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LETTERS TO THE EDITOR

Effects of diethyldithiocarbamate and carbon disulphide on brain tyrosine

Diethyldithiocarbamate (DDC), an inhibitor of dopamine-β-oxidase when injected into rats, brings about a significant decrease in noradrenaline, a slight increase in dopamine (Carlsson, Lindquist & others, 1966), and a significant increase in tyrosine (Goodchild, 1969a) in the brain. As DDC *in vitro* inhibits tyrosine hydroxylase (Taylor, Stubbs & Ellenbogen, 1969), it was suggested by Goodchild (1969a), that the inhibition of tyrosine hydroxylase by DDC was responsible for the *in vivo* accumulation of tyrosine.

However, an earlier observation by Goodchild (1969b), that after the simultaneous administration of 3-iodotyrosine, a competitive inhibitor of tyrosine hydroxylase, the depletion of noradrenaline was significantly slower than that obtained with DDC alone could not be explained by an inhibitory effect of DDC on tyrosine hydroxylase.

In the experiments reported here the concentrations of tyrosine, noradrenaline and dopamine were estimated at intervals after the administration of a single dose of DDC and after repeated exposures to CS_2—a compound which has the same effects on brain catecholamines as DDC (Magos & Jarvis, 1970).

Male albino rats of Porton-Wistar strain, 45–55 days old were used. Sodium diethyldithiocarbamate (Hopkin & Williams Limited, Chadwell Heath, Essex) was given intraperitoneally in 3·5% aqueous solution. Controls were given saline. Exposures to 2·0 mg/litre of CS_2 were made for 4 h each day in a vertical type constant flow inhalation chamber described with the operation procedure for CS_2 elsewhere (Magos, Emery & others, 1970). Control rats were kept in an inhalation chamber without CS_2 for the same period as animals exposed to CS_2. Animals were killed by decapitation either immediately after the last exposure to CS_2, or 1 to 4 h after the administration of DDC. Dopamine and noradrenaline were estimated by a modified version of Chang's (1964) method. This modification with some of the results obtained from CS_2-exposed animals was published by Magos & Jarvis (1970). Tyrosine was estimated by the method of Waalkes & Udenfriend (1957) but time allocated to every step in the procedure was standardized and internal standards were used for every sample. For the three compounds estimated in the brain, normal values $\pm$ s.e. were: noradrenaline, 0·380 ($\pm$0·0090) μg/g; dopamine, 0·709 ($\pm$0·0138) μg/g; tyrosine, 21·52 ($\pm$0·6555) μg/g. Concentrations in the experimental animals were expressed as the percentage of the paired controls.

Fig. 1 shows that after the administration of 500 mg/kg sodium diethyldithiocarbamate, the dopamine concentration in the brain increased, and the noradrenaline concentration decreased. The dopamine concentration reached the maximum 1 h and the noradrenaline the minimum $1\frac{1}{2}$–2 h after injection, and dopamine but not adrenaline returned to the control level 4 h after injection. The decrease in the noradrenaline concentration was significant at any time from $\frac{1}{2}$ to 4 h after injection, but the increase in the dopamine concentration was significant only at 1 to $1\frac{1}{2}$ h. The latter result explains why Carlsson, Lindquist & others (1966), who made the earliest analysis 2 h after DDC, found no significant difference in the brain dopamine concentration.

Tyrosine concentration like that of dopamine reached the maximum 1 h after the injection of DDC, and the increase was followed by a rapid decrease. It reached the control level between 2 and 3 h after injection and at 4 h decreased to 80% of the controls. A similar two-phased change in the brain concentration of tyrosine was observed after repeated daily exposure to 2·0 mg/litre CS_2 but the changes were smaller (Fig. 2). After two days exposure, tyrosine concentration increased to

106·0% and after 10 days exposure it was only 88·8% of the controls. Had the increase in tyrosine arisen from a direct effect on tyrosine hydroxylase by CS_2 or its metabolites, ten days exposure should not have had the opposite effect to a two days exposure. Consequently it seems that, both after a single dose of DDC or repeated exposures to CS_2, at the first phase of the reaction the increase in the

