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Effects of Neuroleptics on Morphine-Induced Tail Erection in Mice[1,2]

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LEE, H. K., C. Y. CHAI, M. J. WAYNER, P. M. CHUNG AND C. H. HSU. *Effects of neuroleptics on morphine-induced tail erection in mice.* PHARMAC. BIOCHEM. BEHAV. 7(2) 153–157, 1977. – Morphine elicits dose-dependent tail erection in mice. Pretreatment of mice with atropine, phenoxybenzamine, propranolol, diphenhydramine, cyproheptadine or para-chlorophenylalanine did not interfere with tail erection induced by morphine. Several neuroleptic drugs which are dopamine receptor blocking agents showed a clear antagonistic effect on morphine-induced tail erection (MITE). Haloperidol and penfluridol blocked MITE at doses which only produced a slight behavioral depression. Pimozide and chlorpromazine were less antagonistic than haloperidol and penfluridol and inhibited MITE only at doses which produced a marked behavioral depression. Results indicated that dopamine might be involved in tail erection induced by morphine. MITE in mice might be a useful model for the evaluation of neuroleptic drugs.

Tail erection Morphine Neuroleptics Haloperidol Penfluridol
Pimozide Chlorpromazine Dopamine receptor blockade

MORPHINE–LIKE drugs elicit tail erection in the mouse [1,3] and the response can be used as an indication of presumed euphoric activity in man [7] and for studying structure-activity relations among opiates and opiate antagonists [1]. Although the results of anatomical studies [3] indicate that morphine-induced tail erection (MITE) is produced mainly by the action of the sacro-coccygeus dorsalis muscle and that the lumbo-sacral cord with its peripheral nervous outflow must be intact for producing the reaction, the exact mechanism by which morphine induces tail erection is not known. Recently, numerous attempts have been made to correlate the effects of morphine with putative neurotransmitters in the brain [5, 10, 13, 14]. However, MITE has never been used as a model for similar studies. The present study was carried out to investigate the effects of several transmitter antagonists on MITE and also to determine what transmitter is involved in this phenomenon. Results indicate that dopamine might be involved in tail erection produced by morphine in the mouse.

METHOD

Male albino mice, weighing 20–25 g, were used. They were placed in individual cages for observation. The ambient temperature was kept at 25° C. To minimize effects of noise the experimental room was kept relatively silent. The dose-response relation of MITE was obtained. Morphine HCl (Chinese Pharmacopeia Standard, supplied by the Bureau of Narcotic Drugs, R.O.C.) was administered subcutaneously to groups of 6–8 mice at doses of 5, 10, 20, 50 and 100 mg/kg. The volume of drug administration was 0.1 ml/20 g. Since elevation of the tail at angles greater than 45° [1] and 90° [7] has been used to define the tail erection response, the latencies for mice to reach both these levels were utilized in the present study. Two latencies were measured; one, from when the morphine was administered to when the tail was elevated to at least 45° to the horizontal and the second, from when the morphine was administered to when the tail was elevated to at least 90° to the horizontal. Tail erection duration was defined as the total time the tail was elevated not less than 45°. All times were measured by means of stop watches. The total test session was 60 min following the first latency. Since all mice tested responded to 100 mg/kg of morphine with elevated tails of at least 90°, this particular dose was selected for all subsequent experiments.

The effects of various transmitter antagonists on MITE was investigated by the pretreatment of each group of 6 to 8 mice with one of the following agents and challenging with a subcutaneous dose of 100 mg/kg of morphine. All drugs were dissolved in normal saline with the noted exceptions. The data for tail erection were collected as mentioned previously.

Atropine sulfate (Sigma) 20 mg/kg, phenoxybenzamine HCl (Smith, Kline and French) 15 mg/kg, propranolol HCl

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TABLE 1

DOSE-RESPONSE RELATIONSHIP OF THE MORPHINE-INDUCED TAIL ERECTION IN MICE

Dose of morphine mg/kg SC	No. of mice responded (≥45°) / No. tested	Latency: median and range (min)	No. of mice responded (≥90°) / No. tested	Latency: median and range (min)	Duration: median and range (min)
5	0/7	—	0/7	—	—
10	1/7	19.3	0/7	—	22
20	3/6	14.7(14.3–26.2)	0/6	—	34(33–60)
50	6/6	11.1(4.8–14.3)	5/6	12.3(7.8–14.9)	60
100	8/8	7.2(6.2–14.0)	8/8	10.0(9.2–16.0)	60

(Sigma) 5 mg/kg, and diphenhydramine HCl (Sigma) 5 mg/kg were administered intraperitoneally 30 min before morphine.

