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COMPULSIVE GNAWING IN RATS AFTER IMPLANTATION OF DRUGS INTO THE VENTRAL THALAMUS. A CONTRIBUTION TO THE MECHANISM OF MORPHINE ACTION

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1 Implantation of morphine into various parts of the corpus striatum of rats evokes only weak gnawing responses.

2 Deposition of apomorphine, morphine or methadone in the region of the nucleus ventralis thalami produces a biphasic response, i.e. general excitation, followed by a period of intense gnawing.

3 The effect of both apomorphine and morphine is blocked by chlorpromazine, haloperidol and pimozide. However, pretreatment with α-methyltyrosine methyl ester or α-methyldopa prevents only the gnawing response to morphine, but not to apomorphine.

4 Systemic nalorphine, morphine or pethidine suppress the gnawing response, evoked by thalamic implants of apomorphine or morphine.

5 Systemic amphetamine potentiates the effect of thalamic deposits of morphine.

6 Compulsive gnawing, following implantation of morphine into the ventral region of the thalamus, probably results from enhanced production and release of catecholamines.

Introduction

Gnawing can be evoked in rodents by the action of apomorphine on the corpus striatum (Smelik & Ernst, 1966). This mechanism has also been considered for the stereotyped behaviour of rats, receiving subcutaneous injections of morphine (Fog, 1970). However, direct evidence for an action of morphine on the corpus striatum is lacking. We have implanted crystals of morphine hydrochloride into the various components of the corpus striatum of rats and have compared the gnawing response with that of apomorphine deposits. These experiments revealed a weak action of morphine after topical application to the globus pallidus, while the alkaloid was ineffective in the caudate nucleus or the putamen.

We have tested other subcortical structures systematically and observed that bilateral deposition of apomorphine as well as morphine into the ventral part of the thalamus caused intense gnawing in a high percentage of the animals. However, the response to the two alkaloids revealed marked differences in latency. In the present study, we shall attempt to elucidate the different mechanisms by which these two drugs cause gnawing.

Methods

Implantations into the rat brain were carried out under ether anaesthesia, using the coordinates of Massopust (1961). Needles of gauge No. 21 were cut to the desired length and were fitted inside with a No. 27 needle. The latter was sealed at its mouth and reached exactly to the end of the outer tube. The head of the outer needle was filled with the material to be deposited; pellets of about 100 μg were ejected by inserting the inner wire. The average weight of the pellets was determined by extruding 20 portions into a small vessel and weighing on an analytical balance.

In all experiments, male white rats of the local sabra strain (160-200 g body weight) were used. During the observation period of about 8 h, they were kept singly in cages made entirely of metal wires and were without water or food.

At the end of the experiment, the animals were killed and their brains fixed in 4% formalin. The brains were later cut in sections 80 μm thick to check the localization of the pellets. The position of the implants was marked on charts of brain sections (Massopust, 1961), as shown in Figures 1 and 2.

Materials

For injection, the drugs were dissolved in 0.9% w/v NaCl solution (saline). For implantation, they were used in dry form and were mixed with the appropriate amount of talc. The latter alone served for control experiments. The apomorphine-talc mixture was moistened with saline before its deposition in the brain.

Drugs used

Apomorphine hydrochloride, Powers Weightman, Rosengarten Co.; morphine hydrochloride, J.F. MacFarlane & Co.; methadone hydrochloride, Eli Lilly & Co. Indianapolis; pethidine hydrochloride, Teva Pharmaceutical Industries, Jerusalem; phenoxybenzamine hydrochloride, (+)- and (−)-amphetamine sulphate, Smith, Kline & French, Philadelphia; (±)-amphetamine sulphate, Assia Chemical Laboratories, Tel-Aviv; chlorpromazine, Taro Pharmaceutical Industries, Haifa; haloperidol, Abic Chemical and Pharmaceutical Industries, Natania; regitine hydrochloride, Ciba-Geigy, Basel; nalorphine hydrochloride, α-methyldopa and disulfiram (Antabuse), Merck, A.G., Darmstadt, West Germany; (±)-α-methyltyrosine methyl ester hydrochloride and (±)-*p*-chlorophenylalanine, Biotex, AB, Stockholm. Pimozide (1-[4-(*N*-4′,4′-bis {*p*-fluorophenyl} *n*-butyl)-piperidyl] benzimidazoline-2-one) was a gift of Dr Paul Janssen, Beerse, Belgium; 0.25% solutions were prepared by adding 20 equivalents of tartaric acid.

