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Involvement of Caudate Nucleus, Amygdala or Reticular Formation in Neuroleptic and Narcotic Catalepsy

ROBIN DUNSTAN, CHRIS L. BROEKKAMP AND KENNETH G. LLOYD[1]

Synthélabo-L.E.R.S., Department of Neuropharmacology, 31, Avenue Paul Vaillant Couturier, 92220 Bagneux, France

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DUNSTAN, R., C. L. BROEKKAMP AND K. G. LLOYD. *Involvement of caudate nucleus, amygdala or reticular formation in neuroleptic and narcotic catalepsy.* PHARMAC. BIOCHEM. BEHAV. 14(2) 169–174, 1981.—Local injection of haloperidol into the caudate nucleus produced catalepsy in contrast to the weak effects of morphine injected at the same site. Injection of either haloperidol or morphine into the amygdala did not have any cataleptogenic effect. Both haloperidol and morphine produced catalepsy when injected into the reticular formation. Naloxone injected into the reticular formation completely reversed the catalepsy following intraperitoneal morphine but not haloperidol. Pretreatment with α-methyl-p-tyrosine potentiated the effect of haloperidol injected into either the reticular formation or caudate nucleus. Phentolamine but not lignocaine or metergoline, injected into the reticular formation also caused a cataleptic response. The results confirm the caudate nucleus as a site for haloperidol catalepsy and in addition, suggest the reticular formation as a primary site for morphine catalepsy and a secondary site for haloperidol catalepsy; additionally a noradrenergic modulation of catalepsy may occur within this brainstem region.

Catalepsy Morphine Haloperidol Reticular formation Caudate nucleus Amygdala

CATALEPSY, a phenomenon induced by a wide variety of compounds including neuroleptics and narcotics [5] was described as early as 1903 by Mavrojannis [21]. It is now a widely used test for the screening of neuroleptic compounds although the exact mechanism of action is still unclear.

A site in the striatum has been thought to be responsible for the catalepsy induced by neuroleptic drugs, as suggested by both lesion and local injection studies [9, 11, 12, 18]. Although morphine alters dopaminergic mechanisms in the striatum, consistent with this structure being an anatomical locus for this effect [18,20], the catalepsy induced by morphine was reported to be potentiated by lesions of the striatum [5,18]. This suggests that the striatum might not be the only site able to induce a cataleptic response. In fact, further lesion studies of the central nucleus of the amygdala revealed that this nucleus may also play an important role in both neuroleptic and narcotic induced catalepsy [6,7].

Morphine injected locally into other areas such as the nucleus accumbens induces a cataleptic state which is antagonised by the specific morphine antagonists naloxone and nalorphine [4]. However, spread of the drug to lower brain structures via the ventricle can easily occur after accumbens injections. Thus, opiates also elicit depressant effects when injected into sites more caudal than the nucleus accumbens, notably the periaqueductal gray area [3,28] whereas the paragigantocellular region of the reticular formation has been related to morphine analgesia [27].

In the following experiments injections of morphine or haloperidol into various brain structures were carried out in order to delineate the role of these areas in neuroleptic and narcotic catalepsy. We show that structures at the mesencephalic level are not excluded from an important role in the induction of catalepsy.

METHOD

Animals

Male Sprague-Dawley albino rats (180–200 g, CD-COBS strain, Charles River, France) were housed in groups of six until the stereotaxic implantation of guide cannulae, after which the animals were housed individually. All rats were kept under a 12 hr light/dark schedule and were allowed free access to food and water until the time of experimentation in the light portion of the cycle. Animals were adapted to the sound-attenuated experimental laboratory for 1 hour before the experiment. The rats were maintained in their home cages, but without access to food or water during the evaluation of catalepsy.

Intracerebral Injection Technique

Rats were anaesthetised (Brietal, 85 mg/kg, SC) and placed in the stereotaxic instrument with the skull positioned according to König and Klippel [19]. Guide cannulae (23 ga) were of 13 or 15 mm in length with stylets (0.3 mm diameter)

[1]Send reprint requests to: Kenneth G. Lloyd, Synthélabo-L.E.R.S., Department of Neuropharmacology, 31, avenue Paul Vaillant Couturier, 92220 Bagneux, France.

which extend 1 mm below the guide cannulae. The cannulae were implanted and fixed to the skull using Sevriton® dental cement and stainless steel screws. Staphylomycine® powder was applied to the wound externally to prevent infection and animals were kept in a warm chamber until completely recovered from the anaesthetic. At least seven days were allowed before experimentation.

