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ANTAGONISM OF APOMORPHINE-INDUCED PECKING IN PIGEONS

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Central nervous system stimulants, tranquillizers and other central nervous system depressants, antiemetics, antihistamine drugs and autonomic blocking agents were examined for their ability to prevent the pecking response in pigeons induced by apomorphine (250 μg/kg intramuscularly). Reduction in the proportion of positive responses or significant increase in the latent period of pecking were taken as the criterion of effectiveness. Protection was afforded by caffeine, lysergic acid diethylamide, morphine, rauwolscine, triflupromazine and yohimbine. In addition, a significant increase in latent period was produced by artane, pentobarbitone, benactyzine, 2-bromolysergic acid diethylamide, cyclizine, diphenhydramine, ergotoxine, hyoscine, promethazine, 5-(2-chloroethyl)-4-methylthiazole and trimethobenzamide. Most of these drugs influenced the pecking and emetic responses to apomorphine in an identical manner. It is possible that identical receptors may be concerned with apomorphine pecking (in pigeons) and emesis (in other species).

Dhawan & Saxena (1960a, b) showed that apomorphine makes pigeons peck. The latent period, intensity and duration of the response were related to the dose. Neither conditioning nor tolerance was observed on chronic administration. The mechanism of this phenomenon is not known. In the present investigation, various groups of neuropharmacological agents have been screened for their ability to prevent pecking caused by apomorphine in order to find out the probable mechanism of this phenomenon. The drugs tested include central nervous system stimulants, tranquillizers and other central nervous system depressants, antiemetics, antihistamine drugs and antagonists of the autonomic nervous system.

A preliminary report of part of this work was presented before the 1959 Session of the Association of Physiologists and Pharmacologists of India at Poona (Dhawan & Saxena, 1960a).

METHODS

The methods used have been described in a previous paper (Dhawan & Saxena, 1960b). Two hundred and ninety pigeons (weight 200 to 400 g) of either sex were used. The birds were not used more than twice a week. During the period of observation birds were placed separately in small cages in a quiet room and food and water were withdrawn.

Pecking was induced by intramuscular injection of 250 μg/kg (approximately $4 \times$ ED50—Dhawan & Saxena, 1960b) of apomorphine hydrochloride (British Drug Houses). The time elapsing between the drug administration and the injection of apomorphine has been shown with each drug. (See Table 1.) In most cases no data were available regarding the time of

TABLE 1

EFFECT OF DRUGS ON APOMORPHINE-INDUCED PECKING IN PIGEONS

Drugs were given intramuscularly except wherein otherwise indicated. Values of latent period (L.P.) marked with an asterisk (*) differ significantly ($P=0.05$) from the control group values

Drug	No. of birds	Dose (mg/kg)	Apomorphine challenge after	% Positive responses to apomorphine	Mean L.P. in min±s.e.	PD50 in mg/kg±s.e. ($P=0.05$)
No antagonist (apomorphine alone)	60	0		100	4·3±0·2	
CNS stimulants:						
Caffeine citrate	10	6·25	30 min	100	5·2±0·8	
	20	9·0		80	6·6±1·5	16·27±4·98
	10	12·5		60	8·0±1·2*	
	10	25·0		30	9·6±0·1*	
	10	100·0		0	—	
Cocaine hydrochloride	10	3·0	30 min	90	5·3±0·4	
	10	6·0		50	7·2±1·1	6·59±4·2
	10	12·0		10	11·0±0·0*	
	10	24·0		20	10·5±0·5*	
Procaine hydrochloride	10	20·0	30 min	90	6·0±1·5	
5-Hydroxytryptamine	10	0·25	30 min	90	4·8±0·7	
	10	0·5		80	4·2±0·8	
	10	1·0		80	6·6±1·2	
	10	2·0		100	5·9±1·1	
Iproniazid phosphate	10	150·0	2 hr	90	4·3±0·37	
Lysergic acid diethylamide	10	0·025	15 min	70	8·1±2·7	
	10	0·05		60	8·8±2·9	0·052±0·031
	10	0·1		20	5·5±1·6	
	10	0·2		20	5·5±0·7	
2-Bromolysergic acid diethylamide	10	0·2	15 min	70	9·4±1·2*	
	10	0·4		90	7·5±1·0*	
Methylamphetamine hydrochloride	10	2·5	30 min	90	5·3±1·1	
	10	5·0		80	6·6±2·8	
Methylphenidate hydrochloride (oral)	10	5·0	30 min	100	4·5±0·5	
Metrazol	10	25·0	30 min	90	6·0±1·2	
Strychnine sulphate	10	0·5	30 min	100	5·8±0·7	
Tranquillizers:						
Azacyclonol hydrochloride (oral)	10	20·0	30 min	100	6·7±0·05	
	10	50·0		80	4·0±0·4	
	10	100·0		100	5·6±0·7	
Benactyzine hydrochloride	10	3·0	30 min	90	13·3±1·9*	
	10	6·0		70	8·5±2·0	
Chlorpromazine hydrochloride	10	1·0	30 min	80	6·6±1·1	
	10	5·0		50	8·2±1·1*	4·44±2·56
	10	10·0		20	7·0±0·0*	
	10	25·0		20	4·5±1·5	
Hydroxyzine hydrochloride	10	10·0	30 min	100	3·2±0·54*	
Meprobamate (oral)	10	10·0	30 min	100	3·2±0·17*	
[illegible]	10	0·5	30 min	100	3·6±0·21*	

