Annu. Rev. Pharmacol. Toxicol. 28:429–449; 1988.
2. Agmo, A.; de Avila, N. Interactions between enkephalin and dopamine in the control of locomotor activity in the rat: A new hypothesis. Pharmacol. Biochem. Behav. 22:599–603; 1985.
3. Blosser, J. C.; Barrantes, M.; Parker, R. B. Correlation between anorectic potency and affinity for hypothalamic (+)-amphetamine binding sites of phenylethylamines. Eur. J. Pharmacol. 134:97–103; 1987.
4. Borison, R. L.; Mosnaim, A. D.; Sabelli, H. C. Brain 2-phenylethylamine as a major mediator for the central actions of amphetamine and methylphenidate. Life Sci. 17:1331–1344; 1975.
5. Bruinvels, J. Norepinephrine. In: Lomax, P.; Schonbaum, E., eds. Body temperature-regulation, drug effects, and therapeutic implications. New York: Marcel Decker; 1979:257–288.
6. Burks, T. F.; Rosenfeld, G. C. Neurotransmitter mediation of morphine hypothermia in rats. Life Sci. 24:1067–1074; 1979.
7. Clark, W. G. Influence of opioids on central thermoregulatory mechanisms. Pharmacol. Biochem. Behav. 10:609–613; 1979.
8. Clark, W. G.; Lipton, J. M. Changes in body temperature after administration of acetylcholine, histamine, morphine, prostaglandins and related agents: II. Neurosci. Biobehav. Rev. 9:479–552; 1985.
9. Clark, W. G.; Lipton, J. M. Changes in body temperature after administration of adrenergic and serotonergic agents and related drugs including antidepressants: II. Neurosci. Biobehav. Rev. 10:153–220; 1986.
10. Cole, S. Brain mechanisms of amphetamine-induced anorexia, locomotion, and stereotypy: A review. Neurosci. Biobehav. Rev. 2: 89–100; 1978.
11. Feldberg, W.; Myers, R. D. A new concept of temperature regulation by amines in the hypothalamus. Nature 200:1325; 1963.
12. Fog, R. Behavioral effects in rats of morphine and amphetamine and of a combination of the two drugs. Psychopharmacologia 16:305–312; 1970.
13. Funahashi, M.; Kohda, H.; Shikata, I.; Kimura, H. Potentiation of lethality and increase in body temperature by combined use of *d*-methamphetamine and morphine in mice. Forensic Sci. Int. 37: 19–26; 1988.
14. Geller, E. B.; Hawk, C.; Keinath, S. H.; Tallarida, R. J.; Adler, M. W. Subclasses opioids based on body temperature change in rats: Acute subcutaneous administration. J. Pharmacol. Exp. Ther. 225: 391–398; 1983.
15. Gilbert, D.; Cooper, S. J. Analysis of dopamine D1 and D2 receptor involvement in *d*- and *l*-amphetamine-induced anorexia in rats. Brain Res. Bull. 15:385–389; 1985.
16. Glick, S. D. Hyperthermic and hypothermic effects of morphine in mice: Interactions with apomorphine and pilocarpine and changes in sensitivity after caudate nucleus lesions. Arch. Int. Pharmacodyn. 213:264–271; 1975.
17. Guze, B. H.; Baxter, L. R. Neuroleptic malignant syndrome. N. Engl. J. Med. 313:163–166; 1985.
18. Hauger, R. L.; Skolnick, P.; Paul, S. M. Specific ^{3}H-phenylethylamine binding sites in rat brain. Eur. J. Pharmacol. 83:147–148; 1982.
19. Holtzman, S. G. Behavioral effects of separate and combined administration of naloxone and *d*-amphetamine. J. Pharmacol. Exp. Ther. 189:51–60; 1974.
20. Howard, J. L.; Pollard, G. T.; Craft, B. M.; Rohrbach, K. W. Metoclopramide potentiates *d*-amphetamine-induced hypermotility and stereotypy in rats. Pharmacol. Biochem. Behav. 27:165–169; 1987.
21. Hulihan-Giblin, B.; Hauger, R. H.; Janowsky, A.; Paul, S. M. Dopaminergic denervation increases [^{3}H](+)-amphetamine binding in the rat striatum. Eur. J. Pharmacol. 113:141–142; 1985.
22. Jasinski, D. R.; Preston, K. L. Evaluation of mixtures of morphine and *d*-amphetamine for subjective and physiological effects. Drug Alcohol Depend. 17:1–13; 1986.
23. Jordan, S. C.; Hampson, F. Amphetamine poisoning associated with

hyperpyrexia. Br. Med. J. 2:844; 1960.