Intracerebral injections were made using an injection cannula 16 mm in length with an external diameter of 0.2 mm attached to a 10 μl Hamilton® syringe. Injections were made at a rate of 1 μl/min; the injection cannula was slowly removed and replaced by the stylet at least 30 sec post-injection.

The degree of catalepsy is expressed as a total score (0–6) which was obtained by summing the individual scores obtained in the following tests.

Test 1

The animal was gently removed from its home cage and placed on the workbench. If the animal rested without moving either of its front paws for 10 sec one point was given.

Test 2

The animal was placed on a grid inclined at an angle of 25° with the nose pointing downwards. If the animal rested for 10 sec without moving the front paws one point was given.

Test 3

The rat was next placed with only the front paws resting on a platform 8 cm above the bench. If the animal rested for 10 sec without descending onto the bench or mounting onto the platform one point was given.

Test 4

The rat was returned to its home cage and gently put into the Buddha position [26,29]. This position consists of placing the animal on the back of its tail and haunches such that he sits upright with the forepaws hanging down between the thighs. The corner of the cage was used as a back support. One point was given if the rat stayed in this position for 10 sec, 2 for 30 sec, and 3 for at least 60 sec without moving.

Rats with a maximum catalepsy were also tested for righting reflex. Means and SEM were calculated for each time interval. All statistical comparisons were carried out using the Mann-Whitney U-test [24].

The manipulations involved in these four different tests maintain a certain level of arousal which prevents false positive results due to sedation or myorelaxation. Thus, the first test involves a novel environment where normal animals will immediately begin to explore: in the second test a normal rat, placed on the inclined plane, will either step down or turn and face in an upward direction well within the ten seconds allowed; the third test eliminates any myorelaxant compounds since rats cannot stand solely on their hindlegs; the fourth test gives a good indication of a fairly strong catalepsy as this is a totally unnatural position.

At the end of the experiment rats were deeply anaesthetised with ether and perfused intra-arterially with 20 ml of a 10% formaldehyde-saline solution. The brains were removed and stored in 10% formaldehyde-saline. The placements of the injection cannulae were then confirmed by comparison of the brain sections with the corresponding sections drawn in the atlases of König and Klippel [19] or Pellegrino and Cushman [22]. Cannula placements were as following: N. Amygdala centralis: A=5230; L=3.45; D= −2.6 [19]; Caudate N: A=8536; L=2.2; D= −0.25 [19]; Reticular formation (cannulae at 30° A-P angle): A= −7.48; L=0; D=7.73 [22]. If the cannulae placements deviated more than 0.3 mm from the projected site, the animal was discarded from the experimental group.

TABLE 1

CATALEPSY BY INTRACAUDATE INJECTIONS

Drug	Dose (μg) per side	Vol (μl)	Degree of Catalepsy mean ± SEM
Lactic acid	—	1	0 ± 0 (4)
Haloperidol	10	1	17.6 ± 4.5 (8)
	25	1	34.5 ± 2.1 (8)
Morphine	25	1	7 ± 3 (6)

The degree of catalepsy is expressed as the percent of the theoretical maximum cumulative catalepsy score over 3 hr period (= 36) for rats bilaterally injected in the caudate nucleus with vehicle, haloperidol or morphine. The numbers in parenthesis represent the number of animals tested.

Animals were tested each 30 min for catalepsy.

Drugs

All doses of drugs refer to the amount of the salt administered.

Morphine chlorhydrate (Bognier), naloxone hydrochloride (Mallet Chemicals), α-methyl-p-tyrosine methylester hydrochloride (Janssen Pharmaceutica) and phentolamine hydrochloride (Ciba-Geigy) were all dissolved in distilled water. Haloperidol (Lebrun) and metergoline (donated by Pharm-Italia) were dissolved in one or two drops of lactic acid and made up to volume with distilled water (final pH 3.5–4.5). Xylocaine® 2% (Lignocaine, Roger Bellon) was injected directly intracerebrally.

