The penetration of catechol and pyrogallol into mouse brain and the effect on cerebral monoamine levels

SIR,—It has previously been reported (Angel & Rogers, 1968) that catechol (1,2-dihydroxybenzene), when administered parenterally to mice readily evokes convulsions, whereas pyrogallol (1,2,3-trihydroxybenzene) does so only in near lethal doses. Since Matsuoka, Yoshida & Imaizumi (1962) have suggested that pyrogallol does not pass the blood-brain barrier, we decided to measure the penetration of both pyrogallol and catechol into the brain and also to investigate the effect of these compounds on the levels of cerebral monoamines, as both have been shown to inhibit cerebral catechol-*O*-methyl transferase *in vivo* (Crout, Crevelin & Udenfriend, 1961; Ross & Haljasmaa, 1964).

Male mice (18–22 g) of an inbred strain were decapitated at suitable times after the intraperitoneal injection of catechol (60 mg/kg) or pyrogallol (120 mg/kg). The phenols in trichloroacetic acid brain extracts were estimated by a modification of the method of Swain & Hillis (1959). The solvent system described by Shore & Olin (1958) was used in the determination of cerebral noradrenaline (Shore & Olin, 1958), dopamine (Carlsson & Waldeck, 1958) and 5-hydroxytryptamine (Weigand & Perry, 1961). Two mouse brains were pooled for each determination. Groups of 10 mice (5 pairs) were used at each dose level.

Spontaneous motor activity of the mice in a container was measured by suspending it from a strain gauge, the output of which was rectified and integrated over time intervals of 2 sec. The integrated activity at the end of each 2 sec period was sampled, stored in a digital computer (Biomac Data Laboratories) and transferred to paper tape for subsequent analysis.

The time course of changes in motor activity and in the cerebral concentration of the phenolic compounds are represented in Figs 1 and 2. Catechol (Fig. 1) elicits convulsions consisting of violent jerks and tremors, which commence within 15–20 sec of injection. The duration of this convulsive activity is transient, lasting approximately 8 min and the peak convulsive activity occurs at 2–3 min. It can be seen that the time course of catechol penetrations into the brain follows closely the time course of the convulsive activity. Mice receiving 120 mg/kg of pyrogallol show no change in motor activity (Fig. 2) even though this dose of pyrogallol is sufficient to produce cerebral concentrations which are about the same as those produced by the convulsive dose of catechol.

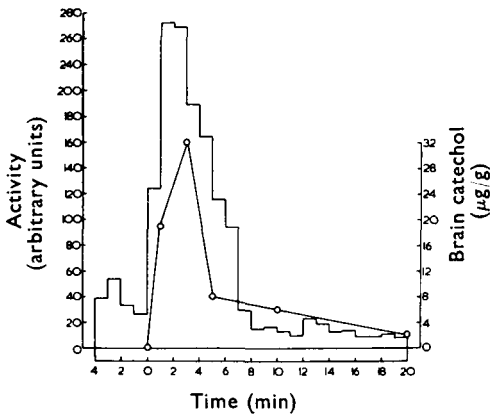

FIG. 1. Penetration of catechol into mouse brain (○) and the effect on motor activity (histogram). Catechol (60 mg/kg) injected intraperitoneally at time zero.

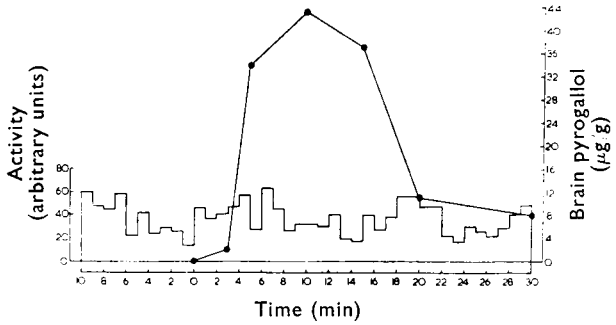

FIG. 2. Penetration of pyrogallol into mouse brain (●) and the effect on motor activity (histogram). Pyrogallol (120 mg/kg) injected at zero time.

