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BLOCKADE OF RESERPINE EMESIS IN PIGEONS [1]

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EARL (12) first reported that reserpine had an emetic effect in pigeons. Recently a similar effect has been described in the guppy fish (26). Occasional reports of nausea and vomiting in human beings are also available (17). The response in pigeons is particularly interesting since a graded dose response relationship is seen (12) and the response has been described to be a sensitive and reliable criterion for evaluating reserpine and reserpine like activity (13). Moreover out of the other Rauwolfia alkaloids tested only rescinnamine (21) and deserpidine (27), which have reserpine like central effects, are active in this respect. The present investigation was primarily undertaken to find out if blockade of emesis could be a satisfactory method for studying antireserpine effect of drugs. In addition, observations were made to find out how reserpine emesis would be affected by antiemetic agents.

METHODS

Two hundred and twenty pigeons of either sex, weighing between 200-400 gm were used. They were kept individually in wire mesh cages after feeding. Food and water were withheld during the experiment. The birds were used only once in a week. Drugs were either dissolved in distilled water or suspended in a 4 % gum accacia solution, except reserpine which was supplied dissolved in a special vehicle. Intramuscular injections were made in the pectoral muscles and oral administration

[1] A preliminary report of this work was presented before the 1959 Annual Session of the Association of Physiologists and Pharmacologists of India at Poona and an abstrac appeared in the *Ind. J. Physiol. Pharmacol.*, 1960, *4*, 117.

by letting the suspension drop in the mouth from a tuberculin syringe.

Emesis was induced by intramuscular injection of reserpine (0.5 mg/kg). The birds were observed for emesis for at least two hours afterwards and actual regurgitation of the crop content was regarded as a positive response. The latent period and frequency of vomiting were also noted. The reserpine challenge was timed to coincide with the peak effect of the drug under investigation. Each dose was tested in a batch of ten birds.

With the effective agents, graded doses were given and at least three points were obtained between levels of hundred percent protection and no protection. Regression lines were then obtained by the method of BLISS (1, 2) and ED_{50} calculated.

RESULTS

All pigeons vomited in response to 0.5 mg/kg reserpine within two hours. The average latent period was about 35 minutes but the latent period and frequency of vomiting in different birds had a wide variation. Due to this reason protection offered by a drug was judged solely on the basis of reduction in incidence of emesis and no consideration was given for any change in the latent period and frequency. EARL *et al.* (13) reported that the pigeons which received reserpine even a week back vomited simply when placed in the cages in which they had been previously tested and so could not be used again. This vomiting, however, lasted for only 15-20 minutes at the most and we found that the birds could be used about an hour after being placed in the observation cages.

Effect of C.N.S. Stimulants.

Seven stimulants of the central nervous system, caffeine, cocaine, iproniazid, LSD-25, methamphetamine, methylphenidate (Ritalin) and metrazol, were tested. The results have been summarised in TABLE I. Protection was afforded by caffeine, iproniazid, LSD-25 and methamphetamine. The regression lines are shown in FIGS. 1 and 2. Partial protection was seen with cocaine and methylphenidate. Bigger doses of these two agents could not be tested as they themselves produced emesis.

Effect of C.N.S. Depressants.

The drugs tested included, tranquilisers (benactyzine and chlorpromazine), anticonvulsant (diphenylhydantoin), analgesic (morphine), hypnotic (pentobarbitone) and antiemetics (chlorpromazine, cyclizine,

TABLE I

Showing the effect of certain C.N.S. stimulant drugs on reserpine (0.5 mg/kg) induced emesis in pigeons

Agent	Dose (mg/kg)	Route of Administration	Reserpine challenge after	% protected	ED50 (mg/kg) ± S.E. (P = 0.05)
Caffeine citras	3.0	intramuscular	30 minutes	30	3.98 ± 1.8
	4.5			60	
	6.0			70	
Cocaine HCl	3.0	intramuscular	30 minutes	10	
	6.0			30	
Iproniazid phosphate	100.0	intramuscular	2 hours	30	144.4 ± 44.9
	150.00			50	
	200.00			70	
LSD-25	0.05	intramuscular	simultaneous	10	0.24 ± 0.01
	0.1			20	
	0.2			30	
	0.3			70	
Methamphetamine HCl	2.5	intramuscular	30 minutes	10	5.82 ± 1.94
	5.0			40	
	10.0			80	
Methylphenidate HCl	5.0	intramuscular	30 minutes	20	
	2.5	oral		50	
	5.0	oral		50	
	10.0	oral		20	
Metrazol	10.0	intramuscular	30 minutes	10	
	20.0			20	

hyoscine butylbromide, prochlorperazine and tigan). The results are shown in TABLE II, except those of hyoscine butylbromide which appear in TABLE III. Morphine was the only effective antagonist. The regression line is shown in FIG. 2. Protection could also be afforded by hypnotic doses of pentobarbitone (See TABLE II).