Levorphanol tartrate	10	2·0	30 min	90	7·8±1·3*	
Mephenesin	10	50·0	30 min	90	4·1±0·4	
Methylpentynol carbamate (oral)	10	25·0	30 min	90	3·1±0·2	
Morphine tartrate	10	1·0	30 min	90	5·5±0·8	
	10	5·0		60	7·7±1·4	
	10	10·0		60	10·3±2·3*	17·24±0·17
	10	20·0		60	10·0±0·9	
	10	40·0		30	8·0±1·8	
Nalorphine hydrochloride	10	10·0	30 min	90	7·0±0·5*	
	10	15·0		90	3·2±0·3*	
Phenobarbitone sodium	10	25·0	30 min	90	3·8±0·5	
5-(2-Chloroethyl)-4-methylthiazole	10	40·0	30 min	90	9·9±2·0*	
Trimethadione	10	200·0	1 hr	100	4·2±0·5	
Antiemetics:						
Promethazine theoclate (oral)	10	25·0	30 min	90	3·8±0·5	
Cyclizine hydrochloride (oral)	10	50·0	3 hr	100	2·5±0·59	
		100·0		100	9·9±1·5*	
Hyoscine hydrobromide	10	2·0	30 min	80	11·6±3·1*	
	10	4·0		90	7·6±1·8	
Prochlorperazine hydrochloride	10	0·38	30 min	60	8·3±1·9	
	10	0·75		30	9·0±2·2*	0·45±0·35
	10	1·5		20	9·0±3·0	
	10	3·0		10	32·0±0·0*	
Trimethobenzamide hydrochloride	10	20·0	30 min	80	8·0±0·3*	
	10	40·0		90	8·0±1·4	
Trifluprομazine hydrochloride	10	0·25	30 min	80	7·0±1·7	
	10	0·50		40	8·0±1·2*	0·51±0·3
	10	1·0		30	14·3±3·8*	
Antihistaminics:						
Diphenhydramine hydrochloride (oral)	10	25·0	30 min	90	7·0±1·9	
Promethazine hydrochloride	10	25·0	30 min	100	10·5±1·3*	
Triprolidine hydrochloride (oral)	10	5·0	30 min	100	4·9±2·1	
Autonomic blocking agents:						
Benzhexol hydrochloride	10	2·0	30 min	80	5·25±1·0	
	10	6·0		70	13·8±2·6*	
Atropine sulphate	10	3·0	30 min	90	5·5±1·2	
Hyoscine butylbromide	10	10·0	30 min	100	6·6±1·2	
Dihydroergotamine methanesulphonate	10	0·5	30 min	100	4·9±0·6	
Ergotoxine ethanesulphonate	10	0·5	30 min	100	4·9±1·7	
Rauwolscine hydrochloride	10	0·3	30 min	100	5·2±0·6	
	10	0·4		80	4·0±0·7	0·51±0·11
	10	0·5		50	6·0±2·0	
	10	0·6		10	10·0±0·0*	
Yohimbine hydrochloride	10	0·15	30 min	90	4·5±1·2	
	10	0·30		50	6·5±1·2	
	10	0·6		20	5·5±2·6	0·32±0·11
	10	5·0		0	—	