Cyproheptadine HCl (Merck, Sharp and Dohme) 2 mg/kg was administered intragastrically 1 hr before morphine while the animal had been deprived from food overnight.

Parachlorophenylalanine (PCPA, Sigma) was administered intraperitoneally in a daily dose of 100 mg/kg for three days. The last dose was given 24 hr before morphine.

Haloperidol (Janssen) was administered intraperitoneally as a suspension (2 drops of surfactant polysorbate in 10 ml of saline) in doses of 1, 2 or 5 mg/kg, 30 min before morphine. Mice which received only solvent and morphine or 5 mg/kg of haloperidol and saline were used as controls.

Penfluridol (Janssen) was prepared as a suspension (2 drops of surfactant polysorbate in 10 ml of water) and administered intragastrically in doses of 20, 50 or 100 mg/kg 2 hr before morphine. Mice which received only solvent and morphine or 100 mg/kg of penfluridol and saline were used as controls.

Pimozide (Janssen) was dissolved in 0.1 M tartaric acid and administered intraperitoneally in doses of 1, 2, 5, 10, 20 or 50 mg/kg 90 min before morphine. Mice which received only solvent and morphine or 20 mg/kg of pimozide and saline were used as controls.

Chlorpromazine HCl (Sigma) was administered intraperitoneally in doses of 1, 2, 5 or 10 mg/kg 30 min before morphine. Mice which received only 5 mg/kg of chlorpromazine and saline were used as controls.

RESULTS

Dose-response Relation of MITE

Table 1 summarizes the dose-response relation of MITE. The number of mice which responded with a tail elevation to at least 45° or 90°, the median and range of latency, and the duration of tail elevation are presented. Morphine had very little effect below 10 mg/kg. In a dose of 20 mg/kg, morphine elicited tail erection of 45° or greater in 3 out of 6 mice with a median latency of 14.7 min. None of the animals tested elevated the tail to 90° or greater. The median duration of tail erection was 34 min. For the 6 animals treated with 50 mg/kg of morphine, all displayed tail elevation of 45° or greater with a median latency of 11.1 min. Only 1 mouse did not reach a tail elevation to at least 90°. The duration of tail erection for mice receiving a dose of 50 mg/kg of morphine or more was 60 min (Table 1). When the dose of morphine was increased to 100 mg/kg, all animals showed tail erection of at least 90°. With this dose of morphine, the median latency for the response greater than 45° and 90° were 7.2 and 10.0 min, respectively.

Effects of Transmitter Antagonists on MITE

Effects of cholinergic blocking agent (atropine), alpha-adrenergic blocking agent (phenoxybenzamine), beta-adrenergic blocking agent (propranolol), histamine antagonist (diphendydramine), 5-hydroxytryptamine (5-HT) antagonist (cyproheptadine), and tryptophan hydroxylase inhibitor (PCPA) on MITE are summarized in Table 2. In general, these agents essentially had no effect on MITE. Without exception, morphine 100 mg/kg elicited tail erection of at least 90° in all mice pretreated with transmitter antagonists. The characteristics of MITE in these drug pretreated animals were very much similar to those in animals pretreated with saline. They had comparable latencies and the duration of tail erection was 60 min (Table 2). Under the present dosage all the transmitter antagonists did not produce any behavioral depression.

Effects of Neuroleptics on MITE

Effects of four neuroleptics: haloperidol, penfluridol, pimozide and chlorpromazine [8,9] on MITE are summarized in Table 3. All these drugs block dopamine receptors [6, 11, 12]. The MITE of mice pretreated with the solvents were similar to those observed in mice pretreated with saline. Therefore, only the data of the saline group are included in Table 3. Administration of the neuroleptics alone did not elicit tail erection in mice.

Haloperidol depressed markedly the MITE. Following 1 mg/kg haloperidol in 7 mice, 5 had tail elevation to at least 45° and only 4 reached 90° or greater. With 2 mg/kg of haloperidol, again in 7 mice, 4 showed an elevation of at least 45° but only 2 reached 90°. When the dose of haloperidol was raised to 5 mg/kg, only 2 out of 7 mice showed a tail elevation of at least 45° and none of them reached 90°. As shown in Table 3, when the dose of haloperidol was increased, the latencies of MITE increased too, while the duration of MITE decreased. Haloperidol, with the doses used in the present study, only slightly reduced the activity of animals, and produced a mild sedation. Catalepsy or dystonia was not observed.

