MODIFICATION OF NEUROPHARMACOLOGICAL ACTIONS OF SOME DRUGS BY BIOGENIC AMINE ALTERING AGENTS

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Summary: The pentobarbitone sleeping time of rats was increased on pretreatment with reserpine, α-mmt, α-methyl dopa, 5-HTP and decreased with nialamide. The analgesic actions of morphine and and phenylbutazone were increased with nialamide and decreased with reserpine, α-methyl dopa and 5-HTP. Pentylenetetrazol seizures were absent in α-mmt or 5-HTP pretreatd rats and present to a varying degree in nialamide or reserpine pretreated rats. TAB vaccine induced pyrexia was a antagonised by 5-HTP, α-methyl dopa, reserpine and α--mmt but enhanced by nialamide. Reserpine-induced emesis in pigeons was antagonised by nialamide and slightly affected by α-mmt, α-methyl dopa and 5-HTP.

Key words: pentobarbitone morphine phenylbutazone pentylenetetrazol pretreatment with α-mmt reserpine α-methyl dopa 5-HTP nialamide

INTRODUCTION

The sedative action of reserpine has been attributed to a fall in the 5-HT (2, 3, 7, 24) or the catecholamine concentration in the brain (5, 14, 13, 25). Further, the analgesic action of morphine, the anticonvulsant property of iproniazid and the stimulant action of amphetamine have been correlated with alterations in the brain catecholamine levels (1, 21, 22, 29). Recently Feldberg and Myers (9) have shown an involvement of biogenic amines in regulating body temperature.

Thus there is some suggestive evidence that the pharmacological actions of a number of centrally acting drugs might be mediated through a change in the level of brain biogenic amines. However, the relative role of a particular amine in such an action is still a matter of investigation. With the introduction of α-methyl-m-tyrosine and α-methyl dopa which cause selective depletion of catecholamines, of 5-HTP which causes selective increase in 5-HT and of other agents like reserpine and iproniazid which effect the tissue concentrations of both amines, it has been possible to study the modification of the neuropharmacological responses to drugs of animals pretreated with these agents. The present study reports the modification of actions of some centrally acting drugs by several agents which influence brain biogenic amine levels.

MATERIALS AND METHODS

Male albino rats weighting 100-200 *g* and male albino pigeons weighing 200-300 *g* were employed. Twenty four hr before the administration of the drugs whose pharmacological

action was to be studied the particular group of animals were pretreated with one of t following agents in normal saline: —

(i) reserpine phosphate 5 *mg/kg* (ii) α-methyl-m-tyrosine (α-mmt) (iii) α-methyl do (iv) 5-hydroxytryptophan (5-HTP) and (v) nialamide. The control group received an equ quantity of normal saline. All the drugs were administered intraperitoneally.

Pentobarbitone-induced sleeping time in rats: Sixty rats were divided into six groups ten animals each. Pentobarbitone sodium (PB) 50 *mg/kg* was administered intraperitoneall 24 hr after pretreatment to each rat of different groups. The time at which the rat lost i righting reflex and regained it was noted; the difference indicated the duration of sleeping tim of the individual animal.

Morphine and phenylbutazone-induced analgesia: Sixty rats were divided into ten group of six animals each. Morphine hydrochloride or phenylbutazone were administered sub cutaneously 24 hr after pretreatment. The analgesic activity was recorded 30 min after th injection of morphine or phenylbutazone with the help of an analgesiometer, the main principl of which is to administer constant painful stimuli to the tail of rat through a heated nichrom wire. The time from application of stimulus to withdrawal of tail was recorded.

Pentylenetetrazol seizures in rats : Sixty rats were divided into 6 groups of 10 animal each. Twenty four hr subsequent to pretreatment, the animals of each group were adminis tered pentylenetetrazol subcutaneously. The number of animals showing clonic convulsion and the duration of convulsive seizures were observed in each animal.

