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Role of Central Dopaminergic Receptors in Manic Response of Cats to Morphine

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Abstract. The administration of morphine in conscious cats produces a manic response characterized by hyperexcitement and aggressive behaviour. This manic response was prevented by pretreatment of cats with either CNS catecholamine depletors (reserpine and tetrabenazine) or central dopaminergic receptor blocking agents eg. haloperidol and chlorpromazine. On the other hand, alpha and beta adrenergic receptor blocking agents-phenoxybenzamine and propranolol did not antagonise the morphine-mania. Similarly, anticholinergic (atropine), antihistaminic (mepyramine) and antiserotonin (LSD-25) agents did not prevent morphine-mania. It is concluded that morphine releases dopamine in the CNS which in turn excites the central dopaminergic receptors to induce the manic response.

Key words: Morphine Mania — Central Dopaminergic Receptors — Catecholamine Depletors — Autonomic Blocking Agents.

Morphine and allied drugs produce depression mainly by acting on supraspinal structures. However, in cats morphine produces a manic response (hyperexcitatory response) in which the animal is continuously restless, seems frightened and avoids handling (Wikler, 1944; Norton, and de Beer, 1956). Morphine causes the stimulation of the hypothalamic centres resulting in depletion of catecholamines in the adrenal medulla and in depletion of noradrenaline in the hypothalamus (Jacobsen, 1959). Morphine also prevents the release of acetylcholine and noradrenaline from post-ganglionic nerve endings (Pelikan, 1960; Trendelenburg, 1957). These observations suggest that morphine-mania may be mediated through the release of some neurohumoral transmitter(s) in the central nervous system. The role of various drugs in the production of morphine-mania in cats was therefore investigated.

Methods

Cats of either sex weighing from 2.5 to 4.0 kg were employed in the present investigation. They were kept in separate cages. The animals were observed before and after the injection of morphine either alone

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Table 1. *Effect of*

Drugs (mg/kg i.p.) before morphine	
None	
Reserpine	2.5
Tetrabenazine	75.0
Phenoxybenzamine	10.0
Propranolol	2.5
Haloperidol	0.5
Chlorpromazine	2.0
Atropine	5.0
Mepyramine	10.0
LSD-25	0.5

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Table 1. *Effect of various drugs on morphine-induced mania in cats*

Drugs (mg/kg i.p.) before morphine		Hours before morphine injection	Morphine (mg/kg i.p.)	No. of cats tested	No. of cats showing manic response	% response
None		—	1.0	5	0	0
			5.0	5	1	20
			10.0	5	2	40
			20.0	5	5	100
Reserpine	2.5	24	20.0	3	0	0
Tetrabenazine	75.0	18	20.0	3	0	0
Phenoxybenzamine	10.0	1	20.0	3	3	100
Propranolol	2.5	1	20.0	3	3	100
Haloperidol	0.5	1	20.0	3	0	0
Chlorpromazine	2.0	1	20.0	3	0	0
Atropine	5.0	1	20.0	3	3	100
Mepyramine	10.0	1	20.0	3	3	100
LSD-25	0.5	1	20.0	3	3	100

or after pretreatment with drugs. In the first series of experiments, the dose of morphine required to induce a manic response in all the cats was determined. Induction of hyper-excitement and aggressive behaviour characterised by violent motor excitement, vigorous movement or jumping in the cage, yowling, piloerection, clawing and biting of the cage bars were taken as the criterion of a positive manic response. In the next series of experiments, the effect of pretreatment of various drugs on morphine-induced mania was studied. All the drugs were given by the intraperitoneal route. The animals were continuously observed until a manic response appeared or for a minimum period of 2 h.

The drugs used in the present study include morphine hydrochloride, phenoxybenzamine hydrochloride, propranolol hydrochloride, atropine sulphate, mepyramine maleate, lysergic acid diethylamide (LSD-25), reserpine, tetrabenazine, haloperidol and chlorpromazine hydrochloride.

Results

The results of the present study are summarized in Table 1. When morphine was given in a dose of 1.0 mg/kg, the cats became quiet 30 to 45 min after its administration. They lay, quietly in the cage and remained in the same position if undisturbed. External stimuli like noise and pinching of the tail with a blunt object caused the animals to stand up and move about restlessly. None of the cats showed a typical manic response with this dose. The cats receiving morphine in a 5.0 mg/kg dose showed varying degrees of sedation mixed with mild excitement. Behavioural changes similar to those observed with the 1.0 mg/kg dose

were seen initially but after a lapse of about $1-1^1/_2$ h these cats exhibited mild spontaneous motor restlessness which was recurrent and of disorderly character. There were apparently purposeless movements of head, neck and limbs. One out of the five cats tested with this dose exhibited a characteristic manic response, showing vigorous motor excitement with periods of rage-like activity. It was unresponsive to mild external stimuli but when it was agitated it showed marked violent motor excitement and attempted to escape from the cage. It produced harsh, loud, prolonged cries. There were rapid movements of the tail, piloerection, clawing and biting of the cage bars. The manic response was observed in 2 out of 5 cats with the 10 mg/kg dose and with the 20 mg/kg dose the manic response was observed in all the cats tested. With this high dose occasional muscle twitchings were also seen. These effects lasted for an average period of 5 h. All the cats appeared normal next day.

The results obtained with pretreatment with various drugs showed that out of all the drugs tested, only reserpine, tetrabenazine, haloperidol and chlorpromazine were able to block the manic response whereas the other drugs i.e. phenoxybenzamine, atropine, mepyramine, LSD-25 and propranolol proved ineffective.

Discussion

The results of the present experiments suggest that the morphine induced manic response in cats is not due to the action of the drug *per se*, but is through the release of monoamines. The blockade of morphine mania by the well known monoamine depletor, reserpine, as well as the central catecholamine depletor, tetrabenazine indicates that the response is brought about through the release of catecholamines in the central nervous system (CNS). This is in agreement with an earlier report of Vogt (1954) who observed that morphine releases catecholamines in the CNS. This concept is further supported by the fact that premedication with small doses of reserpine (25—100 μg/kg) enhanced the morphine mania (Loewe, 1956; Sturtevant and Drill, 1957) whereas higher doses of reserpine (100—500 μg/kg) had an antagonistic effect (Sturtevant and Drill, 1957; Loewe, 1956).

Further studies designed to identify the central adrenergic receptors in the causation of morphine mania have yielded interesting information. Phenoxybenzamine and propranolol, which block central adrenergic receptors (Gupta *et al.*, 1967) were unable to prevent morphine induced mania. On the other hand, haloperidol, a central dopaminergic receptor blocking agent (Van Rossum, 1966) was found to antagonise morphine-mania. Chlorpromazine, another central dopaminergic receptor blocking agent (Anden *et al.*, 1969), also prevented this manic response. We have

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observed that apomorphine, which excites central dopaminergic receptors (Anden *et al.*, 1967), was also able to induce a manic response similar to morphine (unpublished observations).

The inability of atropine, mepyramine and LSD-25 to antagonise the manic response rules out the cholinergic, histaminergic and serotonergic involvement in the causation of morphine-mania.

Thus, in conclusion, it may be stated that the drugs which either deplete dopamine in the central nervous system eg. reserpine and tetrabenazine or block central dopaminergic receptors eg. haloperidol and chlorpromazine are able to antagonise morphine-mania in cats. Furthermore, a similar manic response can be induced by a central dopaminergic receptor excitant eg. apomorphine. These observations indicate that morphine releases dopamine in the CNS which in turn excites the central dopaminergic receptors to produce the manic response in cats.

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