peak action of a particular drug in pigeons. Hence the time at which the peak of other actions (mostly observed in other species) has been reported in literature was used in the present investigation. It is, however, possible that in certain cases apomorphine challenge may not have coincided with the peak effect of the drug. Similarly, the dose levels of various drugs tested were chosen on the basis of doses employed by various workers for other effects in pigeons or in other species (if data for pigeons were not available). The birds were observed for at least 1 hr after apomorphine injection. Only birds pecking more than 10 times during this period (Dhawan & Saxena, 1960b) were considered to be responding to the apomorphine challenge. In these cases the latent period was the period elapsing between apomorphine administration and the first act of pecking. In addition birds were also observed for any signs of neurotoxicity, such as excitement, sedation, or ataxia.

Drugs to be tested were administered intramuscularly (aqueous solution) in the pectoral muscles or orally by allowing a suspension (in 4% homogenized gum acacia solution) to drop in the mouth from a tuberculin syringe. Each dose was tested in one batch of ten pigeons. Since it was not feasible to determine accurately the duration of pecking or to assess its intensity quantitatively, the effect of a drug was assessed on the basis of changes in the latent period of pecking and in % positive responses to apomorphine. If a drug gave protection, graded doses were given and at least three points were obtained between levels of 100% protection and no protection. Regression lines were then obtained by the method of Bliss (1935a, b, c). The lines were tested for goodness of fit by the χ^2 test as described by Finney (1952) and PD50 (dose protecting 50% pigeons from the effect of apomorphine) values along with their standard errors ($P=0.05$) calculated. The significance of drug-induced alteration in latent period was decided by the "Standard Error of the Mean" method of Tippet (1925), at 95% confidence level ($P=0.05$).

RESULTS

Six groups of 10 pigeons each received apomorphine (250 μg/kg) alone. These groups were tested between the various groups treated with additional drugs and a 100% pecking response was obtained with a mean latent period of 4.3 ± 0.2 (s.e.) min.

Central nervous system stimulants

Eight stimulants, caffeine citrate, cocaine hydrochloride, iproniazid phosphate, lysergic acid diethylamide, methylamphetamine hydrochloride, methylphenidate hydrochloride, metrazol and strychnine sulphate, were studied. In addition 5-hydroxytryptamine creatinine sulphate (serotonin) and 2-bromolysergic acid diethylamide were also included because of their possible significance in activity of the brain, and procaine hydrochloride for comparison with cocaine. The results have been summarized in Table 1. Protection was afforded by caffeine, cocaine and lysergic acid diethylamide. Procaine was ineffective (Table 1). Three drugs, 2-bromolysergic acid diethylamide, caffeine and cocaine, significantly prolonged the latent period (Table 1). The pigeons treated with 0.1 and 0.2 mg/kg lysergic acid diethylamide were sedated. Similar observations with this drug have also been reported by Hoffman (1958). Pigeons receiving 5 mg/kg methylamphetamine were very much excited, as evidenced by excessive movements inside the cage, fluttering of feathers and increased head movements. Larger doses, therefore, could not be used. Similarly 20% of the pigeons treated with 2 mg/kg serotonin died, precluding the testing of larger doses.

Tranquillizers

Six drugs, azacyclonol hydrochloride, benactyzine hydrochloride, chlorpromazine hydrochloride, hydroxyzine hydrochloride, meprobamate and reserpine phosphate, were tested. The results are shown in Table 1. Protection was afforded by chlorpromazine. Some protection was afforded by benactyzine in doses tested. Larger doses of benactyzine could not be tested because pigeons appeared confused and excited even with the 6 mg/kg dose. Thus many pigeons tried to escape out of the cage even though the cage was closed. This behaviour was not seen with other agents even though the pigeons were excited, and was probably an indication of the confusion produced by benactyzine. A significant decrease in latent period was produced by reserpine, hydroxyzine and meprobamate; chlorpromazine and benactyzine significantly increased it, while azacyclonol was without effect. Birds treated with larger doses of chlorpromazine and azacyclonol were unduly sedated. Occasional pecking (never more than 10 times during the observation period) was seen in some of the birds treated with benactyzine.