TAB induced pyrexia in rats : Thirty six rats were divided into six groups of six animal each. Food and water were withdrawn 24 hr before the administration of any drug. TAB vaccine was injected subcutaneously simultaneously with the chemical agents used for pretreat ment to each rat. Rectal temperature of each animal was recorded by a clinical thermometer before the administration of any durg and 24 hr after the administration of TAB vaccine.

Reserpine induced emesis in pigeons: Fifty pigeons were divided into five groups of ten birds each. The technique used was similar to that described by Gupta *et al.* (12) and Dhawan *et al.* (8). Twenty four hr after pretreatment each group was administered reserpine in doses of 0.5 *mg/kg*. The birds were observed for emesis for 2 hr after the injection of reserpine, the regurgitation of the crop contents was recorded as a positive response. The latent period and frequency of vomiting were also noted.

RESULTS

Sleeping time: Pretreatment with reserpine, α-methyl dopa and 5-HTP markedly increased the pentobarbitone-induced sleeping time of rats whereas pretreatment with nialamide considerably decreased the sleeping time, but in the group of animals which were pretreated with both nialamide and 5-HTP the pentobarbitone-induced sleeping time was markedly increased (Table I). All the results were high significant ($P < 0.001$).

TABLE 1: Effect of biogenic amine altering agents on pentobarbitone (PB) induced sleeping time in rats.

Group	*Treatment*	*Mean sleeping time (min) ± S.D.*	*Probobllity*
1.	(a) *Normal saline (0.25 ml)*		
	(b) PB 50 *mg/kg*	109.5 ± 6.86	—
2.	(a) Reserpine 5 *mg/kg*		
	(b) PB 50 *mg/kg.*	145.5 ± 3.78	<0.001
3.	(a) α-methyl dopa 50 mg/kg		
	(b) PB 50 *mg/kg*	157.0 ± 6.32	<0.010
4.	(a) 5-HTP 50 *mg/kg*		
	(b) PB 50 *mg/kg*	150.0 ± 16	<0.001
5.	(a) Nialamide 100 *mg/kg*		
	(b) PB 50 *mg/kg*	27 ± 6.06	<0.001
6.	(a) Nialamide 100 *mg/kg.* 5-HTP 50 *mg/kg*	162.5 ± 2.64	<0.001
	(b) PB 50 *mg/kg*		

(a) Drugs used for pretreatment.
(b) PB administered 24 hr after (a).

TABLE II: Effect of biogenic amine altering agents on morphine induced analgesia in rats.

Group	*Treatment*	*Mean pain threshold (sec) ± S.D.*	*Probability*
1.	(a) Normal saline 0.25 *ml*	6.20. ± 0.34	
	(b) Morphine 10 *mg/kg*		
2.	(a) α-methyl dopa 50 *mg/kg*	5.7 ± 0.22	<0.01
	(b) Morphine 10 *mg/kg*		
3.	(a) 5-HTP 50 *mg/kg*	5.6 ± 0.45	<0.01
	(b) Morphine 10 *mg/kg*		
4.	(a) Reserpine 5 *mg/kg*	5.7 ± 0.26	<0.02
	(b) Morphine 10 *mg/kg*		
5.	(a) Nialamide 50 *mg/kg*	7.3 ± 0.45	<0.01
	(b) Morphine 10 *mg/kg*		

(a) Drugs used for pretreatment.
(b) Administered 24 hr after (a).

Analgesic action: The threshold of morphine's analgesic action fell significantly in animals pretreated with reserpine, α-methyl dopa and 5-HTP, however it was raised in animals pretreated with nialamide (Table II). Similar results were obtained with phenylbutazone induced analgesia in rates (Table III).

TABLE III: Effect of biogenic amine altering agents on phenylbutazone-induced analgesia in rats.

