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Blockade of Apomorphine-Induced Aggression by Morphine or Neuroleptics: Differential Alteration by Antimuscarinics and Naloxone

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GIANUTSOS, G AND H. LAL *Blockade of apomorphine-induced aggression by morphine or neuroleptics differential alteration by antimuscarinics and naloxone* PHARMAC BIOCHEM BEHAV 4(6) 639–642, 1976 – Both morphine and the neuroleptics, haloperidol and oxyperomide, dose-dependently reduce the aggression in rats produced by 20 mg/kg of apomorphine, a dopamine receptor stimulant The narcotic antagonist, naloxone, prevents this effect of morphine but not the effect of neuroleptics Dexetimide, a centrally acting antimuscarinic drug, antagonizes the reduction in aggression produced by the neuroleptics, but does not affect morphine's action The cholinergic agonist, pilocarpine, enhances this action of oxyperomide These results suggest that a cholinergic component contributes to the anti-agression action of neuroleptics and demonstrates a difference in the mechanism of action between neuroleptics and morphine

Apomorphine Morphine Haloperidol Oxyperomide Dopaminergic-cholinergic interaction Aggression

HALOPERIDOL and morphine have in common a number of behavioral and neurochemical effects which are related to the dopaminergic systems in the CNS [9,11] However, the lack of addiction liability of the neuroleptics indicates that there is also a major difference in the actions of these drugs This would suggest that the 2 drugs have dissimilar mechanisms, which may reflect different actions on the manner that dopamine interacts with other neurotransmitters in the brain

It has been demonstrated that the narcotic antagonist, naloxone, reverses the action of morphine in producing catalepsy [8] and inhibiting brain self-stimulation [19], but the similar actions of neuroleptics are unaffected by naloxone Conversely, these effects of haloperidol are antagonized by anticholinergics which do not alter the actions of morphine [3,20]

These earlier studies have dealt with simple behavioral effects of these compounds. In the present study, we decided to investigate the ability of neuroleptics and morphine to antagonize the action of a dopaminergic agonist, apomorphine [1,13], in order to examine their dopamine blocking action. Any differences in the ability of substances to oppose this action of morphine or haloperidol may provide further evidence regarding the mechanism of action of these drugs and may further suggest that a difference in the balance between dopamine and other transmitters accounts for some of the differences between the drugs. Specifically, we investigated the ability of these drugs to antagonize the aggression produced by apomorphine [15] Both compounds have been shown to have antiaggression properties in several models of drug-induced aggression [5,15].

METHOD

Male, Long-Evans rats (375–475 g) were tested for aggression by placing them in groups of 4 in a chamber (23 × 19.5 × 19 5 cm) 5 min after an intraperitoneal injection of 20 mg/kg of apomorphine This dose of apomorphine was chosen from previous experiments in which it was shown to produce maximal aggression [5,11]. The rats were observed for 1 hr during which time 3 parameters of aggression were measured as described by Lal [10]. These were attacks or bites by one animal against another, the duration of aggressive posturing (rearing by pairs of rats), and vocalizations, which were automatically counted by a voice operated relay modified to detect sound in the range of 2400–4800 Hz The reliability of these measures has been demonstrated in several recent reports (see [5,11])

Prior to the injection of apomorphine, one or more of the following drugs were injected haloperidol (courtesy of McNeil Laboratories and Janssen Pharmaceutica), oxyperomide (R4714) (courtesy of Janssen Pharmaceutica), morphine, dexetimide (R16470) (courtesy of Janssen Pharmaceutica), naloxone or saline A series of doses, ranging from ineffective to larger effective doses of all drugs were utilized in this study The volume of injection of all drugs (or saline) was 1 ml/kg in all cases. The drugs were freshly dissolved in saline before use except for haloperidol and oxyperomide which were freshly prepared in dilute tartaric acid.