RESULTS

Caudate Nucleus Injections

Various doses of morphine, haloperidol or vehicle were injected into the caudate nucleus and catalepsy was measured every 30 min. During the administration of either vehicle or drug solutions a brief period of biting and head nodding was observed, which was probably due to non-specific irritation effects of the injections. After injection of either distilled water or lactic acid, catalepsy was not observed and rats were normally in a sleeping position 30 min after the injection (Table 1). The injection of morphine, 25 μg/μl/side, into the caudate nucleus caused only three out of six animals to be slightly cataleptic (Table 1).

After administration of haloperidol (10 or 25 μg/μl/side) the animals showed prominent signs of catalepsy but gave relatively low scores because they were not able to maintain the Buddha position (Table 1). The onset of maximum catalepsy was approximately one hour after injection with a duration of action lasting at least 7 hours (Fig. 1). Intracaudate injections of haloperidol induced an exaggerated fear response and rats squealed whenever approached with accompanying urination and defaecation, without being touched by the observer. This response was noted after all intra-caudate injections of haloperidol.

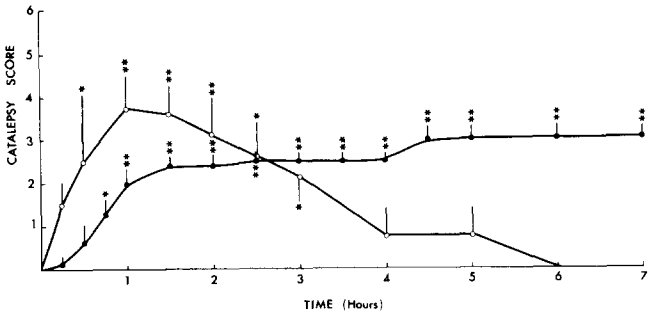

FIG. 1. *Time course of the Catalepsy Induced by the Injection of Haloperidol into the Caudate Nucleus or Reticular Formation.* Haloperidol was injected into the reticular formation (50 μg in 2 μl, 5 rats, open symbols) or caudate nuclei (25 μg in 1 μl in each side, 8 rats, closed symbols) and the catalepsy measured at 30 min intervals thereafter. Each point represents the mean and SEM. Control groups had a score of catalepsy=0 at all time points. Statistical analysis by Mann-Whitney U-test. $*p<0.05$; $**p<0.01$.

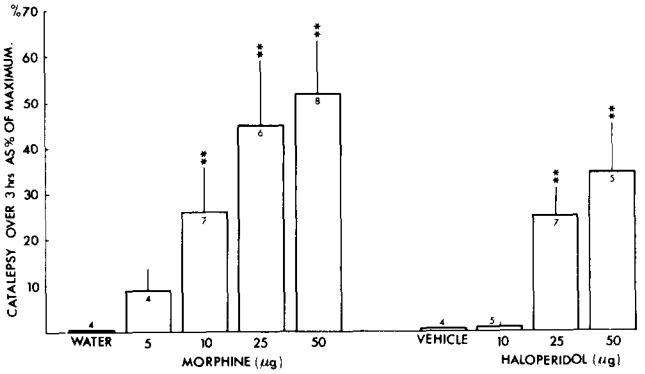

FIG 2. *The Cataleptogenic Effects of Haloperidol or Morphine Injected into the Reticular Formation of Rats.* The ordinate represents the percentage catalepsy which was calculated from the total cumulative catalepsy score in 3 hours as compared to the theoretical maximum. The numbers in the columns indicate the number of animals in each group. $**p<0.01$; Mann-Whitney U-test.

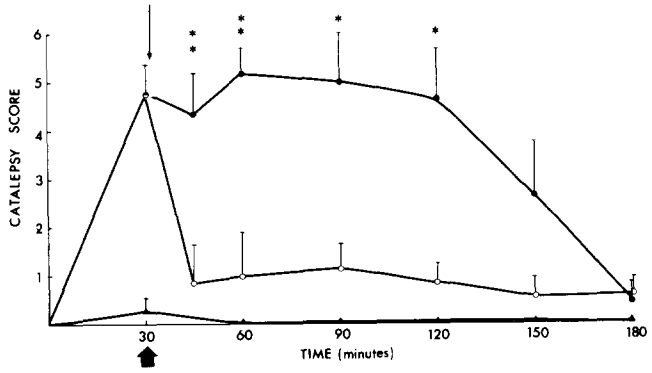

FIG. 3. *Effect of Naloxone Injection into the Reticular Formation on the Catalepsy Induced by the Intraperitoneal Administration of Morphine (25 mg/kg).*/ Rats receiving morphine without naloxone (●) also received 1 μl of distilled water injected into the reticular formation. Rats receiving naloxone without morphine (▲) also received distilled water, 1 ml/kg, IP. Open symbols show rats with naloxone and morphine. Each point represents the mean, with SEM of 6 rats. Statistical analysis by Mann-Whitney U-Test. $*p<0.02$ vs morphine alone; $**p<0.01$ vs morphine alone.