Amounts given in the text refer to the forms of the drugs, listed here.

Results

Compulsive gnawing, following implantation of drugs into the corpus striatum

We have implanted both apomorphine and morphine into the three components of the corpus striatum (Figure 1). In the caudate nucleus and the putamen, bilateral deposits of apomorphine evoked 25-30% positive responses, while morphine proved ineffective. In the globus pallidus, both alkaloids caused gnawing, but the reaction to morphine was weaker and less frequent. Furthermore, a marked difference in latency became manifest: while gnawing started about 20-30 min after implantation of apomorphine, the response to morphine appeared only after 3-4 h (Table 1).

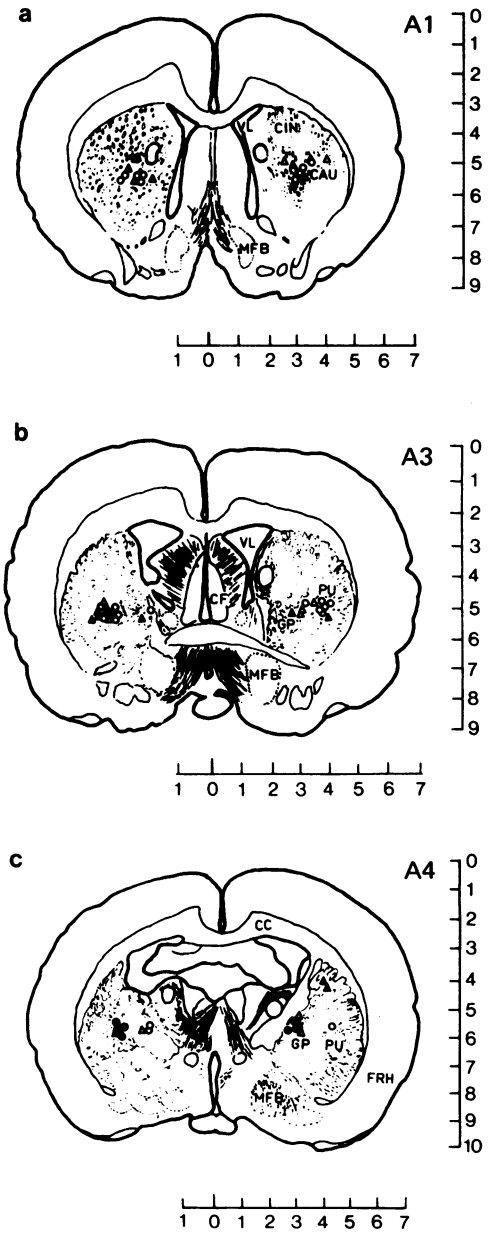

Fig. 1 Transverse sections through rat corpus striatum (Massopust, 1961), to show sites of implantation. (a) caudate nucleus; (b) and (c) putamen and globus pallidus. (△) apomorphine (100 μg, no response); (▲) apomorphine (100 μg, intense gnawing); (○) morphine (65 μg, no response); (●) morphine (65 μg, delayed, intense gnawing).

CAU, caudate nucleus; CC, corpus callosum; CF, columna fornicis; CIN, capsula interna; FRH, fissura rhinalis; GP, globus pallidus; MFB, median forebrain bundle; PU, putamen; VL, ventriculus lateralis.