Group	*Treatment*	*Mean pain threshold (sec) ± S.D.*	*Probability*
1.	(a) Normal saline 0.25 *ml* (b) Phenylbutazone 10 *mg/kg*	6.2 ± 0.21	—
2.	(a) α-methyl dopa 50 *mg/kg* (b) Phenylbutazone 10 *mg/kg*	5.6 ± 0.39	<0.02
3.	(a) 5-HTP 50 *mg/kg* (b) Phenylbutazone 10 *mg/kg*	4.0 ± 0.56	<0.01
4.	(a) Reserpine 5 *mg/kg* (b) Phenylbutazone 10 *mg/kg*	5.4 ± 0.31	<0.01
5.	(a) Nialamide 50 *mg/kg* (b) Phenylbutazone 10 mg/kg	7.3 ± 0.43	<0.01

(a) Drug used for pretreatment.
(b) Administered 24 hr after (a).

TABLE IV: Effect of biogenic amine altering agents on pentylenetetrazol-induced seizures in rats.

Group	*Treatment*	*% of animals showing convulsions*	*Average duration of convulsions (sec) ± S.D.*
1.	(a) Normal saline 0.25 *ml* (b) Pentylenetetrazol 70 *mg/kg*	100	52 ± 35
2.	(a) Reserpine 5 *mg/kg* (b) Pentylenetetrazol 70 *mg/kg*	100	222 ± 33
3.	(a) Nialamide 50 *mg/kg* (b) Pentylenetetrazol 70 *mg/kg*	80	45 ± 9
4.	(a) 5-HTP 50 *mg/kg* (b) Pentylenetetrazol 70 *mg/kg*	0	0
5.	(a) α-methyl dopa 50 *mg/kg* (b) Pentylenetetrazol 70 *mg/kg*	10	12
6.	(a) α-mmt 100 *mg/kg* (b) Pentylenetetrazol 70 *mg/kg*	0	0

(a) In all cases administered first.
(b) Administered 24 hr after (a).

Pentylenetetrazol seizures : Pentyleneterazol induced seizures in 100% of animals pretreated with reserpine, in 80% of those pretreated with nialamide and in 10% of those pretreated with α-methyl dopa. None of the rats pretreated with 5-HTP and α-mmt showed convulsions (Table IV). The duration of clonic convulsions was considerably more in rats pretreated with reserpine and markedly less in animals pretreated with nialamide and α-methyl dopa. Nialamide had no action. Thus while reserpine facilitated pentylenetetrazol induced seizures, 5-HTP and α-mmt offered total protection.

TABLE V: Effect of biogenic amine altering agents on TAB vaccine-induced pyrexia in albino rats.

Group	*Treatment*	*Mean temp (F.±S.D.) after 24 hr*	*Average difference from control tenmperature*	*Probability*
1.	(a) Normal saline 0.25 *ml* (b) TAB vaccine 0.1 *ml.*	99.0±0.57 (control)	—	—
2.	(a) 5-HTP 50 *mg/kg* (b) TAB vaccine 0.1 *ml*	98.0±0.57	—1.4	<0.005
3.	(a) α-methyl dopa 50 *mg/kg* (b) TAB vaccine 0.1 *ml*	97.0±0.57	—2.0	<0.001
4.	(a) Nialamide 100 *mg/kg* (b) TAB vaccine 0.1 *ml*	100.8±0.62	+1.8	<0.005
5.	(a) Reserpine 5 *mg/kg* (b) TAB vaccine 0.1 *ml*	98.0±0.5	—1.4	<0.005
6.	(a) α-mmt 100 *mg/kg* (b) TAB vaccine 0.1 *ml*	98.64±0.42	—0.8	<0.002

Mean normal temperature 98.2±0.58°F
Both (a) and (b) were administered simultaneously.

TAB vaccine induced pyrexia: As can be seen from Table V, there was a significant antagonism of TAB vaccine-induced pyrexia in rats pretreated with 5-HTP, α-methyl dopa, reserpine and α-mmt. However, there was marked enhancement of rectal temperature in rats pretreated with nialamide.

Emesis in pigeons: Nialamide offered maximum portection against reserpine-induced emesis, while α-methyl dopa, 5-HTP and α-mmt offered very little protection against the emetic effect of reserpine in pigeons (Table VI).