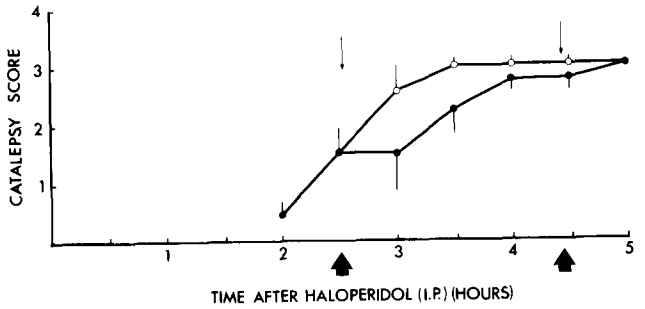

FIG. 4. *Absence of Effect of Naloxone Injected into the Reticular Formation on the Catalepsy Induced by the Systemic Administration of Haloperidol.* Open symbols represent rats treated with haloperidol plus naloxone. Closed symbols represent rats treated with haloperidol plus distilled water. Arrows show injection of naloxone. Points are the mean with SEM of 5 rats.

Central Nucleus of the Amygdala

Injection of either haloperidol (25 μg/μl/side) or morphine (25 μg/μl/side) bilaterally into the central nucleus of the amygdala did not induce any cataleptic responses in any of the rats injected (6 animals per drug).

Reticular Formation

Midline injections into the reticular formation of doses of morphine greater than 5 μg/μl caused a dose-dependent catalepsy; vehicle injection was without significant effect (Fig. 2). The maximum dose of morphine was limited by the solubility of the compound, with 50 μg being administered in 2 μl. The animals with morphine in the reticular formation showed a marked catalepsy but appeared to be devoid of the rigidity noted after the peripheral administration of morphine.

Haloperidol injected into the reticular formation also induced catalepsy (Figs. 1 and 2) with the response to 50 μg in the reticular formation (34.4 ± 9.2% of the maximal response) being equal to the effect of a bilateral injection of 25 μg/side in the caudate nucleus (34.5 ± 2.1% of the maximal response). However, although the total percentage catalepsy was the same for these two sites, the onset and duration of action of haloperidol was very different. Haloperidol in the reticular formation had an immediate onset of action which was finished about 6 hours after injection; in contrast the response after caudate nucleus injections was slow to reach onset and was of a longer duration (Fig. 1).

Morphine administered systemically (25 mg/kg, IP) produced a clearcut catalepsy. Naloxone (10 μg/μl; 30 min post morphine) injected into the reticular formation immediately reversed the cataleptic state (Fig. 3); the rats were seen to "wake up" and started walking around. Injection of naloxone (10 μg/μl) into the reticular formation of control rats was without any notable behavioural effects (Fig. 3). Naloxone injected into the reticular formation was without effect on the catalepsy induced by the systemic administration (1.5 mg/kg, IP) of haloperidol (Fig. 4).

