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5-HYDROXYTRYPTAMINE AND MYOCLONUS INDUCED BY 1,2-DI-HYDROXYBENZENE (CATECHOL) IN THE GUINEA-PIG

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Myoclonus induced by catechol in the guinea-pig is not altered by manipulation of cerebral 5-hydroxytryptamine (5-HT). The administration of catechol does not alter brain levels of 5-HT or its metabolite 5-hydroxyindole acetic acid. This form of myoclonus therefore is not of relevance to the 5-HT-sensitive post-anoxic action myoclonus occurring in man.

Introduction A number of types of myoclonus have been attributed to altered cerebral 5-hydroxytryptamine (5-HT) function. Post-anoxic action myoclonus in man is associated with reduced cerebrospinal fluid concentrations of the 5-HT metabolite 5-hydroxyindoleacetic acid (5-HIAA) and can be relieved by treatment with the 5-HT precursors tryptophan plus a monoamine oxidase inhibitor (MAOI) and 5-hydroxytryptophan (5-HTP) (see Chadwick, Hallett, Harris, Jenner, Reynolds & Marsden, 1977; Chadwick, Hallett, Jenner & Marsden, 1978a). Myoclonus induced in rodents by 1,1,1-trichloro-2,2-bis(*p*-chlorophenyl)-ethane(*p,p'*-DDT) is potentiated by 5-HT receptor antagonists (methysergide, methergoline, cinanserin) and is reduced by 5-HT precursor (5-HTP), 5-HT agonists (quipazine, 5-methoxy-*N,N*-dimethyltryptamine), or 5-HT uptake blockers (chlorimipramine, fluoxetine) (Hwang & Van Woert, 1978; Pratt, Jenner & Marsden, unpublished observations). By contrast, 5-HTP administration actually provokes myoclonus in guinea-pigs (Klawans, Goetz & Weiner, 1973; Chadwick, Hallett, Jenner & Marsden, 1978b).

Angel and his colleagues have studied the physiology and pharmacology of stimulus-sensitive myoclonus and convulsions induced by catechol in rodents, because it appears to be a useful model of epileptogenesis (Angel, 1969; Angel & Lemon, 1973a, b; 1975; Angel, Clarke & Dewhurst, 1977; Angel & Dewhurst, 1975; 1978). In their pharmacological studies in the anaesthetized mouse, Angel *et al.* (1977) established that cerebral catecholamines played no part in the mechanism of action of control, and concluded that the convulsive action of the drug was related to activation of a central cholinergic system. Their studies on the role of cerebral 5-HT on the actions of catechol were inconclusive. *p*-Chlorophenylalanine (PCPA) reduced catechol convulsions, but this effect could not be overcome by concurrent 5-HTP administration; tryptophan potentiated the action of catechol, but reserpine and methysergide had no effect. We have also examined the effect of manipulating cerebral 5-HT action on catechol-induced myoclonus in the guinea-pig, and have studied the effect of catechol on cerebral 5-HT and 5-HIAA concentrations in a variety of brain areas.

Methods Guinea-pigs (Duncan-Hartley, 200 to 300 g) of either sex were studied. Catechol (60 mg/kg i.p.) caused myoclonic jerking on movement within 1 min of administration, and spontaneous repetitive jerking with occasional loss of balance within 2 min, with recovery occurring after 10–15 min.

The following drugs were administered intraperitoneally at the time intervals stated before catechol: 5-HTP (Cambrian Chemicals Ltd.; 100 mg/kg; 30 min) plus carbidopa (Merck, Sharp and Dohme; 25 mg/kg; 60 min), clonazepam (Roche Products Ltd.; 1 or 2 mg/kg; 30 min), quipazine maleate (Miles Laboratories Inc.; 50 mg/kg; 30 min), cyproheptadine hydrochloride (Merck, Sharp and Dohme; 10 mg/kg; 60 min), methergoline (Farmitalia; 5 mg/kg; 60 min), *p*-chlorophenylalanine methylester hydrochloride (PCPA, Sigma Chemical Co.; 300 mg/kg daily for 4 days, last dose 20 min prior). Each drug was given to at least six animals. The doses chosen were those known to antagonize other 5-HT-induced behaviour in rodents.

Animals were killed by cervical dislocation and decapitation 10 min after catechol administration (60 mg/kg i.p.). The brain was rapidly removed, cooled on ice, dissected into parts which were then frozen at −20°C until analysed. 5-HT and 5-HIAA concentrations were determined by the technique of Curzon & Green (1970).

Results None of the drugs affected the intensity or frequency of catechol-induced myoclonus in the guinea-pig.

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Table 1 5-Hydroxytryptamine (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) concentrations in eight regions of guinea-pig brain 10 min following catechol (60 mg/kg i.p.) or saline ($n = 6$)

Treatment		*Concentration of 5-HT or 5-HIAA (ng/g brain)*							
		Pons	*Midbrain*	*Corpus striatum*	*Hippocampus*	*Cerebellum*	*Hypothalamus*	*Mesolimbic*	*Cortex*
Saline	5-HT	836 ± 59	563 ± 35	586 ± 50	454 ± 35	131 ± 13	2307 ± 284	1191 ± 145	390 ± 38
	5-HIAA	204 ± 24	209 ± 16	254 ± 39	154 ± 14	43 ± 9	484 ± 66	297 ± 42	110 ± 13
Catechol	5-HT	772 ± 76	859 ± 194	569 ± 42	474 ± 30	171 ± 14	2519 ± 376	1192 ± 119	391 ± 45
	5-HIAA	229 ± 26	268 ± 17*	298 ± 47	195 ± 14	73 ± 22	548 ± 157	346 ± 63	103 ± 15

* $P < 0.05$ Student's t test compared to saline-treated animals

There was no change in 5-HT levels in any of the brain areas examined, and only 5-HIAA increased in the mid-brain (by 28%). This is unlikely to be of significance, for there was no change in 5-HIAA levels in the major sites of projection of 5-HT neurones arising from the mid-brain, namely in cerebral cortex and striatum.

Discussion We have been unable to demonstrate any effect of a range of drugs chosen to increase brain 5-HT action (5-HTP plus carbidopa or quipazine), antagonize 5-HT receptor action (cyproheptadine or methergoline) or prevent 5-HT synthesis (PCPA) on catechol-induced myoclonus in the guinea-pig. Nor did clonazepam, a drug known to be effective in controlling 5-HT-dependent post-anoxic action myoclonus in man, have any effect on catechol-induced myoclonus. Finally, we could find no clear change in 5-HT or its major metabolite in a variety of brain areas in animals killed while exhibiting muscle jerking after catechol administration. We conclude that catechol-induced myoclonus is not associated with changes in cerebral 5-HT function, and therefore is not relevant to human post-anoxic action myoclonus.

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