TABLE VI: Effect of pretreatment with biogenic amine altering agents on reserpine-induced emesis in pigeons

Group	*Treatment*	*% protection*
1.	(a) Normal saline 0.25 *ml* (b) Reserpine 0.5 *mg/kg*	0
2.	(a) α-methyl dopa 50 *mg/kg* (b) Reserpine 0.5 *mg/kg*	10
3.	(a) 5-HTP 50 *mg/kg* (b) Reserpine 0.5 *mg/kg*	0
4.	(a) α-mmt 100 *mg/kg.* (b) Reserpine 0.5 *mg/kg*	10
5.	(a) Nialamide 50 *mg/kg* (b) Reserpine 0.5 *mg/kg*	80

(a) Drugs used for pretreatment.
(b) Administered 24 hr after (a).

DISCUSSION

A correlation between the neuropharmacological actions of drugs and brain biogenic amine levels (2, 23, 24) is corroborated by the present results. The brain biogenic amine altering properties of agents used in the present study are well documented (13, 28). Pretreatment with reserpine or α-methyl dopa or 5-HTP markedly enhanced while that with nialamide considerably decreased the pentobarbitone sleeping time. This is in conformity with a depressant action of reserpine and a stimulant action of nialamide. However, pretreatment with nialamide followed by 5-HTP, markedly increased pentobarbitone sleeping time. Nialamide being a MAO inhibitor would obviously raise the brain level of both catecholamines and 5-HT. But pretreatment with both nialamide and 5-HTP the 5-HT concentration in the brain would be more than that of catecholamines. Accordingly, increase in catecholamine levels in the brain might be associated with excitatory effects while increase in 5-HT and decrease in catecholamine levels might be associated with depressant effects.

Pretreatment with α-methyl dopa or reserpine or 5-HTP significantly decreased the pain threshold elevating action of morphine. The anti-analgesic effect of reserpine has been reported by others (4, 16, 26, 27). The anti-analgesic effect of reserpine and α-methyl dopa could be attributed to a decrease in catecholamine rather than 5-HT levels. That in 5-HTP treated rats there was a decrease in the pain threshold elevating action of morphine supports this contention. 5-HT antagonises the action of morophine peripherally (18) and this antagonism may be exerted at the central level too. Further, nialamide significantly increased the pain threshold elevating action of morphine. Other MAO inhibitors also possess and enhance

analgesic action of morphine (17). Thus potentiation of morphine effect by nialamide could well be due to an increase in the brain catecholamine level (11). This finds support in the view that adrenaline exerts an analgesic effect (15). Essentially similar results were obtained with phenylbutazone.

In agreement with the literature reports (6) reserpine significantly increased the duration of pentylenetetrazol-induced seizures. Nialamide had no significant effect on pentylenetetrazol induced convulsions. However others have reported anticonvulsant effect of MAO inhibitors (20). In 5-HTP or α-mmt treated rats pentylenetetrazol failed to induce seizures. It can be concluded that a relative increase in the brain 5-HT level resulting from pretreatment with 5-HTP or α-mmt (which causes selective depletion of catecholamines and thus a proportionate increase in 5-HT levels) afforded protection against the pentylenetetrazol convulsions. This is in conformity with earlier reports (19).

Pretreatment with α-methyl dopa or α-mmt or reserpine or 5-HTP resulted in a significant decrease in TAB-vaccine induced pyrexia whereas pretreatment with nialamide markedly increased this reaction. Thus decrease in catecholamine level and selective increase in 5-HT level was associated with hypothermia and increase in catecholamine level was associated with hyperthermia. This is in line with the reported hyperthermic effect of the intraventricularly injected adrenaline, and noradrenaline and hypothermic effect of 5-HT in rats (10).

Pretreatment of pigeons with α-methyl dopa, 5-HTP or α-mmt had no protective effect against emetic action of reserpine. However, nialamide offered protection in 80% of cases. Other stimulants of the central nervous system have also been shown to block reserpine-induced emesis in pigeons (8, 12). These effects when interpreted in terms of alteration in brain biogenic amine level would indicate that increase in catecholamine level might offer protection against while decrease in catecholamine might facilitate reserprine-induced emesis.

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