Morphine and oxyperomide were injected intraperitoneally 45 min before testing, while haloperidol was injected intraperitoneally 2 hr before testing These pretreatment times were based on pilot experiments in which it was determined that the peak drug effect occurred

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TABLE 1

EFFECT OF DRUGS ON APOMORPHINE-INDUCED AGGRESSION*

Drug†	Dose (mg/kg)	N‡	Aggressive Responses/Hour (Mean ± SE/group) Attacks	Rearing	Vocalizations
Vehicle	—	5	61 ± 9	2750 ± 251	2219 ± 204
Haloperidol	0 63	2	59 ± 5	2358 ± 756	1351 ± 97
	1 25	5	28 ± 8§	2358 ± 544	1190 ± 487
	2 5	5	2 ± 2§	89 ± 89§	17 ± 15§
Oxyperomide	1 25	2	52 ± 2	2621 ± 220	889 ± 95
	2 5	5	15 ± 6§	1163 ± 510§	386 ± 148§
	5 0	5	2 ± 2§	33 ± 33§	25 ± 25§
Saline	—	5	58 ± 10	1787 ± 301	1188 ± 252
Morphine	5	5	28 ± 11§	1150 ± 285	702 ± 221
	10	5	1 ± 1§	30 ± 30§	1163 ± 196

*Apomorphine (20 mg/kg) was injected into all groups
†Haloperidol was injected two hours before testing while oxyperomide was injected 40 min before testing
‡Number of groups (four rats per group) tested
§Significantly different ($p<0.05$) from saline control (Dunnet's Test)

after these pretreatments Dexetimide and naloxone were injected subcutaneously, 35 or 10 min before testing, respectively. These pretreatment times were also based on pilot experiments Haloperidol is a well known neuroleptic, while oxyperomide is a neuroleptic agent with little if any cataleptic activity at the doses used in this study (C J. E Niemegeers, personal communication). Dexetimide is a centrally acting anticholinergic drug [7].

The results were analyzed statistically using Dunnet's Test [21]

RESULTS

Following the injection of 20 mg/kg of apomorphine, the rats, as expected, demonstrated a high degree of aggression characterized by long intervals of rearing accompanied by loud vocalization, frequent biting and periods of boxing. These behaviors were antagonized by all 3 of the test compounds utilized in this study Haloperidol was maximally effective at a dose of 2.5 mg/kg, oxyperomide at a dose of 5 mg/kg and morphine at a dose of 10 mg/kg (Table 1)

Naloxone, which had no effect on apomorphine-induced aggression on its own, was able to antagonize the blockade of aggression produced by morphine (Table 2), so that high levels of fighting resulted after the combined administration of morphine + naloxone + apomorphine. However, this narcotic antagonist failed to alter the blockade of aggression produced by haloperidol or oxyperomide.

In contrast to these results, the antimuscarinic compound, dexetimide, partially antagonized the blockade of aggression produced by either neuroleptic (Table 2) The dose of dexetimide which was effective in reversing the neuroleptic effect (2.5 mg/kg) apparently has little, if any, effect on apomorphine-induced aggression on its own (Gianutsos and Lal, in preparation) Larger doses of dexetimide returned the aggression to essentially saline control levels. However, even this large dose of dexetimide was unable to prevent the anti-aggression action of morphine (Table 2).

These results suggested that a cholinergic component contributed to the anti-aggression action of the neuroleptics. In order to test this assumption, a marginally effective dose of oxyperomide (2 5 mg/kg) was combined with a marginally effective dose (2 mg/kg) of the cholinergic drug, pilocarpine (previously determined from pilot experiments) The combination of these 2 drugs markedly reduced the aggression produced by apomorphine (Table 3)

DISCUSSION

The results of this study indicate that the anti-aggression action of neuroleptics and morphine may be differentially antagonized by different compounds Both morphine and the neuroleptics reduced the aggression induced by a large dose of apomorphine. However, naloxone prevented the reduction of apomorphine-induced aggression produced by morphine, but not by haloperidol, while the anticholinergic, dexetimide, reversed the effect of the neuroleptics, but not that of morphine. Previously, it was demonstrated that narcotic antagonists and anticholinergics also differentially antagonize some behavioral effects of narcotics and neuroleptics (see Introduction) It should be pointed out that apomorphine induced aggression was used in this study as a model of dopamine hyperactivity (see [5, 9, 11]) and the results may be not generalized to all forms of aggression.

