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Central and peripheral monoaminergic membrane-pump blockade by some addictive analgesics and antihistamines

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The ability of various analgesics and antihistamines to block the amine-uptake mechanism (the so-named membrane pump) of central and peripheral monoamine-storing neurons was investigated in mice. Activities indicating such blockade were observed within both groups but did not seem to correlate with analgesic or antihistaminic activity. The antihistamine chlorpheniramine proved remarkably potent on central 5-hydroxytryptamine neurons.

Previously we have investigated the membrane-pump blocking action of some di- and tricyclic thymoleptic drugs on central and peripheral noradrenaline and on central 5-hydroxytryptamine (5-HT) neurons (Carlsson, Corrodi & others, 1969a, b; Carlsson, Fuxe & others, 1969; Carlsson, Jonason & others, 1969). The degree of blockade differed in the three types of neuron depending on the chemical structure and physical properties of the agents investigated. Moreover, it was observed that agents possessing strong membrane-pump blocking activity on 5-HT neurons also potentiated the actions of 5-hydroxytryptophan and the monoamine oxidase inhibitor nialamide.

In man also, the combined treatment with monoamine oxidase inhibitors and tricyclic thymoleptics may give rise to strong, even fatal reactions. Similar reactions have been observed after monoamine oxidase inhibitors and pethidine. In rabbits Nymark & Møller-Nielsen (1963) made similar observations. In animals pretreated with a monoamine oxidase inhibitor they found that amitriptyline caused hyperthermia and various signs of excitation. Pethidine had similar actions following monoamine oxidase inhibition. We have confirmed the last-mentioned observation in rabbits and mice. The question then arose whether pethidine, like the tricyclic thymoleptics, was capable of blocking the membrane pumps of monoamine-carrying neurons. Attempts to answer this question led to the investigations described below.

EXPERIMENTAL AND RESULTS

Several drugs were examined for nialamide and 5-hydroxytryptophan potentiation (Table 1). As mentioned, pethidine (50 mg/kg, i.p.) caused potentiation of both these agents, whereas methadone and morphine appeared to be inactive in this respect.

Membrane pump blockade was studied by utilizing the principle of endogenous 5-HT and noradrenaline displacement by the amines H 75/12 (Carlsson & others, 1969b) and H 77/77, respectively (Carlsson & others, 1969a). Pethidine (50 mg/kg, i.p.) inhibited 5-HT displacement by H 75/12 by about 50% (Table 2). Of other analgesics, methadone appeared to possess some activity in a dose of 12·5 mg/kg (higher doses could not be studied because of toxicity), whereas morphine, pentazocine, and nalorphine

Table 1. *Potentiation of nialamide and 5-hydroxytryptophan syndromes by analgesics and antihistamines.* Groups of 5 mice were treated with nialamide (100 mg/kg i.p.) 1 h before or 5-HTP (300 mg/kg, i.p.) 30 min after the test drug. The test drugs were given i.p. in doses indicated in brackets. In the doses employed neither nialamide nor 5-HTP caused any marked behavioural changes. When potentiation occurred, the gross symptoms induced by 5-HTP were extension and abduction of hind limbs, lordosis, tremors, head movements and excitation; the syndrome induced by nialamide was similar.

	Nialamide potentiation		5-hydroxytryptophan potentiation	
Pethidine HCl	Yes	(50)	Yes	(50)
Methadone HCl	No	(12·5)	No	(12·5)
Morphine HCl	No	(50, 25)	No	(50)
Chlorpheniramine maleate	Yes	(50, 12·5)	Yes	(25)
Chlophedianol HCl	No	(50, 12·5)	Yes	(25)
Recipavrin HCl[1]	Yes	(50, 12·5)	Yes	(50)
Terodiline HCl[2]	Doubtful	(50, 12·5)	Doubtful	(25)
Diphenhydramine HCl	Yes	(50,[3] 12·5)	Yes	(25)
Chlorphenoxamine HCl	No	(50, 12·5)	Yes	(25)
Tripelennamine HCl	Yes	(50, 25, 12·5)	Yes	(25)
Promethazine HCl	No	(50, 12·5)	Doubtful	(25)
Phenindamine tartrate	Doubtful[4]	(50, 12·5)	Doubtful[4]	(25)
Cyproheptadine HCl	No	(50,[5] 12·5)	No	(25)

[1] 4,4-diphenyl-2-dimethylaminobutane hydrochloride.
[2] *N*-Butyl-1-methyl-3,3-diphenylpropylamine hydrochloride
[3] Four out of 5 animals died within 60 min.
[4] Difficult to judge because of the stimulating effect of the drug itself.
[5] All animals died within 80 min.

had no significant activity. The structure of methadone is similar to that of certain antihistamines, which like the thymoleptics possess a dimethylaminopropyl side-chain. Moreover, certain antihistamines have been reported to block the membrane pump of peripheral adrenergic neurons, which would explain their noradrenaline-potentiating activity (Isaac & Goth, 1965, 1967), and to antagonize reserpine and tetrabenazine in various animal tests for thymoleptic activity (Garattini & Jori, 1967; Barnett, Taber & Roth, 1969).

