oximes had no effect (Table 1). Reserpine did not modify the induced hyperglycaemia but atropine given immediately after malathion completely prevented it. Cerebral glycogen in oxime- and atropine-treated animals was not significantly different from the control values (Table 1).

The results indicate that the oximes given 15 min after malathion had no effect on the induced hyperglycaemia (Table 1). But both atropine and the oximes given immediately after malathion, prevented the hyperglycaemia and depletion in the level of cerebral glycogen induced by malathion (Table 1). 2-PAM besides reactivating the inhibited enzyme, has also been reported to possess a weak atropine-like action (Kuhnen-Clausen 1972). The drugs may be less effective when given 15 min after malathion because at this time the rise in blood glucose level mediated through acetylcholine would most likely have been fully established. It has also been reported that the organophosphorous compounds increase the concentration of cyclic (c)AMP in the cerebral cortex (Coult et al 1979); cAMP also affects storage of glycogen (Larner et al 1968) which is hydrolysed or reduced with the rise in blood sugar level (Vane 1962).

Since malathion-induced changes in the level of cerebral glycogen and blood glucose are not modified by prior treatment with reserpine but are blocked by simultaneous treatment with oximes or atropine, the results provide partial support to the involvement of cholinergic activity in the production of hyperglycaemia in malathion treated rats.

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Low concentrations of cocaine and iprindole increase the neuronal accumulation of noradrenaline in the rat anococcygeus muscle

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The ability of cocaine and of the clinically commonly used tricyclic antidepressants e.g. amitriptyline, imipramine, to inhibit the neuronal accumulation of noradrenaline is well known (e.g. Doggrell & Woodruff 1977). In contrast, iprindole, which is also an antidepressant of tricyclic structure, is reported to be a poor inhibitor of the neuronal noradrenaline accumulation process (Gluckman & Baum 1969; Ross et al 1971). I have re-examined the effects of cocaine and tricyclic antidepressants on the accumulation of ^3H from a medium containing (−)-[^3H]noradrenaline using the rat anococcygeus muscle.

Mature male Wistar rats were killed by a blow at the base of the skull and exsanguinated. Anococcygeus muscles were dissected as described by Gillespie (1972). All experiments were in the presence of a modified Krebs solution of the following composition (mM): NaCl 166, KCl 5·4, $CaCl_2$, 2·5, $MgCl_2$ 1·2, NaH_2PO_4 1·2, $NaHCO_3$ 22·0, D-glucose, 11·2 and Na_2EDTA 0·04, equilibrated with 5% CO_2 in O_2 at 37 °C. Each anococcygeus muscle was mounted on a wire frame under approximately 0·5 g tension in 5 ml Krebs solution. The tissues were equilibrated for 15 min and 5×10^{-8} M (−)-[^3H]noradrenaline was then added for 10 min. The muscles were blotted and transferred to 5 ml of drug-free Krebs solution for a final 10 min wash after which they were blotted and weighed. Each muscle was placed in a test tube with 1 ml of 'Protosolve' (NaOH 120 g in one litre of methanol). When the tissue had dissolved, 10 ml of a toluene-based scintillation fluor and 0·5 ml of glacial acetic acid were added. The tritium in the tissue and medium was determined by liquid scintillation spectrometry.

When the effects of either cocaine or a tricyclic antidepressant on ^3H accumulation were studied, parallel experiments were performed in which different concentrations of these drugs were added to the Krebs solution 5 min before the incubation with (−)-[^3H]noradrenaline. Tissue: medium ratios were calculated and the values obtained in the presence of a drug were expressed as a % ratio in Krebs