Other central nervous system depressants

Hypnotics. Methylpentynol carbamate, phenobarbitone sodium, pentobarbitone sodium and methyl-4β-chlorethyl-5 thiazol (Charonnat, Lechat & Chareton, 1953) were screened. Some protection was afforded by pentobarbitone (10 mg/kg), methylpentynol and methyl-4β-chlorethyl-5 thiazol at neurotoxic dose levels (Table 1). Phenobarbitone failed to protect even at neurotoxic dose levels (25 mg/kg, Table 1). Ataxia was the main neurotoxic manifestation in all the cases. The pigeons were unable to maintain the posture and frequently fell on their sides. Further, they staggered while moving inside the cage. Latent period was significantly increased by neurotoxic (ataxic) doses of all the agents except methylpentynol, which decreased it. While the increase in latent period may be due to ataxia produced by these drugs, it is difficult to explain the decrease produced by methylpentynol.

Analgesics. Morphine tartrate, levorphanol tartrate and nalorphine hydrochloride were tested. Protection was afforded by morphine (PD50: 17.24 ± 0.17 mg/kg). The pigeons were very much sedated with 2.0 mg/kg levorphanol, thereby preventing the testing of larger doses. All the agents significantly increased the latent period for pecking (Table 1).

Two anticonvulsants (diphenylhydantoin sodium and trimethadione) and one internuncial blocking agent (mephenesin) were also included in the study, but none of them gave any protection.

Antiemetic drugs. Apomorphine-induced pecking in pigeons has some resemblance with apomorphine-induced vomiting in other species. For example, both have a short latent period and both can be produced by minute amounts of apomorphine. To investigate this similarity further, a number of antiemetic agents were tested for their ability to antagonize this pecking. The drugs tested were cyclizine hydrochloride, hyoscine hydrobromide, prochlorperazine hydrochloride, promethazine theoclate (Avomine), trimethobenzamide hydrochloride (Tigan) (Schallek, Heise, Keith & Bagdon, 1959) and triflupromazine hydrochloride. In addition chlorpromazine (considered with tranquillizers) is also an antiemetic agent.

Protection was afforded by chlorpromazine (*vide supra*), prochlorperazine (PD50: 0.65 ± 0.34 mg/kg) and triflupromazine (0.7 ± 0.3 mg/kg). Koster (1957) reported a reduction in the intensity of pecking by 75 mg/kg cyclizine orally. However, no appreciable alteration in intensity was seen in the present investigation even after 100 mg/kg dose. Birds receiving 4.0 mg/kg hyoscine were very much excited.

Antihistamine drugs

Many antihistamine agents antagonize apomorphine vomiting in animals (Boyd, Cassell, Boyd & Miller, 1955). As some antiemetic agents could block apomorphine-induced pecking some antihistamines were tested. Diphenhydramine hydrochloride, promethazine hydrochloride and triprolidine hydrochloride (Actidil) were tested. None of the agents afforded significant protection (Table 1). The latent period was increased by promethazine (cf. effect of other phenothiazines—*vide supra*).

Antagonists of the autonomic nervous system

Antiadrenergic drugs. Ergotoxine (Hatcher & Weiss, 1923) and dibenamine (Freedman & Giarman, 1956) are known to antagonize vomiting induced by apomorphine. Hence 4 antiadrenergic drugs, dihydroergotamine methanesulphonate, ergotoxine ethanesulphonate, rauwolscine hydrochloride and yohimbine hydrochloride, were studied. Protection was afforded by rauwolscine ($PD50 = 0.51 \pm 0.01$) and yohimbine ($PD50 = 0.32 \pm 0.11$). Ergotoxine produced a significant increase in the latent period (see Table 1) only.

Anticholinergic drugs. Bernheim & Bernheim (1936) and Kuhn & Surles (1938) have shown that apomorphine has a high anticholinesterase activity. To investigate a possible cholinergic mechanism of pecking 5 cholinergic antagonists, atropine sulphate, benactyzine hydrochloride, hyoscine butylbromide (Buscopan), hyoscine hydrobromide and benzhexol hydrochloride (Artane), were tested. Two of these agents have already been mentioned, benactyzine as a tranquillizer and hyoscine as an antiemetic. None of the agents tested afforded protection. Latent period was significantly prolonged by artane, benactyzine and hyoscine.

DISCUSSION

It is difficult to localize the site or mechanism of this effect of apomorphine in pigeons on the basis of the present results. It might be some sort of feeding hallucination (Koster, 1957), but, as pointed out in a previous communication (Dhawan & Saxena, 1960b), it is not produced by other hallucinogenic agents. Again, it cannot be blocked by azacyclonol—believed to be a specific antihallucinogenic drug (Brown, Feldman & Braun, 1955)—in the doses tested (see tranquillizers).