All animals pretreated with 20 mg/kg (8 mice) or 50 mg/kg (6 mice) of penfluridol responded to morphine with tail elevations to at least 45°. Only 3 mice receiving a dose

TABLE 2

EFFECTS OF NEUROTRANSMITTER ANTAGONISTS ON MORPHINE-INDUCED TAIL ERECTION

Pretreatment			Morphine mg/kg SC	No. of mice responded (≥45°)	Latency: median and range (min)	No. of mice responded (≥90°)	Latency: median and range (min)	Duration: median and range (min)
Time	Drug	Dose mg/kg IP		No. tested		No. tested		
30 min	saline	—	100	6/6	6.5(3.0–8.8)	6/6	9.5(7.0–9.8)	60
30 min	atropine	20	100	6/6	7.0(6.0–11.5)	6/6	8.8(8.5–13.3)	60
30 min	phenoxy-benzamine	15	100	6/6	10.5(6.5–13.3)	6/6	15.5(7.0–17.6)	60
30 min	propranolol	5	100	6/6	5.4(4.3–5.8)	6/6	6.8(6.0–7.0)	60
30 min	diphen-hydramine	5	100	6/6	6.8(3.0–9.8)	6/6	9.7(5.8–13.9)	60
60 min	cyproheptadine	2*	100	6/6	5.3(3.2–31.0)	6/6	7.4(4.8–35.3)	60
24 hr	parachloro-phenylalanine	100 3 days	100	8/8	6.2(3.0–9.0)	8/8	9.3(4.0–11.8)	60

*Cyproheptadine was administered intragastrically.

TABLE 3

EFFECTS OF NEUROLEPTIC DRUGS ON MORPHINE-INDUCED TAIL ERECTION

Pretreatment			Morphine mg/kg SC	No. of mice responded (≥45°)	Latency: median and range (min)	No. of mice responded (≥90°)	Latency: median and range (min)	Duration: median and range (min)
Time	Drug	Dose mg/kg IP		No. tested		No. tested		
30 min	saline	—	100	6/6	7.5(3.0–10.5)	6/6	9.3(7.0–11.0)	60
30 min	haloperidol	5	0	0/6	—	0/6	—	—
30 min	haloperidol	1	100	5/7	7.0(4.8–12.5)	4/7	7.9(7.5–13.1)	40(34–60)
30 min	haloperidol	2	100	4/7	12.8(9.2–39.8)	2/7	9.7 and 13.4	34(28–51)
30 min	haloperidol	5	100	2/7	19.3 and 27.1	0/7	—	32 and 41
2 hr	penfluridol	100*	0	0/6	—	0/6	—	—
2 hr	penfluridol	20*	100	8/8	11.5(5.0–32.8)	3/8	7.1(5.3–21.3)	38(3–60)
2 hr	penfluridol	50*	100	6/6	10.0(3.8–52.2)	1/6	15.0	36(5–60)
2 hr	penfluridol	100*	100	2/7	7.5 and 35.0	0/7	—	18 and 19
90 min	pimozide	20	0	0/6	—	0/6	—	—
90 min	pimozide	1	100	6/6	7.3(4.5–18.0)	6/6	8.0(5.0–18.3)	60
90 min	pimozide	2	100	6/6	6.3(5.0–8.5)	6/6	7.5(5.5–10.5)	60
90 min	pimozide	5	100	6/6	11.5(7.5–34.0)	6/6	12.9(8.3–34.5)	60
90 min	pimozide	10	100	6/6	9.6(3.0–15.8)	6/6	10.2(3.8–16.1)	60
90 min	pimozide	20	100	6/6	22.1(4.0–30.0)	3/6	27.0(4.3–29.4)	53(45–60)
30 min	chlorpromazine	5	0	0/6	—	0/6	—	—
30 min	chlorpromazine	1	100	6/6	6.9(5.5–8.8)	5/6	9.3(6.1–14.5)	60
30 min	chlorpromazine	2	100	4/6	7.6(4.5–11.1)	3/6	8.8(5.5–9.2)	60
30 min	chlorpromazine	5	100	2/6	7.3 and 8.8	2/6	11.1 and 12.2	60
30 min	chlorpromazine	10	100	0/6	—	0/6	—	—

*Penfluridol was administered intragastrically.

of 20 mg/kg and 1 receiving 50 mg/kg of penfluridol showed a tail elevation of at least 90°. When the dose of penfluridol was increased to 100 mg/kg, only 2 out of 7 mice showed a tail erection to 45° or greater and none of them reached 90°. The latencies of MITE were not appreciably prolonged but the duration was reduced by penfluridol pretreatment (Table 3). Similar to haloperidol, penfluridol with the doses used in the present study produced only a mild sedation in mice.