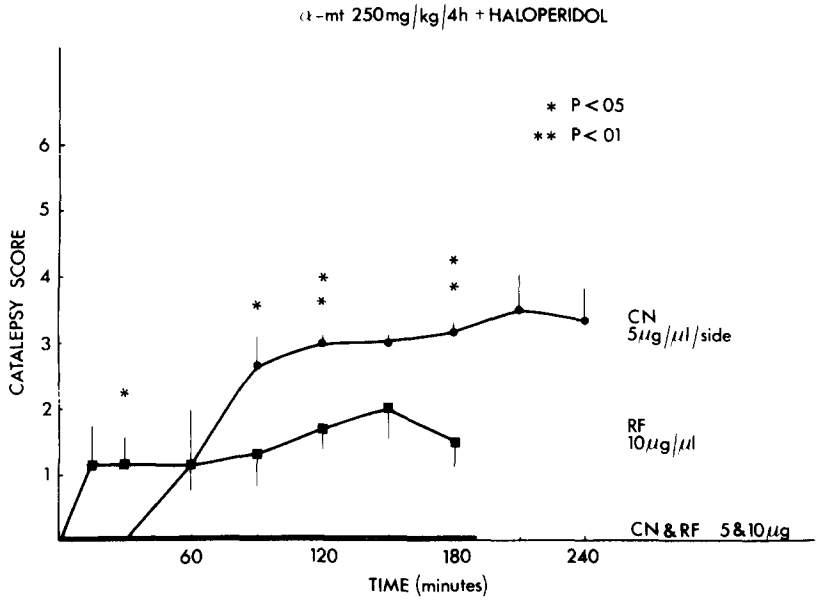

FIG. 5. *Cataleptic Effect of Low Doses of Haloperidol Injected in the Caudate Nucleus (CN) or Reticular Formation (RF) of α-MT Pretreated Rats.* α-MT was administered (250 mg/kg, IP) 4 hours prior to the intracerebral haloperidol injections ($t=0$). Each point represents mean with SEM of at least 6 rats. Statistical significance by the Mann-Whitney U-Test. *$p<0.001$ vs rats with haloperidol alone.

Effect of Alpha-Methyl-p-Tyrosine (αMT)

A dose of 10 μg haloperidol in 1 μl injected in the reticular formation of α-MT pretreated rats (250 mg/kg, IP, 4 hours) gave approximately the same percentage catalepsy as 25 μg haloperidol in 1 μl in the same site of non-pretreated animals (23.67 ± 6.04 and 25.14 ± 5.78%, respectively, Fig. 5). A bilateral injection of 5 μg haloperidol in 1 μl into the caudate nucleus of α-MT treated rats produced the same catalepsy response as haloperidol, 25 μg in 1 μl in the caudates of non-pretreated rats (36.00 ± 3.04 and 34.5 ± 2.1%, respectively). Thus, α-MT potentiates the catalepsy induced by haloperidol injections in both the reticular formation and the caudate nucleus (Fig. 5). As a control, rats were pretreated (4 hours) with distilled water (2 ml/kg) and then were administered (in 1 μl) either 10 μg haloperidol into the reticular formation or 5 μg bilaterally into the caudate nucleus. Neither of these treatments were cataleptogenic (Fig. 5).

In addition to DA receptor blockade, other mechanisms could play a role in the cataleptogenic action of haloperidol. Therefore, metergoline, a serotonin antagonist [2], lignocaine, a potent local anesthetic, or phentolamine, an α-adrenergic antagonist, were injected into the reticular formation.

Neither metergoline (25 μg in 1 μl), nor lignocaine (40 μg/2 μl) caused any observable effects when injected into the reticular formation. However phentolamine (25 μg/2 μl) injected into the reticular formation caused a clear cataleptic response (Fig. 6). This effect of phentolamine paralleled that of haloperidol injected into the same site (Fig. 6).

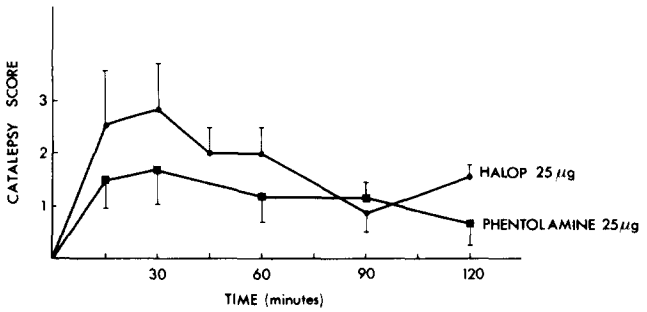

FIG. 6. *Catalepsy Induced by Phentolamine (25 μg in 2 μl) in the Rat Reticular Formation: Comparison with Haloperidol (25 μg in 1 μl, Halop).* Each point represents the mean ± SEM of 6 rats. The animals were significantly cataleptic ($p<0.02$) at all time intervals from 15–90 minutes. The difference between the two groups was not statistically significant.