We therefore tested several antihistamines for 5-hydroxytryptophan and nialamide potentiation (Table 1); some were active, others inactive. In general there seemed to be a good agreement between nialamide and 5-hydroxytryptophan potentiation. Only in two cases out of 13 was clear-cut potentiation observed with one of the agents, but not with the other. In both cases the negative result was obtained with nialamide, suggesting that the potentiation "threshold" is higher for this drug than for 5-hydroxytryptophan under the present conditions. When considered together with our earlier observations (Carlsson, Jonason & others, 1969), the data indicate a close association between nialamide and 5-hydroxytryptophan potentiation, suggesting that 5-HT is involved in both cases. The activities also correlated fairly well with those observed by the above-mentioned workers for blockade of peripheral adrenergic membrane pumps, noradrenaline potentiation and reserpine: tetrabenazine antagonism. Five antihistamines of varying chemical structure were examined for their ability to block H75/12-induced 5-HT displacement (Table 2). The two agents having a dimethylaminopropyl side-chain, i.e. chlorpheniramine and Recipavrin (used in Sweden as a

Table 2. *Effects of various drugs and* 4-*methyl-a-ethyl*-m-*tyramine* (*H* 75/12), *given alone or in combination, on the brain-5-hydroxytryptamine level in mice*

Treatment	First dose (mg/kg)	Brain 5-HT (μg/g) Drug alone	Brain 5-HT (μg/g) Drug + H75/12	Inhibition (%)
No drug		0·54 (7) ±0·018	0·23 (15) ±0·011	
Pethidine HCl	50	0·55 (3) ±0·056	0·41 (3) ±0·014	56
	25	0·59 (2) ±0·015	0·29 (2) ±0·020	17
Methadone HCl	12·5	0·59 (3) ±0·012	0·31 (3) ±0·032	22
Morphine HCl	50	0·54 (4) ±0·038	0·27 (4) ±0·036	13
Pentazocine	25	0·67 (1)	0·24 (1)	2
	12·5	0·55 (1)	0·27 (1)	13
Nalorphine HCl	25	0·57 (2) ±0·045	0·24 (2) ±0·010	3
Chlorpheniramine maleate	25	0·57 (3) ±0·035	0·52 (2) ±0·040	85
	12·5	0·53 (3) ±0·030	0·42 (3) ±0·021	63
	6·25	0·63 (1)	0·41 (1)	45
No drug		0·54 (7) ±0·018	0·23 (15) ±0·011	
Recipavrin HCl	25	0·62 (2) ±0·100	0·41 (2) ±0·035	46
	12·5	0·53 (2) ±0·020	0·38 (2) ±0·055	50
	6·25	0·61 (1)	0·34 (1)	29
Diphenhydramine HCl	25	0·56 (2) ±0·025	0·44 (2) ±0·055	64
	12·5	0·56 (2) ±0·095	0·29 (2) ±0·025	18
Tripelennamine HCl	25	0·53 (2) ±0·025	0·33 (2) ±0·015	33
	12·5	0·58 (2) ±0·015	0·27 (2) ±0·040	11
	6·25	0·49 (1)	0·18 (1)	0
Phenindamine tartrate	25	0·59 (1)	0·29 (1)	17
	12·5	0·60 (1)	0·27 (1)	11

Shown are the means ± s.e. Figures in brackets indicate number of experimental groups, each comprising 5 animals.