Pimozide with doses of 1, 2, 5 or 10 mg/kg produced increasing sedation in mice but had no antagonistic effect on the MITE (Table 3). When the dose of pimozide was increased to 20 mg/kg, it produced marked catalepsy and severe sedation in mice. However, all 6 mice pretreated with this dose responded to morphine with tail elevations to at least 45°. Only 3 of them did not reach 90°. The latency of MITE seemed prolonged with this dose and there was a slight decrease in the duration (Table 3). All 6 mice tested with 50 mg/kg of pimozide died 2–3 min after the drug administration. Therefore, there are no results for this dose in Table 3.

Chlorpromazine with doses of 1 or 2 mg/kg produced mild to moderate sedation in mice and caused some depression of MITE. As shown in Table 3, following 2 mg/kg chlorpromazine in 6 mice, 4 displayed tail elevations to at least 45° and shortly after 3 reached 90° or greater. An increase of chlorpromazine to 5 mg/kg produced catalepsy, general hypotonia, and severe sedation in all 6 mice tested. However, 2 of them still displayed tail elevation to at least 90°. Latencies for the MITE did not seem to be prolonged and there was also no reduction in the duration of MITE (Table 3). When the dose was further increased to 10 mg/kg, all 6 animals tested fell into sleep and lost the righting reflex completely. Morphine elicited no tail erection at all in these mice.

DISCUSSION

A more precise quantitative method was used in the present study to investigate morphine elicited dose-dependent tail erection in mice. The results indicate that MITE is not affected by pretreatment with large doses of cholinergic blocking agent, alpha- and beta-adrenergic blocking agents, histamine antagonist, and 5-HT antagonists. Therefore, MITE might not be related to the actions of acetylcholine, norepinephrine, histamine, or 5-HT.

Four neuroleptic drugs used in the present experiments vary in their ability to depress MITE. Haloperidol is the most effective. At a dose which did not produce sedation, haloperidol prevented tail elevation to at least 90° in mice treated with 100 mg/kg of morphine. In comparison to haloperidol, a larger dose of penfluridol was required to depress MITE. Also, penfluridol did not produce any obvious sedation. On the other hand, pimozide at doses which produced severe sedation in mice did not affect MITE very much. The ability of chlorpromazine to antagonize the effect of morphine on tail erection correlated closely with its tranquilizing effect. Only in large doses when chlorpromazine produced a marked sedation in the mice, it simultaneously depressed or abolished MITE. The data agree with some previous findings that MITE was abolished during general anesthesia induced by pentobarbital or ether [3]. Therefore, the depressive effect of neuroleptics on MITE can not be attributed to their tranquilizing effects.

Many of the pharmacological actions of morphine are similar to those of haloperidol, pimozide, and other neuroleptics [10]; for example, blockade of stereotyped behavior induced by apomorphine and amphetamine [10,12]. However, this is not the case for MITE. Although the neuroleptics used in the present study seem to selectively block dopamine receptors in the central nervous system [6, 11, 12], it is not clear why the depressive effects on MITE vary so much. Nonetheless, these results suggest that a possible interaction between morphine and dopamine receptors might be responsible for the tail erection phenomenon observed in mice. In addition, the differences observed between neuroleptics on MITE suggest the possible use of the phenomenon for screening or evaluating new neuroleptics in the future.

All the neuroleptics studied in the present experiments are used extensively in the treatment of psychosis [2,6]. Recently, several endogenous morphinemimetic brain peptides have been found to produce profound behavioral effects in rats and suggest some etiological significance in mental illness [4]. Results of the present study indicate that neuroleptics can antagonize a unique behavioral effect of morphine. However, more research on the interaction of neuroleptics with behavioral changes induced by endogenous morphinemimetic brain peptides is necessary before the role of neuroleptics in the treatment of mental disorders can be elucidated.

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