24. Kapas, L.; Obal, F., Jr.; Penke, B.; Obal, F. Cholecystokinin-octapeptide-induced hypothermia in rats: dose-effect and structure-effect relationships, effect of ambient temperature, pharmacological interactions and tolerance. Neuropharmacology 26:131–137; 1987.
25. Kelley, A. E.; Stinus, L.; Iversen, S. D. Interactions between D-ala-metenkephalin, A10 dopaminergic neurons, and spontaneous behavior in the rat. Behav. Brain Res. 1:3–24; 1980.
26. Kimura, H.; Yoshida, K.; Ohsawa, M.; Arai, T.; Tsujimura, T. An autopsy case of malignant hyperthermia. Forensic Sci. Int. 27:25–30; 1985.
27. Kohda, H.; Funahashi, M.; Shikata, I.; Kimura, H. Decrease in *d*-methamphetamine sensitivity in mice due to ethanol: Apparent inhibitory and stimulatory effects of ethanol on *d*-methamphetamine-induced locomotor activity. Pharmacol. Biochem. Behav. 25:1035–1039; 1986.
28. Lee, T. F.; Mora, F.; Myers, R. D. Dopamine and thermoregulation: An evaluation with special reference to dopaminergic pathway. Neurosci. Biobehav. Rev. 9:589–598;1985.
29. Lotti, V. J.; Lomax, P.; George, R. *N*-Allylnormorphine antagonism of the hypothermic effect of morphine in the rat following intracerebral and systemic administration. J. Pharmacol. Exp. Ther. 150: 420–425; 1965.
30. Lomax, P.; Green, M. D. Neurotransmitters and temperature regulation. Prog. Brain Res. 42:251–261; 1975.
31. Mantegazza, P.; Riva, M. Amphetamine-like activity of β-phenylethylamine after a monoamine oxidase inhibitor in vivo. J. Pharm. Pharmacol. 15:472–478; 1963.
32. Martin, J. R.; Takemori, A. E. Increased sensitivity to dopamine agonists following a single dose of morphine or levorphanol in mice. Eur. J. Pharmacol. 119:75–84; 1985.
33. Murphy, P. A.; Simon, P. I.; Willoughby, W. F. Endogenous pyrogens made by rabbit peritoneal exudate cells are identical with lymphocyte activating factors made by rabbit alveolar macrophage. J. Immunol. 124:2498–2501; 1980.
34. Quock, R. M. The potentiating effect of naloxone upon apomorphine-induced hyperthermia. Life Sci. 20:2005–2012; 1977.
35. Richards, R. K. A study of the effect of *d*-amphetamine on the toxicity, analgesic potency and swimming impairment caused by potent analgesics. Arch. Int. Pharmacodyn. 216:225–245; 1975.
36. Rosow, C. E.; Miller, J. M.; Pelikan, E. W.; Cochin, J. Opiates and thermoregulation in mice. I. Agonists. J. Pharmacol. Exp. Ther. 213:273–283; 1980.
37. Rosow, C. E.; Miller, J. M.; Poulsen-Burke, J.; Cochin, J. Opiates and thermoregulation in mice. II. Effects of opiate antagonists. J. Pharmacol. Exp. Ther. 220:464–467; 1982.
38. Sharp, T.; Zetterstrom, T.; Ljungberg, T.; Ungerstedt, U. A direct comparison of amphetamine-induced behaviours and regional brain dopamine release in the rat using intracerebral dialysis. Brain Res. 401:322–330; 1987.
39. Vaccarino, F. J.; Amalric, M.; Swerdlow, N. R.; Koob, G. F. Blockade of amphetamine but not opiate-induced locomotion following antagonism of dopamine function in the rat. Pharmacol. Biochem. Behav. 24:61–65; 1986.
40. Wirtshafter, D.; Asin, K. E.; Kent, E. W. Nucleus accumbens lesions reduce amphetamine hyperthermia but not hyperactivity. Eur. J. Pharmacol. 51:449–452; 1978.
41. Woo, S. K.; Hitzeman, R. J.; Loh, H. H. Specific opioid-amphetamine interactions in the caudate putamen. Psychopharmacology (Berlin) 85:371–376; 1985.
42. Yamawaki, S.; Lai, H.; Horita, A. Dopaminergic and serotonergic mechanisms of thermoregulation: Mediation of thermal effects of apomorphine and dopamine. J. Pharmacol. Exp. Ther. 227:383–388; 1983.
43. Zetterstrom, T.; Sharp, T.; Ungerstedt, U. Further evaluation of the mechanism by which amphetamine reduces striatal dopamine metabolism: a brain dialysis study. Eur. J. Pharmacol. 132:1–9; 1986.