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Effects of chlorpromazine on the metabolism of catecholamines in dog brain

H. C. GULDBERG and CELIA M. YATES* (introduced by T. B. B. CRAWFORD), *M.R.C. Unit for Research in Brain Metabolism, University of Edinburgh*

A technique was developed whereby the catecholamines and their metabolites could be estimated in the same brain sample. Using solvent extractions, these compounds were separated from a perchloric acid extract of brain into three groups, namely the acids, the amines and the amino-acids. Homovanillic acid and 3,4-dihydroxyphenylacetic acid were estimated in aliquots of the acid fraction. The amines were separated as their acetylated derivatives, using paper chromatography, eluted and estimated fluorimetrically. A new method, more sensitive than that described in the literature (Carlsson & Waldeck, 1964), was developed for the determination of methoxydopamine.

The analytical method was applied to a study of the effects of chlorpromazine (5 mg/kg and 15 mg/kg intravenously) on the catecholamine metabolism in various areas of the brains of beagle dogs. Two hours after drug administration, the following changes were observed in the caudate nucleus: the dopamine concentration was unaltered by 5 mg/kg and decreased by 15 mg/kg; the levels of homovanillic acid and 3,4-dihydroxyphenylacetic acid were increased by 5 mg/kg and unchanged by 15 mg/kg; the concentration of methoxydopamine fell after both doses of chlorpromazine. Similar changes in the levels of dopamine and its metabolites were observed in the globus pallidus. In those areas of brain containing more noradrenaline than dopamine—the hypothalamus, midbrain, thalamus and hindbrain—the concentration of noradrenaline was increased by both doses of chlorpromazine but there were generally no significant alterations in the concentrations of dopamine and its metabolites.

The main effect of chlorpromazine was considered to be a stimulation of catecholamine synthesis (Carlsson & Lindqvist, 1963). Our results could not, however, be explained entirely on the basis of increased synthesis and it was concluded that chlorpromazine exerted more than one action on the brain amines.

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Influence of drugs on catecholamine metabolism in brain as studied by ^{14}C-tyrosine

H. NYBÄCK* and G. SEDVALL, *Department of Pharmacology, Karolinska Institute and Psychiatric Clinic, St. Göran's Hospital, Stockholm, Sweden*

Results from clinical and pharmacological investigations indicate that changes in the metabolism of brain monoamines exist in diseases of the central nervous system. Several of the most potent psychotropic drugs have been shown to exert specific actions on mono-

amine metabolism in brain (Carlsson & Lindqvist, 1963; Neff & Costa, 1966; Burkard, Gey & Pletscher, 1967). During recent years, different pharmacological and isotopic methods have been elaborated for the study of *in vivo* synthesis and turnover of monoamines.

A study of the influence of some psychotropic drugs on catecholamine synthesis and turnover in the brain *in vivo* is presented. Catecholamine synthesis was studied by measuring the conversion of ^{14}C-tyrosine to ^{14}C-dopamine and ^{14}C-noradrenaline in rat and mouse brain (Sedvall, Weise & Kopin, 1968). Turnover of the amines was estimated from the decline in radioactivity following the pre-labelling of the brain amine stores by ^{14}C-tyrosine administration (Udenfriend & Zaltzman-Nirenberg, 1963). The influence of promethazine, chlorpromazine, haloperidol and desipramine was studied.

Chlorpromazine and haloperidol increased both accumulation and disappearance of ^{14}C-dopamine following administration of ^{14}C-tyrosine. Haloperidol and promethazine slightly increased the disappearance of ^{14}C-noradrenaline, whereas desipramine significantly decreased accumulation of ^{14}C-noradrenaline. The results are taken as evidence that desipramine selectively acts on noradrenaline neurones in the brain, whereas chlorpromazine and haloperidol primarily affect dopamine neurones where synthesis and turnover of the transmitter is increased.

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Excitation of cortical neurones by noradrenaline

E. S. JOHNSON*, M. H. T. ROBERTS†, A. SOBIESZEK‡ and D. W. STRAUGHAN, *Department of Pharmacology and Department of Psychiatry, University of Edinburgh*

A recent study showed that the predominant effect of noradrenaline, applied iontophoretically to cortical cells, was one of excitation (Roberts & Straughan, 1968). The present experiments confirm these findings and deal with the pharmacology of this effect.

Eight hundred neurones from eighty-four adult cats have been studied; about half of the preparations were *encéphale isolé* (in which all possibly painful sites were treated regularly with local anaesthetics) and the remainder were anaesthetized with either a N_2O-halothane mixture, or a barbiturate.

In animals anaesthetized with N_2O-halothane, noradrenaline excited 61% of the neurones tested, depressed 14%, had a mixed effect on 7%, and had no effect on 18%. In the *encéphale isolé* preparations, noradrenaline excited 35%, depressed 18%, gave mixed responses on 12% and did not affect 35%. In the animals under barbiturate anaesthesia, only 8% of neurones were excited by noradrenaline, whereas 62% were depressed and 30% showed no response. This supports the suggestion of Roberts & Straughan (1968) that the use of barbiturate anaesthesia might be responsible for previous failures to obtain excitations with noradrenaline (Krnjević & Phillis, 1963).