In the present study, naloxone and dexetimide were shown to selectively antagonize the ability of morphine and neuroleptics, respectively, to counteract the behavioral effects resulting from the administration of a dopamine agonist A reduction of dopamine receptor activation would be consistent with a blockade of apomorphine-induced aggression, since apomorphine is believed to directly stimulate dopamine receptors [1,13] and this form of aggressive behavior appears to be dependent on dopamine activity [4,5] Both neuroleptic drugs [2,12] and morphine [6,14] apparently increase the turnover of dopamine as a consequence of reduced receptor activity, but it would

TABLE 2

REVERSAL OF THE BLOCKADE OF APOMORPHINE-INDUCED AGGRESSION*

Pretreatment Drug	Dose (mg/kg)	Post-Treatment Drug	Dose (mg/kg)	N	Aggressive Responses/Hour (Mean ± SE/group) Attacks	Rearing	Vocalization
Saline	—	Saline	—	5	47 ± 10	1633 ± 315	1119 ± 306
Haloperidol	2 5	Saline	—	3	3 ± 3	71 ± 71	22 ± 23
		Dexetimide	1 25	2	18 ± 4	986 ± 152	583 ± 120
			2 5	6	14 ± 3	571 ± 191	403 ± 109
			5 0	3	45 ± 4	1392 ± 209	1214 ± 342
		Naloxone	4.0	3	0	0	0
Oxyperomide	5	Saline	—	3	0	0	0
		Dexetimide	1 25	4	19 ± 9	615 ± 278	433 ± 207
			2 5	4	20 ± 4	562 ± 118	388 ± 110
			5.0	3	37 ± 13	1087 ± 389	998 ± 303
		Naloxone	4.0	3	0	0	0
Morphine	10	Saline	—	3	0	0	0
		Dexetimide	1 25	3	1 ± 0	6 ± 5	12 ± 9
			2 5	3	0	0	0
			5 0	6	4 ± 2	76 ± 52	101 ± 51
		Naloxone	4 0	5	42 ± 5	1654 ± 384	1163 ± 196
Saline	—	Naloxone	4 0	3	46 ± 5	2189 ± 263	1283 ± 107

*All groups were injected with apomorphine (20 mg/kg) following treatment with other drugs

TABLE 3

EFFECT OF PILOCARPINE PLUS OXYPEROMIDE ON APOMORPHINE*-INDUCED AGGRESSION

Drug	N†	Aggressive Responses/Hour (Mean ± SE/group) Attacks	Rearing (Secs)	Vocalization
Saline	6	53 ± 4	2702 ± 122	1693 ± 221
Pilocarpine‡	6	30 ± 6	1621 ± 334	451 ± 88
Oxyperomide§	6	28 ± 6	1410 ± 434	745 ± 245
Pilocarpine‡ + Oxyperomide§	6	4 ± 3¶	465 ± 307¶	125 ± 94

*20 mg/kg of apomorphine injected into all groups
†Number of groups (4 rats per group) tested
‡2 mg/kg 10 min before testing
§2 5 mg/kg 35 min before testing
¶Significantly different ($p<0$ 05) from pilocarpine or oxyperomide alone (by Test of Individual Comparisons, 21)

appear that the precise mechanism involved is different for these two classes of compounds.

The neuroleptics are believed to directly block dopamine receptors [2,12] and this may account for their ability to reduce apomorphine-induced aggression These drugs also increase the release and turnover of acetylcholine (ACh) as a consequence of dopamine receptor blockade [17,18] Since cholinergic stimulation also reduces apomorphine-induced aggression [5], it is possible that the release of ACh by the neuroleptics contributes to their anti-aggression activity. Indeed, it was shown in this study that combined treatment of oxyperomide and a cholinergic agonist enhanced the anti-aggression property of oxyperomide Thus, anticholinergic drugs may partially reverse the action of the neuroleptics by counteracting the effects of released ACh

The mechanism by which morphine blocks the aggression (and reduces dopamine receptor activity) is unclear, but appears to be different from the action of haloperidol. Morphine may work indirectly via some neuronal effect other than direct receptor blockade, although this conclusion is speculative at this time. In addition, it would appear that ACh is unimportant for this behavioral effect of morphine suggesting that morphine disturbs the normal dopamine/ACh balance in a manner unlike the neuroleptics.

Lastly, it has been demonstrated that antimuscarinic drugs may antagonize some of the clinical therapeutic activity of anti-psychotic drugs [16]. The relevance of the present results in which the anti-aggression action of the neurolpetics is similarly antagonized by anti-muscarinic compounds remains to be established.

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