DISCUSSION

Catalepsy and the Caudate Nucleus

This large nucleus contains high concentrations of both dopamine and opiate receptors. The role of the dopamine receptors appears to be related to motor phenomena as shown by stereotyped behaviour after receptor stimulation and catalepsy after receptor blockade [9, 10, 13, 14]. In this context it appears surprising that rather high doses of haloperidol injected directly into the caudate (25 μg/μl bilaterally) are needed to produce catalepsy; however, similar findings have been previously reported [9]. This suggests that blockade of DA receptors near the site of injection in the caudate is not sufficient to attain a maximal catalepsy. A possible explanation is that those DA receptors within the caudate nucleus that are too distant from the injection site to be affected by the drug can attenuate the effect by mediating a compensatory activation, e.g., by an increased nigrostriatal impulse flow. An alternative possibility is that DA (or

other) receptors in extra-striatal brain structures also play a role in neuroleptic induced catalepsy.

Inhibition of catecholamine synthesis by α-MT leads to a potentiation of the cataleptogenic effect of systemic haloperidol injection [8]. In the present study, the local injection of haloperidol into the caudate was also potentiated by α-MT pretreatment, demonstrating that when whole brain catecholamine synaptic activity is diminished the effects of intrastriatal DA receptor blockade are augmented. It is possible that this effect of α-MT on the cataleptic response is not localized entirely in the caudate nucleus. Interference with catecholaminergic transmission in extra-striatal brain structures may be important for the induction of maximal haloperidol catalepsy. Although other structures may participate in haloperidol catalepsy, the caudate nucleus still appears to be a primary site of action, as demonstrated by the durability of the time course of the catalepsy after intracaudate or intraperitoneal administration.

Although evidence points to the caudate nucleus as being an important site for neuroleptic-induced catalepsy, such does not appear to be the case for morphine-induced catalepsy. In the present experiments injections of morphine of up to 25 μg in each caudate nucleus did not induce a significant cataleptic response. Costall, Fortune and Naylor [4] found similar results after injection of morphine into the anterior portion of the caudate nucleus.

Catalepsy and the Amygdala

It has been reported that lesions of the central nucleus of the amygdala lead to a reduction of morphine and haloperidol-induced catalepsy [6,7]. However, the present results show that local injections of haloperidol or morphine into the nucleus do not result in catalepsy. Therefore the central nucleus of the amygdala does not seem to be a primary site for narcotic or neuroleptic catalepsy.

Catalepsy and the Reticular Formation

Autoradiographic studies [1] have shown the reticular formation and periaqueductal gray to contain moderate concentrations of opiate receptors and both areas have been implicated in morphine analgesia [16, 17, 25, 27]. These regions also seem important for narcotic catalepsy as the present studies have shown that local injection of morphine into the reticular formation produces catalepsy. A dose of at least 5 μg was needed to induce catalepsy. This relatively high dose is in proportion to the high dose required to induce catalepsy after systemic injection (25 mg/kg) of morphine. This high dose excludes a specific delineation of the cataleptogenic site within the reticular formation. For a more precise localization of the site, further scanning studies of the neighbouring areas are required. Injection of naloxone into the reticular formation is able to completely reverse the catalepsy following intraperitoneally administered morphine. This indicates that a site in this area is likely to be an essential link for morphine catalepsy. The similarity between the catalepsy observed after injection of morphine into the reticular formation and that induced by systemic administration of morphine is not complete. Thus, the rigidity which is prominent after systemic morphine administration was lacking after the injection of morphine into the reticular formation. In order to explain the effects of systemically injected morphine, a two-component system can be envisaged: (1) catalepsy, mediated by the reticular formation; (2) rigidity, possibly due to a striatal involvement as previously suggested [15]. This can incorporate the finding that intrastriatal naloxone reverses catatonia in approximately 50% of rats previously systemically injected with morphine [30].

The doses of haloperidol which induced catalepsy were similar for both intra-caudate and intra-reticular formation injections. This finding was unexpected since dopamine receptors (as indicated by ^{3}H-spiroperidol binding) are almost undetectable in the reticular formation [23]. Although DA receptor blockade may be solely responsible for the cataleptogenic response to haloperidol, other effects of the drug may also be important. In addition to being a dopamine-receptor antagonist haloperidol possesses serotonergic antagonist, α-adrenergic antagonist and local anaesthetic properties. From the results with lignocaine and metergoline it appears that neither the local anaesthetic nor the anti-serotonergic properties of haloperidol are involved. However, α-adrenergic receptor antagonism may play a role, as phentolamine injected into the reticular formation induced a clearcut cataleptic response. Therefore in addition to being a site for morphine catalepsy the reticular formation may also be a region for noradrenergic modulation of catalepsy.

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