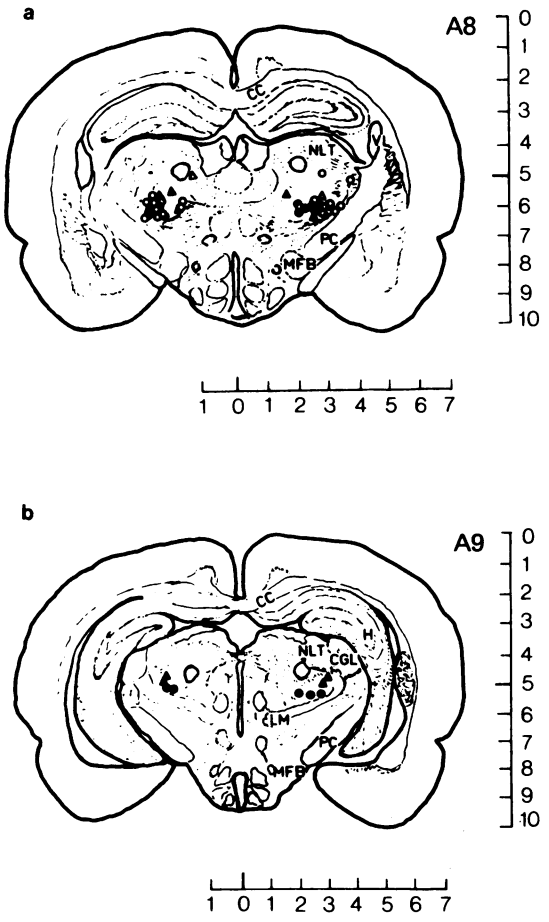

Fig. 2 Transverse sections through the rat thalamus to show sites of implantations. Symbols as in Figure 1. Approximately equal numbers of positive and negative results are plotted, although the actual ratio is 8 : 1 or 9 : 1.

CGL, corpus geniculatum laterale; H, hippocampus; LM, lemniscus medialis; NLT, nucleus lateralis thalami; PC, pedunculus cerebri.

Implantation of drugs into the ventral thalamus

Much stronger effects were evoked by deposition of the alkaloids into the ventral region of the thalamus (Figure 2). Here morphine (100-200 μg) caused strong excitation within 30-60 minutes. The rats were sniffing, rubbing their noses, running through the cage, turning in a horizontal plane or around their sagittal body axis, and biting. Occasionally brief clonic convulsions were observed. Towards the end of this initial, excitatory period, i.e. about 2-3 h after implantation, intensive gnawing of the cage wires and of the limbs or of the tail (leading sometimes to bleeding wounds) set in. This activity continued for a further 1-5 hours. With lower doses of morphine, the general excitatory symptoms at the beginning were less marked and subsided about 90 min after implantation. Again 2-3 h after implantation, compulsive gnawing started, no other signs of activity being recognizable during this period. Gnawing appeared periodically or was continuous for 2-4 hours.

Table 1 shows that the highest percentage of positive responses was obtained when 65 μg morphine were deposited on each side of the thalamus, while larger doses reduced the percentage of gnawing responses.

The sensitive region in the ventral nucleus of the thalamus is well defined (Fig. 2), i.e. small deviations from the area, marked in Fig. 2, lead to negative results. Thus deposits made 4.5 mm caudal of the vertex of the bregma and 2.5-3.0 mm from the midline, were ineffective at a depth of either 4 or 7 mm. The critical depth was sharply defined as 5-6 mm; here morphine deposits of 65 μg evoked about 80% positive responses. Similarly, implantations at the same distance from the bregma and at a depth of 5-6 mm, were ineffective when applied at 1 or 4 mm from the midline. Deposits in other parts of the thalamus, e.g. in the nucleus lateralis thalami, were completely ineffective.

A considerable delay in morphine-induced gnawing can also be observed after i.p. injection of morphine. A dose of 10 mg/kg caused gnawing in 75 out of 88 rats (Table 1). Thirty-five animals responded within 45-60 min, 37 during the second, and 3 during the third hour.

Apomorphine deposits in the ventral thalamus were also effective in the dose range of 50-100 μg. General excitatory symptoms were less conspicuous than in the case of morphine. Gnawing usually started 20-30 min after implantation and lasted for 2-3 hours. Doses of less than 50 μg did not produce reliable results. At a dose of 100 μg, which evoked gnawing in more than 90% of the rats, about 20% died during convulsive fits. With still larger implants, mortality increased steeply. This was also true for doses of morphine above 100 μg (Table 1).

Apomorphine proved more effective in the ventral thalamus than in the corpus striatum. This was demonstrated in the following way: the rats, which had received deposits into the caudate nucleus or the putamen, and had only given limited responses (Table 1), were implanted 2 days later with the same drug in the ventral thalamus. Now all animals showed strong gnawing. Similarly,

groups of rats which lacked any response to morphine deposited in the caudate or the putamen, showed 70 and 80% positive reactions, respectively, when the alkaloid was applied two days later to the ventral thalamus.

Implants of methadone, at a dose of 100-200 μg, evoked about 50% positive responses, with a delay similar to that after morphine (Table 1). In general, gnawing of moderate intensity was the only visible effect, other excitatory symptoms being absent.

Pethidine deposits (up to 200 μg) did not produce any behavioural change. Likewise, thalamic application of amphetamine did not evoke any marked behavioural responses (Table 1).