The results show that protection is afforded by caffeine, chlorpromazine, cocaine, lysergic acid diethylamide, morphine, rauwolscine, trifluprazine and yohimbine. It is interesting to note that 2-bromolysergic acid diethylamide, which does not share the central action of lysergic acid diethylamide (Rothlin, 1957), is ineffective. Similarly, it fails to block apomorphine-induced emesis in dogs (Dhawan & Gupta, 1960b) which is antagonized by lysergic acid diethylamide (Dhawan & Gupta, 1960a). It is not possible to correlate the anti-pecking effect

TABLE 2

CORRELATION BETWEEN EFFECT OF DRUGS ON APOMORPHINE-INDUCED PECKING AND EMESIS

+ indicates blockade, − no blockade, ± only latent period prolonged (pecking) or inconclusive results (emesis), and ? effect not studied so far.

Drug	Blockade of pecking	Blockade of emesis	Reported by
Chlorpromazine	+	+	Brand, Harris, Borison & Goodman, 1954
Lysergic acid diethylamide	+	+	Dhawan & Gupta, 1960a
Morphine	+	+	Hatcher, 1924
Prochorperazine	+	+	Boyd & Cassell, 1957
Triflupromazine	+	+	Piala, High, Hassert, Burke & Craver, 1959
Cocaine	+	?	
Caffeine	+	?	
Rauwolscine	+	?	
Yohimbine	+	?	
Atropine	—	—	Eggles ton, 1916
Azacyclonol	—	—	Boyd& Cassell, 1957
2-Bromolysergic acid diethylamide	±	—	Dhawan & Gupta, 1960b
Hyoscine	±	—	Boyd and Cassell, 1957
Cyclizine	±	+	Koster, 1957
Diphenhydramine	±	+	Boyd, Cassell, Boyd & Miller, 1955
Ergotoxine	±	+	Hatcher & Weiss, 1923
Methylamphetamine	−	+	Boyd & Cassell, 1957
Promethazine	±	+	Boyd & Cassell, 1957
Reserpine	−	±	Malhotra & Sidhu, 1956 Ballinger & Borison, 1957
Trimethobenzamide	±	+	Schallek, Heise, Keith & Bagdon, 1959

TABLE 3

LACK OF CORRELATION BETWEEN EFFECTS OF DRUGS ON LATENT PERIOD FOR PECKING AND PROTECTION AFFORDED BY THEM

+ indicates significant increase of latent period/protection ; − a significant decrease in latent period ; and 0 no effect.

Agent	Effect on latent period	Protection
Benzhexol	+	0
Benactyzine	+	0
Caffeine	+	+
Chlorpromazine	+	+
Cocaine	+	+
Cyclizine	+	0
Ergotoxine	+	0
Hydroxyzine	−	0
Hyoscine	+	0
Levorphanol	+	0
Lysergic acid diethylamide	0	+
2-Bromolysergic acid diethylamide	+	0
Meprobamate	−	0
Morphine	+	+
Phenobarbitone	+	0
Prochlorperazine	+	+
Promethazine	+	0
Rauwolscine	+	+
Reserpine	−	0
Triflupromazine	+	+
Yohimbine	0	+

of the various drugs with their central nervous system stimulant, tranquillizing, central nervous system depressant, antihistamine or autonomic blocking activity.

However, many agents have influenced the pecking and emetic response to apomorphine in an identical manner (see Table 2). It has not been possible to antagonize apomorphine-induced pecking with a drug that is known to be ineffective against apomorphine-induced emesis. With some of the drugs found effective against pecking, no reports as regards their activity against apomorphine emesis are available (see group 2 in Table 2). These drugs are being tested against apomorphine emesis and the results will be reported later. It is possible that the cellular receptors involved in the mechanism of apomorphine-induced pecking in pigeons may be similar to that of apomorphine-induced emesis in other species.

It has been pointed out earlier (see methods) that two criteria—effect on the latent period and changes in % positive responses—were employed for assessing the drug effects. In nearly all cases (except with lysergic acid diethylamide and yohimbine) drugs affording protection also prolonged the latent period. On the contrary there were many agents which produced an increase in latent period without affording protection even in higher doses (see Table 3).

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