Effect of Autonomic Blocking Agents.

Both adrenergic and cholinergic blocking agents were studied. Two of the adrenergic blocking agents, rauwolscine and yohimbine, afforded

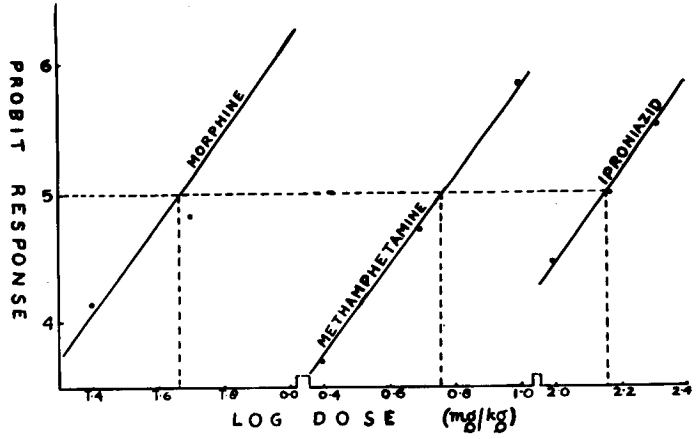

FIG. 1

Showing the regression lines of caffeine, LSD-25, rauwolscine and yohimbine for blockade of reserpine induced emesis in pigeons. The ordinate shows the transformed probit values for percentage of birds protected. The ED50 values are marked. The points refer to the experimental data obtained.

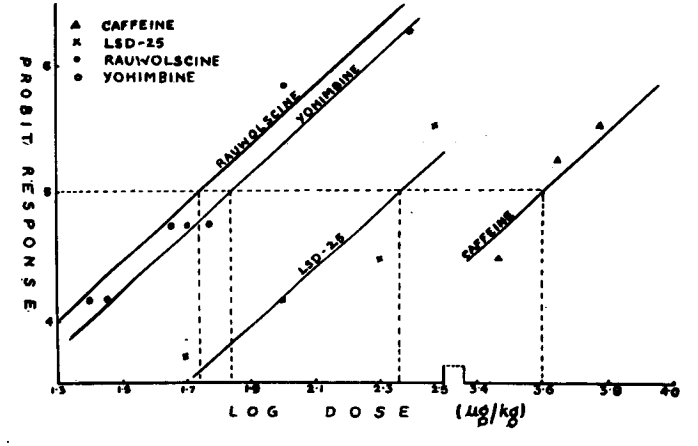

FIG. 2

Showing the final regression lines of iproniazid, morphine, methamphetamine for antagonism of reserpine emesis. The points actually obtained during the experiments are also shown. The ED50 values have been marked. Transformed probit values for percentage protection are given along the ordinate.

protection while the third one, DHE, was ineffective. None of the cholinergic blocking agents tested (atropine, artane, benactyzine and hyoscine butylbromide) were effective. The results are given in TABLE III. The regression lines for rauwölscine and yohimbine are shown in FIG. 1.

TABLE II

Showing the effect of certain C.N.S. depressants and antiemetic agents on reserpine emesis in pigeons. Note the protective effect of morphine

Agent	Dose (mg/kg)	Route of Administration	Reserpine challenge after	% protected	ED50 mg/kg ± S.E. (P = 0.05)
Benactyzine HCl	30.0	intramuscular	30 minutes	20	
Diphenylhydantoin sodium	40.0	oral	60 minutes	20	
	80.0			0	
Morphine HCl	0.25	intramuscular	30 minutes	20	0.47 ± 0.16
	0.50			43	
	1.0			90	
	5.0			100	
Pentobarbitone sodium	2.5	intramuscular	30 minutes	20	
	5.0			80 (1)	
Chlorpromazine HCl	25.0	intramuscular	simultaneous	10	
Cyclizine HCl	25.0	oral	2½ hour	0	
Prochlorperazine HCl	6.25	intramuscular	simultaneous	0	
Tigan HCl	20.0	intramuscular	30 minutes	10	

(1) All the birds were sleeping with this dose of pentobarbitone.