Mechanism of the gnawing effect of morphine

The following experiments were undertaken to elucidate the mechanism of morphine-induced compulsive gnawing.

Drugs, blocking catecholamine receptors (Table 2). Phentolamine, in doses up to 2 mg/kg intraperitoneally, or phenoxybenzamine subcutaneously, in amounts up to 20 mg/kg, were injected 20-40 min after intense gnawing, induced by morphine deposits, had started. Neither of these two drugs antagonized the response effectively. Occasionally, a rat which developed a weak gnawing response, showed a further

Table 1 Compulsive gnawing after implantation of drugs into cerebral structures or after systemic injections

Drug	*Dose*	*No. of rats gnawing/ no. of rats used*	*No. of rats succumbing*	*Gnawing* *Latency*	*Gnawing* *Duration (h)*
(1) Implantation into corpus striatum (Dose in μg)					
(a) Caudate nucleus					
Apomorphine	100	5/20	0	20-40 min	1-2
Morphine	65	0/10			
(b) Putamen					
Apomorphine	100	3/10	0	30-60 min	1-2
Morphine	65	0/10			
(c) Globus pallidus					
Apomorphine	100	8/10	0	20 min	3
Morphine	65	4/10*	0	210-270 min	1.5-3
	100	5/10*	0	3 h	2-3
(2) Implantation into the ventral region of the thalamus (Dose in μg)					
Apomorphine	50	2/9	1	20-40 min	2
	100	225/245	46**	10-60 min	3
Morphine	30	5/19	–	5-6 h	1
	50	11/38	1	4-6 h	1
	65	280/340†	1	1-6 h	5
	100	6/14†	2	4-7 h	1
	200	3/10†	5	5-6 h	2
Methadone	65	7/40	–	1-4 h	1
	100	9/20	–	1-4 h	3
	200	8/15	–	1-2 h	2-3
Pethidine	200	0/10			
(±)-Amphetamine	200	0/10			
(+)-Amphetamine	200	0/10			
(−)-Amphetamine	200	0/10			
Talc	200	0/12			
(3) Systemic injections (Dose in mg/kg)					
Morphine i.p.	10	75/88	–	45-150 min	1-2
(+)-Amphetamine s.c.	2	0/10	–		
	3	0/10	–		
	4	2/10	–	1-2 h	(brief)
	6	10/20	–	1-2 h	2-3

* Weak biting and gnawing.

** In most of these animals death followed strong convulsions. Out of the 46 animals, 36 died after gnawing, while 10 started convulsing without gnawing.

† The excitatory period, preceding the gnawing response, lasted 1-2 hours.

reduction of this activity after phentolamine or phenoxybenzamine and would eventually stop gnawing altogether. However, the two α-adrenoceptor blockers had no influence on well-established gnawing activities. Phentolamine proved ineffective against apomorphine-induced gnawing.

In contrast, chlorpromazine (2 mg/kg) or haloperidol (10 mg/kg), when applied after the gnawing was well established, stopped the reaction whether evoked by morphine or apomorphine (Table 2).

Pimozide has been described as a selective blocker of dopamine receptors (Andén, Butcher, Corrodi, Fuxe & Ungerstedt, 1970), and its antagonism to intraperitoneal apomorphine was demonstrated by Janssen, Niemegeers, Schellekens, Dresse, Lenaerts, Pinchard, Schaper, Van Nueten & Verbruggen (1968). We confirm these observations (Table 2). Rats received pimozide (4 mg/kg) intraperitoneally 22 and 4 h before intraperitoneal apomorphine. This treatment prevented the gnawing response completely. Even a single injection of the blocking agent, given 4 h before, abolished the gnawing effect of apomorphine. The compound also proved antagonistic to morphine, although in this case proper timing was more difficult. In the experiment recorded in Table 2, the rats received pimozide (4 mg/kg), 4 h before the intraperitoneal injection of morphine. During the second hour after morphine application, three out of ten rats occasionally showed a weak tendency to biting by taking the wire net of the cage into the mouth. However, they did not perform the characteristic gnawing, which was so conspicuous in the controls.

Intraperitoneal injection of pimozide (4 mg/kg) completely suppressed the gnawing response to apomorphine or morphine, when these drugs were implanted into the thalamus 4 h later.

Inhibitors of catecholamine biosynthesis (Table 3). Three representative enzyme inhibitors were tested.

