the central nervous system by drainage into the cerebrospinal fluid and transport across the choroid plexus,[19] interindividual differences in the activity of the latter mechanism could account for these observations. Alternatively, differences in binding to macromolecules within the brain might be responsible for the variability in brain salicylate concentrations.

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Effects of some isoquinoline compounds and certain derivatives on brain phosphodiesterase activity

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RECENT investigations have shown that endogenous formation of certain isoquinoline compounds may occur in the central nervous system,[1,2] where they could have a physiological role. Several isoquinoline derivatives are also known to affect various excitable tissues, including the nervous system.[3–6]

In view of these studies and others on the mechanism of action of representative isoquinoline derivatives,[7-10] we have looked at the effects of these drugs on the control of the adenosine 3',5'-monophosphate (cyclic AMP) content of brain. We tested the response of particulate and soluble 3',5'- cyclic nucleotide phosphodiesterase.

The particulate enzyme was represented by the 2000–70,000 *g* fraction; the soluble enzyme was obtained by precipitation of the 70,000 g supernatant with ammonium sulphate at 70 per cent saturation. All sediments were resuspended in a small volume of 10% sucrose–2 mM Tris pH 7·5.

Cyclic AMP hydrolysis activity was assayed according to Butcher and Sutherland.[11] Inorganic phosphate (Pi) was analyzed by the method of Fiske and Subbarow.[12]

The activities of the soluble and of the particulate preparations were respectively 6·95 and 4·40 μmoles cyclic AMP hydrolysed mg protein^{-1} hr^{-1}. Both preparations were inhibited by 2 mM theophylline and stimulated by 20 mM imidazole.

Seventeen drugs have been tested including: six isoquinoline compounds,* six benzyl-isoquinoline derivatives (Table 1) and five pyridylmethyl-isoquinoline derivatives.†

TABLE 1. EFFECTS OF SOME BENZYL-ISOQUINOLINE DERIVATIVES ON PDEASE ACTIVITY ASSOCIATED WITH THE SOLUBLE AND A PARTICULATE FRACTION OF GUINEA-PIG BRAIN

Drugs (mM conc)		μmoles of cyclic AMP (hydrolysed/mg protein^{-1}hr^{-1}) Soluble fraction	Particulate fraction
0		6·95 (−)	4·40 (−)
Papaverine	0·1	5·5 (−22%)	3·04 (−31%)
	0·2	4·3 (−38%)	2·4 (−46%)
3,4-Dihydropapaverine	0·1	negligible	negligible
	0·2	negligible	negligible
6-Bromopapaverine	0·1	4·87 (−30%)	2·16 (−51%)
	0·2	3·60 (−48%)	1·72 (−61%)
6-Bromopapaverinol	0·1	5·84 (−16%)	2·73 (−38%)
	0·2	4·8 (−31%)	1·9 (−43%)
Papaveroline	0·1	negligible	negligible
	0·2	negligible	negligible
Tetrahydropapaveroline	0·1	negligible	negligible
	0·2	negligible	negligible
N-benzyl-salsolidine	0·1	negligible	negligible
	0·2	negligible	negligible

Percentage inhibition is given in parentheses with respect to the control preparations. Every value represents the mean of three experiments. The enzymes were incubated in test tubes containing Tris HCl pH 7·5 40 mM, $MgCl_2$ 2 mM, cyclic AMP 1·5 mM; 50 μg 5'-nucleotidase after 10 min. The reaction was stopped with 0·1 ml TCA 50% after 20 min incubation. Final volume 1·2 ml. Protein 550 μg.

The results demonstrate that the isoquinoline compounds and pyridylmethyl-isoquinoline derivatives are ineffective at 1×10^{-3} to 2×10^{-2} M whereas some benzyl-isoquinolines are strong inhibitors (Table 1). In agreement with the findings of Toson and Carpenedo[13] on PDEase isolated

* 1-Methyl-isoquinoline hydrochloride; 2-methyl-3,4-dihydroisoquinoline hydrochloride; 1-methyl-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride; 1-methyl-*N*-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride; 1-methyl-6,7-dihydroxy-1,2,3,4-hydroisoquinoline hydrobromide; 1,2-dimethyl-6,7-dimethoxy-3,4-dihydroisoquinoline hydroiodide.

† 1-(2-pyridylmethyl)-6,7-Dimethoxy-3,4-dihydroisoquinoline dihydrochloride; 1-(3-pyridylmethyl)-6,7-dimethoxy-3,4-dihydroisoquinoline hydrochloride; 1-(4-pyridyl-methyl)-6,7-dimethoxy-3,4-hydroisoquinoline dihydrobromide; 1-(2-pyridyl-methyl)-6,7-dihydroxy-3,4-dihydroisoquinoline dihydrobromide; 1-(3-pyridylmethyl)-6,7-dihydroxy-3,4-dihydroisoquinoline dihydrobromide.

from skeletal muscle, the various compounds are more effective on the particulate preparation. The halogenation of papaverine enhances the inhibitory activity, mainly on the particulate enzyme. The hydroxyl-derivative (6-bromopapaverinol) retains a significant activity, whereas dihydrogenation of papaverine (3,4-dihydropapaverine) results in an almost complete loss of activity. In comparison with the recent findings of Hanna *et al.*,[14] our results indicate that the replacement of the benzyl-groupment by the pyridyl-methyl one results in a complete loss of activity. Finally, it should be pointed out that the compounds with neurotropic activity (carnegine and other isoquinolines, *N*-benzyl-salsolidine, tetrahydropapaveroline) are devoid of any effect on brain PDEase. The activity of these drugs on brain adenyl-cyclase is at present being studied.

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