The regression lines of caffeine, LSD-25, rauwolscine and yohimbine were tested for parallelism with each other (16) and the X^2 values were not significant (P = 0.05). Similarly the regression lines of iproniazid, methamphetamine and morphine were found to be parallel to one another (See FIGS. 1 and 2).

TABLE III

Showing the effect of certain autonomic blocking agents on reserpine emesis. All agents were given intramuscularly. The dose of atropine employed is the vagal paralytic dose for pigeons (SOLLMAN and HANZLIK, 1939)

Agent	Dose (mg/kg)	Reserpine challenge after	% protected	ED50 (mg/kg) ± S.E. (P = 0.5)
Atropine sulphate	3.0	30 minutes	0	
Artane HCl	4.0	30 minutes	20	
	8.0		0	
Dihydroergotamine tartrate (DHE)	0.5	simultaneous	30	
	1.0		0	
Hyoscine butylbromide	10.0	30 minutes	20	
	20.0		12.5	
Rauwolscine HCl	0.025	simultaneous	20	0.055 ± 0.003
	0.05		40	
	0.10		80	
Yohimbine HCl	0.03	simultaneous	20	0.068 ± 0.03
	0.045		40	
	0.06		40	
	0.25		90	

DISCUSSION

Most of the drugs which have been able to block the emetic response of reserpine in pigeons have been shown to have anti-reserpine effects elsewhere also (See TABLE IV). A few of these agents — LSD-25 (10), methamphetamine (3) and morphine (11, 19, 23, 24) — are effective in preventing other types of vomiting as well. The protection against reserpine emesis, however, appears to be related to antireserpine activity of these compounds, since, antiemetic agents without antireserpine effects elsewhere (e.g. chlorpromazine, prochlorperazine etc., See RESULTS) are incapable of blocking this response. Reserpine emesis thus differs from other types of drug induced vomiting. It differs from reserpine induced emesis in guppy fish (26) also in not being blocked by chlorpromazine.

TABLE IV

Showing the correlation between blockade of reserpine emesis by drugs and their anti-reserpine effects. Figures in parentheses refer to numbers in the list of References

Agent	Antagonism of Reserpine	
	Emesis	Other effects
Caffeine	+	?
Chlorpromazine	—	Emesis in fish (26)
5-HT	+ (28)	?
Iproniazid	+	Clinical (15) Hypotension (7) Lethality (7) Miosis (7) Sedation (4, 7, 34)
LSD-25	+	Barbiturate potentiation (5, 30, 31,) Miosis (18) Nictitating membrane (18) Sedation (6, 29)
Methamphetamine	+	Barbiturate potentiation (33) Blockade of C.R. (20) Sedation (6, 8, 14) Seizure facilitation (22)
Methylphenidate	±	Clinical (15) Sedation (8)
Morphine	+	Hypothermia (25) Miosis (35) Nictitating membrane (7) Sedation (18)
Rauwolscine	+	?
Yohimbine	+	?

+ blockade; ? data not available; C.R. conditioned responses.

SCHNEIDER (28) reported that reserpine emesis in pigeons could be antagonised by administration of repeated intramuscular doses of 5-hydroxytryptamine (5-HT). The protective effect of iproniazid may be

due to preservation of 5-HT in the brain. No other effect of reserpine has so far been shown to be blocked by 5-HT even though the two agents have opposite effects at some places (28). These findings suggest that reserpine emesis in pigeons is not mediated through 5-HT. Moreover, emesis could not be induced in pigeons either by intravenous or intramuscular administration of varying doses of 5-HT or by intramuscular injection of 50 and 100 mg/kg tetrabenazine, a central 5-HT releasing agent (unpublished observations). The protection afforded by yohimbine and its isomer rauwolscine, may be due to their structural similarity with reserpine.

EARL *et al.* (13) have suggested that reserpine emesis in pigeons may be due to a predominance of central parasympathetic tone. This appears to be unlikely, however, in view of the fact that none of the cholinergic blocking agents tested, could antagonise it (See TABLES II and III).

A perusal of TABLE IV shows that a close parallelism exists between the ability of drugs to block reserpine emesis and their other antireserpine effects. The response offers a convenient method for studying the interaction of other drugs with reserpine.

SUMMARY

1. Various groups of pharmacological agents were tested for their ability to block reserpine induced emesis in pigeons.

2. The emesis was prevented by caffeine, iproniazid, LSD-25, methamphetamine, morphine, rauwolscine and yohimbine. Partial protection was observed with cocaine and methylphenidate. Antiemetics were ineffective.

3. A parallelism was found to exist, in most cases, between the ability of a drug to block this emesis and its other antireserpine effects.

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