PHARMACOLOGY

Choline Acetylase Inhibitors as Potential Antihallucinogens

It has been suggested that acetylcholine and catecholamines are involved both in central and peripheral transmission in mammals[1-3] and that they show a similar pattern of antagonism in each situation[4]. Further, it has been shown clinically that monoamine oxidase inhibitors, which increase the concentration of catecholamines in the central nervous system (CNS), usually produce mental excitation whereas anti-cholinesterase drugs which raise the level of acetylcholine in the CNS generally produce depression. The latter effect has been shown by Grob[5-7] and Rowntree[8] in normal and psychotic patients.

These observations are consistent with the proposition that a balance exists between the actions of cholinergic and adrenergic mechanisms in the CNS and that behavioural disturbances may result from impairment of this relationship leading to an imbalance in the relative central concentrations of acetylcholine and catecholamines. If this is so, it seems possible that drugs which can modify the central concentrations of acetylcholine or catecholamines can bring about their remedial effects clinically by restoring this imbalanced state towards a physiological level.

Since choline acetylase inhibitors which reach important central sites might be expected to lower the concentration of acetylcholine there, it follows that such substances could also modify the balance between the actions of the cholinergic and adrenergic systems.

Such substances should favour the alleviation of depressive behavioural states in man. This suggestion was tested using a series of drugs, the parent substance of which, *p*-phenylmandelic acid, was shown[9] to be a choline acetylase inhibitor. The ability of these substances to modify a model psychosis induced in conscious dogs by 'Ditran' (*JB*329, *N*-ethyl-3-piperidyl phenyl *cyclo*pentyl glycolate)[10] was compared with their capacity to inhibit choline acetylase in an *in vitro* system proposed by Hestrin[11]. These drugs all contained a large lipid-soluble moiety attached to a glycolic acid group and were initially based on a series of compounds investigated by Garratini *et al.*[12].

It should be noted that the lipophilic characteristic of such compounds should permit ready penetration into the CNS while the glycolic acid group was found to be necessary for the production of central pharmacological effects. The polyaromatic acid residue contained in the structure of the drugs is associated with the blocking of acetate transfer from coenzyme A to choline[13].

It has been proposed[14] that 'Ditran' antagonists (Table 1) act by competitive displacement of the hallucinogen from receptor sites. However, if this were so, 9-hydroxy-9-fluorenecarboxylic acid (Table 1) might be expected to show antagonism to 'Ditran' since its analogue *N*-ethyl-3-piperidyl-9-hydroxy-9-fluorene carboxylate is an active hallucinogen[15]. Further, it might be anticipated that phenyl-*cyclo*pentyl-glycolic acid should show a marked antagonism to the hallucinogenic effect of 'Ditran' since it constitutes the glycolate component of this substance. Since neither of the glycolic acids antagonizes the effects of 'Ditran', the above suggestion appears to have questionable validity.

Table 1. Drug Inhibition of Choline Acetylase Activity and 'Ditran'-induced Model Psychosis in Dogs

Drug	Antagonism to 'Ditran' effect in dogs	Choline acetylase inhibition Drug concentration (mg/ml.)	% Inhibition
p-Phenylmandelic acid	Active	0·6	24
		4·1	46
3-Phenanthrylglycolic acid	Active	1·0	85
		1·5	100
		2·0	100
		2·5	100
p-Phenoxymandelic acid	Inactive	No inhibition	
p-Chloromandelic acid	Inactive	No inhibition	
Benzilic acid	Active	1·0	67
		2·0	93
		3·0	100
9-Hydroxy-9-fluorene-carboxylic acid	Inactive	*	*
Phenyl-*cyclo*pentyl-glycolic acid	Inactive	*	

* Not tested.

It may be seen from this limited series of drugs that a correlation exists between the antihallucinatory activity in the dog and the presence of choline acetylase inhibition *in vitro*, thus providing support for the enzyme inhibition theory. Information concerning the action of these drugs may be provided by the use of tritiated compounds and by the use of hallucinogens structurally unrelated to 'Ditran'.

The applicability of the experimental results discussed here to naturally occurring psychotic states in human beings is being tested in current clinical trials.

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Effect of Tranylcypromine on the Blood Pressure Response of Tyramine

There has lately been a growing awareness of an association between hypertensive crises, death and monoamine oxidase inhibitors[1,2]. Tranylcypromine has been involved in a number of cases, producing intracranial bleeding, sometimes fatal, in patients who had exhibited paradoxical hypertension and severe headache[3,4]. Some reports have suggested that the ingestion of cheese by patients undergoing tranylcypromine treatment may give rise to hypertensive crises[5-7]. Asatoor[8] has shown that certain types of cheese contain amines such as β-phenylethylamine, tryptamine and tyramine. According to these findings, tyramine appears to be one of the amines present in sufficient quantity to be pharmacologically active. It therefore seems possible that ingestion of cheese containing significant amounts of tyramine may play an important part or may be the most important factor in many cases of hypertensive crisis associated with tranylcypromine therapy.

In our work, modification of the blood pressure response to tyramine, 1,1-dimethyl-4-phenyl piperazinium iodide (DMPP), noradrenaline and adrenaline has been accomplished by the pretreatment of dogs (10–12 kg), cats (2–2·5 kg) and rabbits (2–3·5 kg) with tranylcypromine.

Experiments were carried out with pentobarbital-anaesthetized animals. The trachea was cannulated and systemic blood pressure was recorded with a mercury manometer from the left carotid artery or from the left femoral artery. Drugs were administered into the cannulated right femoral vein, or orally.

In preliminary experiments, it was observed that tranylcypromine when given orally or subcutaneously to