α-Methyltyrosine methyl ester, which blocks

Table 2 Effects of drugs blocking catecholamine receptors on gnawing, evoked by thalamic deposition of drugs

Blocking agent	*Dose (mg/kg)*	*Route of application*	*Latency of action (min)*	*No. of rats gnawing/ no. of rats used*
(1) Bilateral implantation of 65 μg morphine				
Phentolamine	2	i.p.	40-60	10/12*
Phenoxybenzamine	20	s.c.	10-30	7/9*
Chlorpromazine	1	i.p.	15	4/4
	2	i.p.		0/6
Haloperidol	2	oral	30-60	6/8
	3	oral		2/9
	5	oral		1/8
	10	oral		0/8
Pimozide	4	i.p.	—**	0/10
	4	i.p.	—†	(3)/10††
(2) Bilateral implantation of 100 μg apomorphine				
Phentolamine	2	i.p.	—	7/7
	3	i.p.	—	5/5
Chlorpromazine	0.5	i.p.	—	3/3
	1	i.p.	60-120	9/12
	2	i.p.	60-120	2/11
Haloperidol	5	oral	30-60	7/10
	10	oral	30-60	0/13
Pimozide	4	i.p.	—**	1/10
	4	i.p.	—†	0/10
	8	i.p.	—§	0/10

* Only in those rats which responded with weak gnawing after morphine implantation, was the reaction blocked by injection of phentolamine or phenoxybenzamine.

** Pimozide was injected 4 h before implantation of morphine or apomorphine into the ventral thalamus.

† Morphine (10 mg/kg i.p.) or apomorphine (2.5 mg/kg s.c.) were injected 4 h after pimozide.

†† Three rats showed a tendency to keep the wire net in their mouth, but did not gnaw.

§ Pimozide was injected in two portions of 4 mg/kg each, 22 and 4 h before subcutaneous injection of apomorphine.

conversion of tyrosine to DOPA (Corrodi & Hanson, 1966), was given i.p. one to three times, each single dose amounting to 100 mg/kg, during the day preceding implantation into the thalamus. The inhibitor considerably reduced the percentage of rats responding to morphine, but had no influence on the effect of apomorphine.

α-Methyldopa, an inhibitor of dopa decarboxylase, was given by single intraperitoneal injection 0-3 h before implantation. Doses of 200 mg/kg or more reduced the percentage of animals that gnawed after morphine application, but again no measurable effect was found against apomorphine.

Disulfiram, an inhibitor of dopamine-β-hydroxylase, reduced the effect of intrathalamic morphine considerably, especially when given in repeated doses (e.g. 200 mg/kg subcutaneously, 4 and 2 h before implantation). However, the action of apomorphine was not altered.

p-Chlorophenylalanine reduces or abolishes the analgesic action of morphine (Tenen, 1968; Major & Pleuvry, 1971). This amino acid was ineffective with respect to gnawing, evoked by the alkaloid.

Antagonistic effect of nalorphine

Many symptoms of morphine action can be weakened or suppressed by its antagonist, nalorphine. This is also true for the gnawing response, studied in the present experiments. Nalorphine was injected subcutaneously 20-30 min after intensive gnawing had been started by morphine implantation; this activity was stopped within a few min by a dose of nalorphine (10 mg/kg) (Table 4). After an interval of about 2 h, many of the animals began to gnaw again. The antagonist had no influence on the response to apomorphine.

Influence of systemic morphine and similar drugs on the gnawing response

It has been mentioned before that moderate doses of morphine (10 mg/kg), injected intraperitoneally, cause gnawing in rats. However, five times larger doses markedly reduced the compulsive gnawing, following thalamic implantation of the alkaloid (Table 4); a similar dose of pethidine subcutaneously abolished the response altogether. Peripheral application of morphine or pethidine also suppressed the reaction to intrathalamic apomorphine completely (Table 4).

Synergism of morphine and amphetamine (Table 5)

The foregoing results indicate that the gnawing

Table 3 Effect of inhibitors of catecholamine synthesis on gnawing evoked by thalamic implantation of drugs.