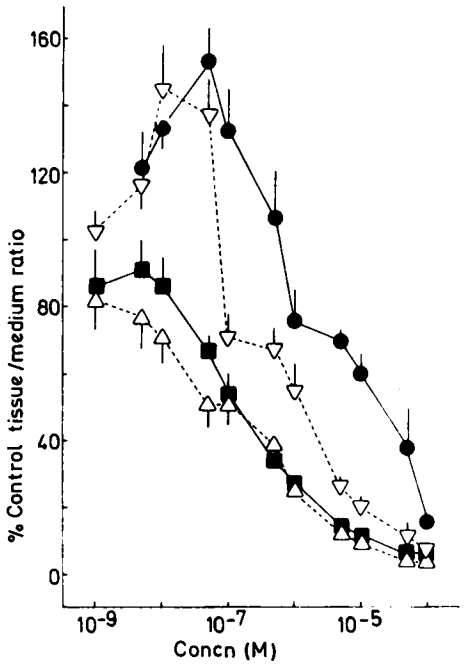

FIG. 1. The effects of cocaine and of tricyclic antidepressants on the accumulation of ^3H in the rat anococcygeus muscle from a medium containing 5×10^{-8} M (−)-[^3H]noradrenaline. Accumulation of ^3H in the presence of cocaine (▽--▽), iprindole (●——●), amitriptyline (△--△), and imipramine (■——■). Accumulation is expressed as a % of the control tissue/medium ratio (ordinate) and plotted against the molar concentration of drug (abscissa). Each value is the mean ± s.e.m. from 4–10 observations.

solution only. Tissue/medium ratios, under different conditions, were compared by Student's unpaired *t*-test and were considered to be significantly different when $P < 0.05$. (−)-[^3H]noradrenaline with a specific activity of 2·2 Ci mmol^{-1} was obtained from the New England Nuclear Corporation. The other drugs used were imipramine hydrochloride* (Ciba-Geigy), amitriptyline hydrochloride* (John Wyeth) and cocaine hydrochloride (May & Baker). (Compounds indicated * were donated).

The rat anococcygeus muscle accumulated ^3H from a medium containing 5×10^{-8} M (−)-[^3H]noradrenaline giving a tissue/medium ratio of 8·80 ± 0·44 (41) [mean ± s.e. mean, n = 41]. The effects of cocaine and of tricyclic antidepressants on the accumulation of ^3H are illustrated in Fig. 1. In the presence of low concentrations of cocaine (5×10^{-9}, 10^{-8}, 5×10^{-8} M) and of iprindole (10^{-8}, 5×10^{-8}, 10^{-7} M) the accumulation of ^3H was greater than in Kerbs solution alone. Amitriptyline and imipramine at low concentrations, 10^{-9} and $10^{-9} - 10^{-8}$ M, respectively, had no effect on the accumulation of ^3H. Higher concentrations of all of the agents tested (cocaine $\geq 10^{-7}$ M, iprindole $\geq 5 \times 10^{-6}$ M, amitriptyline $\geq 5 \times 10^{-9}$ M, imipramine $\geq 5 \times 10^{-8}$ M) reduced the accumulation of ^3H.

After incubation with low concentrations of (−)-[^3H]noradrenaline the ^3H in the rat anococcygeus muscle predominantly represents the neuronal accumulation of noradrenaline (discussed by Doggrell & Woodruff 1977). The present study confirms the widely reported ability of cocaine, amitriptyline, imipramine, and high concentrations of iprindole to inhibit the neuronal accumulation of noradrenaline (reviewed by Maxwell et al 1976). The order of potency of these compounds in this aspect, amitriptyline ≥ imipramine > cocaine > iprindole, is in agreement with previous studies using the rat anococcygeus muscle (Doggrell & Woodruff 1977). The ability of low concentrations of cocaine and iprindole to increase the neuronal accumulation of noradrenaline has not previously been reported. Similar low concentrations of amitriptyline and imipramine did not share this property. The only agent that has previously been reported to increase the neuronal accumulation of noradrenaline is lithium (Colburn et al 1967). Further studies are required (i) to elucidate the mechanism underlying this increased noradrenaline accumulation with low concentrations of cocaine and iprindole in the rat anococcygeus muscle and (ii) to establish whether this phenomenon occurs with these agents in other tissues.

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