Table 3. *Effects of various drugs and* 4,*a-dimethyl*-m-*tyramine* (*H* 77/77), *given alone or in combination, on noradrenaline in brain and heart*

Treatment	First dose mg/kg	Brain noradrenaline μg/g Drug alone	Brain noradrenaline μg/g Drug+ H77/77	Heart noradrenaline μg/g Drug alone	Heart noradrenaline μg/g Drug+ H77/77	% Inhibition Brain	% Inhibition Heart
None		0·40 (4) ±0·030	0·18 (6) ±0·013	0·60 (4) ±0·029	0·11 (6) ±0·022		
Pethidine HCl	50	0·38 (2) ±0·000	0·24 (2) ±0·055	0·54 (2) ±0·120	0·17 (3) ±0·023	30	14
Methadone HCl	12·5	0·35 (1)	0·16 (1)	0·67 (1)	0·13 (1)	0	4
Morphine HCl	50	0·40 (1)	0·17 (1)	0·61 (1)	0·11 (1)	0	0
Chlorpheniramine	25	0·42 (3) ±0·047	0·32 (3) ±0·046	0·71 (3) ±0·087	0·53 (3) ±0·054	58	70
Maleate	12·5	0·43 (3) ±0·055	0·27 (3) ±0·045	0·86 (3) ±0·165	0·61 (3) ±0·141	36	67
Recipavrin HCl	25	0·52 (1)	0·24 (1)	0·79 (1)	0·54 (1)	18	63
	12·5	0·48 (2) ±0·030	0·24 (2) ±0·015	0·90 (2) ±0·045	0·39 (2) ±0·150	20	35
	6·25	0·47 (1)	0·20 (1)	1·16 (1)	0·31 (1)	7	19
Diphenhydramine HCl	12·5	0·36 (1)	0·16 (1)	0·50 (1)	0·25 (1)	0	36
Tripelennamine HCl	25	0·33 (2) ±0·010	0·18 (2) ±0·010	0·59 (2) ±0·045	0·30 (2) ±0·010	0	40
	12·5	0·40 (1)	0·17 (1)	—	0·16 (1)	0	—
	6·25	0·36 (1)	0·17 (1)	0·75 (1)	0·20 (1)	0	14
Phenindamine tartrate	25	0·28 (2) ±0·025	0·24 (2) ±0·015	0·71 ±0·155	0·49 ±0·145	60	63
	12·5	0·32 (1)	0·23 (1)	0·66 (1)	0·34 (1)	36	42

Shown are the means ± s.e. Figures in brackets indicate number of experimental groups, each comprising 6 mice.

spasmolytic), proved most active. Tripelennamine, with an ethylenediamine side-chain, had some activity, and this was also true of diphenhydramine, an aminoalkyl-ether. Phenindamine and promethazine (Carlsson & others, 1969b) had little or no activity.

In general there appeared to be a good agreement between nialamide: 5-hydroxy-tryptophan potentiation and blockade of H 75/12-induced 5-HT displacement (*cf.* Tables 1 and 2), supporting our previous observations (Carlsson, Jonason & others, 1969). Both phenomena may therefore well be due to one and the same basic action, that is, blockade of the membrane pump of 5-HT neurons.

Three analgesics and five antihistamines were examined for their ability to block H 77/77-induced noradrenaline depletion (Table 3). Chlorpheniramine proved active on central noradrenaline but was probably less potent than on 5-HT. Recipavrin was less active. Tripelennamine and diphenhydramine (one experiment only) appeared to be inactive on central noradrenaline. On peripheral noradrenaline (heart) all four compounds appeared to be active. The findings agree with our earlier observations that membrane pump blockade by various agents is generally more pronounced in peripheral than in central noradrenaline neurons. Phenindamine, an antihistamine with central stimulant properties in animals and man, was peculiar in reducing brain noradrenaline levels by itself. It also seemed rather efficient in blocking H 77/77-induced noradrenaline release centrally as well as peripherally. Further analysis of these observations may throw some light on the central stimulation caused by this agent. The analgesics examined had little or no activity.

In agreement with our earlier data on di- and tricyclic thymoleptics, the types of drugs investigated did not seem to influence H 77/77-induced dopamine displacement, thus further supporting the view that the structural requirements for blockade of the membrane pumps of noradrenaline and dopamine neurons are different.

DISCUSSION

It would thus appear that certain addictive analgesics and antihistamines possess some biochemical and pharmacological properties similar to those of the thymoleptic drugs. The question arises whether the agents in question do indeed have antidepressant activity in man. It is interesting to note that opium was used as an antidepressant agent before the advent of the modern thymoleptics. However, in the present study morphine showed little or no activity. It might prove interesting to investigate the other components of opium. In any event there does not seem to be any clearcut correlation between analgesic effect and the biochemical activities observed in this investigation. As to the antihistamines, it appears that only diphenhydramine has been examined for antidepressant activity in man. The result was considered negative (Hankoff, Grundlach & others, 1964) but the conclusion has been disputed (Barnett & others, 1969). Chlorpheniramine proved considerably more potent than diphenhydramine in the present study. In fact it compares favourably with imipramine and amitriptyline with respect to actions on both 5-HT and noradrenaline neurons. It appears worth while to study the possible antidepressant properties of this and related agents in man.

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