TABLE 1. EFFECTS OF CATECHOL (60 MG/KG) AND PYROGALLOL (120 MG/KG) ON THE CONCENTRATION OF MONOAMINES IN MOUSE BRAIN

Time after injection (min)	5-HT μg/g ± s.e.	Noradrenaline μg/g ± s.e.	Dopamine μg/g ± s.e.
Catechol—			
0	0·53 ± 0·02	0·41 ± 0·02	0·58 ± 0·02
5	0·53 ± 0·03	0·40 ± 0·04	0·56 ± 0·02
10	0·51 ± 0·04	0·41 ± 0·02	0·56 ± 0·03
30	0·56 ± 0·02	0·45 ± 0·02	0·61 ± 0·03
Pyrogallol—			
0	0·53 ± 0·02	0·41 ± 0·02	0·58 ± 0·02
10	0·56 ± 0·06	0·36 ± 0·03	0·57 ± 0·03
30	0·60 ± 0·02	0·42 ± 0·02	0·58 ± 0·03

The concentrations of noradrenaline, dopamine and 5-hydroxytryptamine in the brains of mice treated with either catechol or pyrogallol (Table 1) were found to be not significantly different from the levels in control animals. Pyrogallol, administered parenterally to rats has previously been shown to produce no change in the cerebral concentration of catecholamines (Crout & others, 1961; Maitre, 1966) although intra-cisternal injection of this compound has been reported to increase the levels of catecholamines in rabbit brain (Matsuoka & others, 1962). Despite the fact that both catechol and pyrogallol are potent inhibitors of catechol-*O*-methyltransferase it is reasonable to assume that the levels of cerebral catecholamines may be unaltered by these compounds since re-uptake mechanisms are largely responsible for the "removal" of noradrenaline liberated at nerve terminals (see Iversen, 1967).

In conclusion therefore, the results indicate that both catechol and pyrogallol enter the brains of mice after intraperitoneal injection, catechol alone evoking convulsions. Neither of these hydroxyphenolic catechol-*O*-methyltransferase inhibitors produce changes in the gross levels of noradrenaline, dopamine or 5-hydroxytryptamine in mouse brain.

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Departments of Pharmacology and Physiology,
University of Sheffield,
Sheffield, England.

K. J. ROGERS
A. ANGEL
LINDA BUTTERFIELD

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The effect of electroconvulsive shock on the cerebral metabolism of dopamine and 5-hydroxytryptamine

SIR,—Previous reports concerning the effects of convulsive treatment on the levels of 5-HT in brain have been at variance. While Garattini & Valzelli (1956, 1957), Jori, Valsecchi & Valzelli (1957), Fresia, Valsecchi & Valzelli (1957), Garratini, Kato & others (1960) and Breitner, Picchioni & Chin (1964) found significant increases in brain 5-HT concentration after a single electroconvulsive stimulation (ECS) in the rat and other species, Bonnycastle, Giarman & Paasonen (1957) and Bertaccini (1959) could detect no significant increase in 5-HT in rat brain after similar experiments.

Using dogs we have studied the effect of a course of electroconvulsive shock on the cerebral metabolism of 5-HT and dopamine by estimating the concentrations of their amino-acid precursors, tryptophan and tyrosine, and acid metabolites, 5-hydroxyindol-3-ylacetic acid (5-HIAA) and 3-methoxy-4-hydroxyphenylacetic acid (HVA), in samples of cerebrospinal fluid (CSF) drawn serially from the lateral ventricle. On each occasion that electroconvulsive shock was given, the dog was lightly anaesthetized with intravenous sodium thiopentone and 0·7 ml samples of CSF were withdrawn through a needle introduced percutaneously into a cannula previously implanted in the skull (Ashcroft, Crawford & others, 1968). The samples of CSF were taken at 0, 60, 120 and 150 min and an electroconvulsive shock of 150 V for 1 sec, was administered through bitemporal leads at 90 min. 5-HIAA and HVA were estimated by a modification (Ashcroft, Crawford & others, 1968) of the methods of Ashcroft & Sharman (1962) and Andén, Roos & Werdinius (1963); tryptophan and tyrosine were

TABLE 1. CONCENTRATIONS (μG/ML) OF 5-HYDROXYINDOL-3-YLACETIC ACID (5-HIAA) AND 3-METHOXY-4-HYDROXYPHENYLACETIC ACID (HVA) IN DOG LATERAL VENTRICULAR CSF DURING A SERIES OF ELECTROCONVULSIVE SHOCKS (ECS)

Day	Treatment	Dog 1		Dog 2	
		5-HIAA	HVA	5-HIAA	HVA
	Pre-ECS. Mean of two estimates at 0 and 60 min	0·18	1·21	0·17	1·28
1	Post-ECS. Mean of two estimates at 120 and 150 min	0·15	1·02	0·17	1·19
3	Pre-ECS	-	1·06	0·27	1·41
	Post-ECS	- -	1·03	0·27	1·82
8	Pre-ECS	0·31	1·44	0·29	1·43
	Post-ECS	0·31	1·51	0·24	1·43
10	Pre-ECS	0·31	1·35	Methodological difficulties	
	Post-ECS	0·32	1·33		
15	Pre-ECS	0·30	1·28		
	Post-ECS	0·30	1·15		
17	Pre-ECS	0·30	1·19		
	Post-ECS	0·32	1·24		