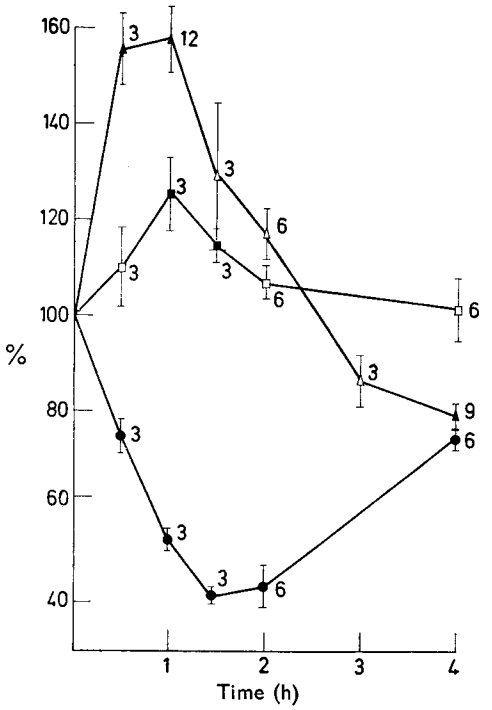

FIG. 1. Effects of 500 mg/kg of DDC on the brain levels of tyrosine (triangles), noradrenaline (circles) and dopamine (squares). Concentrations in the experimental animals are expressed as the percentage of the paired controls. Vertical lines indicate the standard error of means. Solid symbols designates statistically significant differences from the controls at $P < 0.05$ level using the Student *t*-test. Numbers besides the symbols show the number of pairs tested.

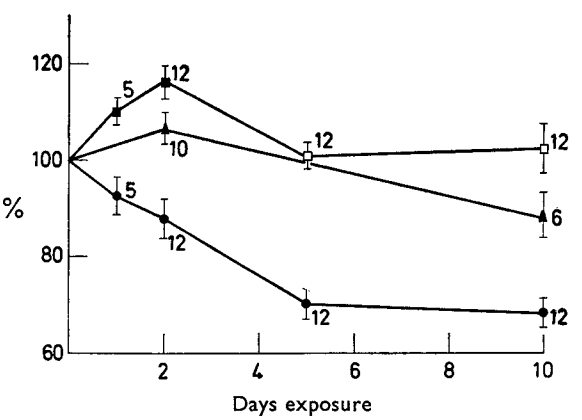

FIG. 2. Effects of repeated daily 4 h exposures to 2·0 mg/litre CS_2 on the brain levels of tyrosine (triangles), noradrenaline (circles) and dopamine (squares). Concentrations in the experimental animals are expressed as the percentage of the paired controls. Vertical lines show the standard error of means; solid symbols designate significant differences from controls at $P < 0.5$ level using the Student *t*-test. Numbers besides the symbols show the number of pairs tested.

dopamine concentration slowed down the conversion of tyrosine to dopa by a feedback mechanism resulting in a subsequent decrease in the concentrations of both noradrenaline and dopamine. When dopamine approached or reached the control level, the feedback effect of noradrenaline became dominant which by increasing the conversion of tyrosine to dopa restored a new balance on the one hand between catecholamines and tyrosine, and on the other hand between noradrenaline and dopamine. Since the deflection in tyrosine concentration after CS_2 was not so extensive as after DDC, and at least after the first or second exposures the increase in dopamine corresponded to the decrease in noradrenaline, CS_2 seems to be more suitable than DDC as an agent for the study of dopamine receptors.

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Blockade of adrenergic transmission by dehydroemetine

The synthetic amoebicidal drug, dehydroemetine, is effective as the natural alkaloid, emetine, in the treatment of amoebiasis and is better tolerated by the patient (Powell, Wilmot & others, 1967), but, as with emetine, gastrointestinal complications like diarrhoea and abdominal colic occur after injections of dehydroemetine in therapeutic doses (Herrero, Brossi & others, 1960). Ng (1966a,b) demonstrated an adrenergic neuron-blocking action for emetine and suggested that diarrhoea produced by this drug might reflect a reduction in intestinal sympathetic activity. I now report that dehydroemetine also has this adrenergic neuron-blocking action.

Segments of rabbit jejunum (Finkleman, 1930) were suspended in 70 ml aerated Tyrode solution (NaCl, 8·0; KCl, 0·2; $CaCl_2$, 0·2; $NaHCO_3$, 1·0; $MgCl_2$, 0·1; NaH_2Po_4, 0·5; Glucose, 1·0 g/litre) at 37°. The periarterial nerves were stimulated with square pulses (20 V; 0·5 ms) for 15 s every 3 min. Cats were anaesthetized with chloralose (80 mg/kg) and pentobarbitone sodium (5 mg/kg, i.v.). The cervical sympathetic nerve was stimulated with square pulses of 20 V and 0·5 ms for 10 s every 2 min, and isotonic contractions of the nictitating membrane were recorded on smoked paper.

Dehydroemetine (0·5–10 μg/ml) had no effect on the tone and pendular movements of the rabbit jejunum but antagonized the relaxation of tone and cessation of pendular movements produced by sympathetic stimulation. The inhibition of pendular movements produced by added noradrenaline (0·2–2 μg/ml) was either not affected or increased. Concentrations of dehydroemetine higher than 10 μg/ml reduced the tone of the intestine and the amplitude of the pendular movements in addition to antagonizing the effects of sympathetic stimulation. The sympathetic block was