Inhibitor	*Dose (mg/kg)*	*Route of application*	*Latency of action (h)*	*No. of rats gnawing/ no. of rats used*
(1) Bilateral implantation of 65 μg morphine				
α-Methyltyrosine	100*	i.p.	1-6	4/12
methyl ester	200*, **	i.p.	1-5	3/12
	300*, **	i.p.	1-6	2/6
α-Methyldopa	200†	i.p.	1-4	4/12
	400†	i.p.	1	2/10
	800††	i.p.	2	1/10
Disulfiram	400§	s.c.	2	2/6
	400§§	s.c.	2	8/20
(±)-*p*-Chloro-phenylalanine	300/	oral	–	11/11
(2) Bilateral implantation of 100 μg apomorphine				
α-Methyltyrosine methyl ester	300*, **	i.p.	–	7/7
α-Methyldopa	400¶	i.p.	–	10/10
Disulfiram	400§§	s.c.	0.3	8/10

* Injected on the day before implantation.
** In single doses of 100 mg/kg, spread over a period of 12 hours.
† Simultaneously with implantation.
†† In two doses of 400 mg/kg each, three and zero h before implantation.
§ A single injection was given 4 h before implantation.
§§ Two injections of 200 mg/kg each, 4 and 2 h before implantation.
/ Three gavages of 100 mg/kg each, spread over 12 h on the day preceding implantation.
¶ Three hours before implantation.

response to intrathalamic morphine may be mediated by release of catecholamines. Amphetamine, when injected subcutaneously, also evokes stereotyped behaviour (Fog, 1970). We have been able to demonstrate a synergism of morphine, deposited in the thalamus, and (+)-amphetamine, injected peripherally. A dose of (+)-amphetamine (3 mg/kg) subcutaneously alone had no effect in our strain of rats, while bilateral implantation of morphine (50 μg) caused gnawing in about 30% of the animals (Table 1). Combination of these two doses raised the response to 100%. Similarly, deposits of 30 μg of morphine caused gnawing in about 25% of the animals, but combination of these implants with (+)-amphetamine (3 mg/kg) raised the response to 60%. An analogous synergism was observed for the combination of methadone implants with injections of (+)-amphetamine (Table 5).

Discussion

In the corpus striatum, the globus pallidus appears to be more sensitive to local application of apomorphine than the caudate nucleus or the putamen. This agrees in a general way with the conclusions of Wolfarth, Grabowska, Lacki, Dulska & Antkiewicz (1973) that the globus pallidus is mainly responsible for stereotyped behaviour after apomorphine. Morphine proved moderately effective when implanted into the globus pallidus, but did not evoke gnawing in the other parts of the corpus striatum.

Table 4 Effect of morphine and related compounds on gnawing, evoked by intrathalamic application of drugs.

Drug injected	*Dose (mg/kg)*	*Route of injection*	*Latency of action (min)*	*No. of rats gnawing/ no. of rats used*
(1) Bilateral deposition of morphine (65 μg)				
Nalorphine	5	s.c.	1-5	10/16*
	10	s.c.		0/8**
Morphine	20	i.p.	15-30	6/11†
	50	i.p.		3/9††
Pethidine	50	s.c.	5-15	0/6§
(2) Bilateral deposition of apomorphine (100 μg)				
Nalorphine	5	s.c.	–	13/13
	10	s.c.	–	7/7
Morphine	20	i.p.	5-10	5/5
	50	s.c.		0/10§§
Pethidine	50	s.c.	15	0/8//

* Two of the 6 rats which stopped gnawing, started again after 2 hours.
** All 8 rats resumed gnawing about 2 h after nalorphine injection.
† All 5 rats, which stopped gnawing, resumed this activity 1-2 h later.
†† Two of the 6 rats which ceased to gnaw, started again after 3.5 and 4 h, respectively.
§ Three rats resumed gnawing after several hours.
§§ Eight out of these 10 animals started again to gnaw 1.5-3 h after morphine injection.
// Five out of the 8 rats resumed gnawing 2-2.5 h after pethidine application.

Table 5 Synergism between drugs, deposited in the thalamus, and subcutaneous injections of (+)-amphetamine

Drug implanted	*Amount (μg)*	*Interval* (h)*	*(+)-Amphetamine (mg/kg)*	*Latency** (min)*	*No. of rats gnawing/ no. of rats used*
Morphine	30	1	3	45-60	12/20
	50	1	1	30-180	8/10
		1	2	30-180	9/10
		1	3	30-60	10/10
Methadone	65	0.5	3	25-300	8/29
	65	0.5	6	45-60	10/11

* Time elapsing between implantations and subcutaneous injection of (+)-amphetamine.
** Time elapsing from injection of (+)-amphetamine to onset of gnawing.

The present experiments reveal a second cerebral region from which compulsive gnawing can be evoked in the rat. Both apomorphine and morphine proved more effective when deposited in the ventral thalamus than in the corpus striatum.

However, the two alkaloids evoke gnawing by different mechanisms. The effect of apomorphine is due to direct stimulation of dopamine receptors (Ernst, 1965; Pinder, Buxton & Green, 1971). The action of morphine, however, cannot be a direct one. The response to this drug is reduced or suppressed not only by agents which block catecholamine receptors, like chlorpromazine, haloperidol or pimozide, but also by antagonists, which inhibit certain steps in the biosynthesis of catecholamines. Thus it is indicated that morphine acts via the release of catecholamines.

The similarity of action of morphine and methadone has been demonstrated by Sasame, Perez-Cruet, Dichiara, Tagliamonte, Tagliamonte & Gessa (1972) and by Kuschinsky & Hornykiewicz (1972). The present results show that both drugs are antagonized by a variety of blocking agents in a parallel fashion.

We found that pethidine, when implanted into the thalamus, did not evoke gnawing. It should be recalled that fundamental differences between pethidine on one hand and morphine or methadone on the other have been observed for other pharmacological actions. Thus only pethidine blocks the monoaminergic membrane pump (Carlsson & Lindquist, 1969) and causes severe toxic reactions when combined with monoamine oxidase inhibitors (Shee, 1960; Penn & Rogers, 1971).

On the other hand, subcutaneous pethidine suppresses the gnawing, evoked by thalamic deposits of apomorphine or morphine. In this respect, the action of pethidine resembles that of morphine, injected peripherally (Table 4). It is known that gnawing, evoked by systemic application of apomorphine, is suppressed either by morphine or pethidine (Ther & Schramm, 1962). Thus systemic morphine and pethidine can activate a brain mechanism inhibiting gnawing, similar to their antagonistic effect on vomiting in mammals.

Dahlström & Fuxe (1965) describe a dense network of catecholaminergic nerve terminals in the nucleus ventralis anterior of the rat thalamus. In the adjacent regions of the thalamus, comprising the nucleus ventralis and lateralis thalami and the nucleus dorsalis anterior thalami, catecholaminergic elements are distributed only sparsely. At present, a detailed localization of the elements responsible for the gnawing effect of apomorphine and morphine implants in the ventral thalamus is not possible.

The indirect effect of intrathalamic morphine and methadone may be mediated by noradrenaline or dopamine. The lack of action of α-adrenoceptor blocking agents and the efficacy of haloperidol and pimozide (Table 2) point to dopamine as the mediator for morphine-induced gnawing. On the other hand, the considerable inhibition of this response by disulfiram supports the involvement of noradrenaline. Possibly both transmitters participate in morphine-induced gnawing (Ayhan & Randrup, 1972).

The long latency of the gnawing response, observed in the present experiments, requires explanation. Although biting is one of the symptoms of the first period of general excitation, in addition to sniffing, running, turning and convulsing, pure gnawing activity becomes manifest only in the second phase, i.e. 2-3 h after implantation. This delay cannot be ascribed to slow diffusion because apomorphine, with a molecular weight only slightly less than that of morphine, acts much faster than the latter, when implanted into the ventral thalamus (see Table 1). Furthermore, the initial excitatory signs of morphine action appear after a latent period of only 30-60 minutes. A relatively long latency of the gnawing response is also observed after intraperitoneal injections of morphine (Table 1). This delay is therefore characteristic for morphine-induced gnawing in general and may be related to the turnover of catecholamines: increased release of catecholamines (in the first phase) stimulates their biosynthesis. This 'metabolic' effect of morphine is delayed, as was demonstrated by Clouet & Ratner (1970) and by Fukui, Shiomi & Takagi (1972).

The delayed gnawing response to morphine resembles similar observations with subcutaneous application of amphetamine to the rat (Menge & Brand, 1971). Here again an excitatory phase precedes stereotypy, the latter developing fully only 2 h after injection.

The gnawing activity, evoked by morphine implants, is stopped rapidly by nalorphine injection, while this drug does not influence the apomorphine-induced response (Table 4). Presumably, nalorphine blocks the presynaptic 'receptor', responsible for morphine action (Albus, Schott & Herz, 1970).

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