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Effect of oximes and atropine on the concentration of cerebral glycogen and blood glucose in malathion-treated rats

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Organophosphorus compounds inhibit cholinesterase and produce toxic effects such as hyperexcitability, tremors and convulsions (Stewart 1952; Nachmansohn 1959); these effects are controlled by oximes which have been reported to reactivate the phosphorylated (inhibited) cholinesterase (Wilson & Ginsburg 1955; Child et al 1955). Although certain organophosphorus compounds have been reported to produce hyperglycaemia (Dybing & Sognen 1958; Holmstedt 1959; Weiss et al 1964), the effect of oximes on this state has not been determined. We have examined the effect of atropine and two oximes, 2-formyl 1-methyl pyridinium oxime chloride (2-PAM) and diacetyl monoxime (DAM) on the concentration of blood glucose in malathion-treated rats; cerebral glycogen concentration in some of the animals was also determined.

Methods

Adult female albino rats, 150 ± 10 g, fasted for 18 h before use (since this was found to give more uniform results) were divided into several groups. The animals of group I were treated with malathion (500 mg kg^{-1} i.p). The animals of group II received malathion followed immediately or after 15 min by 2-PAM or DAM (each, 100 mg kg^{-1} i.p). The animals of the group III were given malathion followed immediately by atropine (75 mg kg^{-1} i.p). The animals of group IV were treated with reserpine (1·0 mg kg^{-1} i.p.) daily for three days before the administration of malathion. Controls had 0·9% NaCl. The animals were decapitated 1 h after treatment with malathion. Blood glucose was determined by the method of Nelson (1944). Cerebral glycogen was extracted according to Lebaron (1955) and estimated colorimetrically (Montgomery 1957). The data were analysed using Student's *t*-test.

* Cor spondence.

Results and discussion

The level of blood glucose was raised and cerebral glycogen reduced after treatment with malathion (Table 1). 2-PAM or DAM given immediately after malathion prevented the increase in blood glucose but when given 15 min later, the

Table 1. Effect of oximes (2-PAM, DAM) and atropine on the level of cerebral glycogen and blood glucose in malathion-treated rats. Each group consisted of eight animals. All the animals were killed 1 h after treatment with malathion.

	Malathion 500 mg kg^{-1} i.p., followed by							
	(1) Controls	(2) None	(3) 2-PAM 100 mg kg^{-1} (after 15 min)	(4) 2-PAM 100 mg kg^{-1} (immediately)	(5) DAM 100 mg kg^{-1} (after 15 min)	(6) DAM 100 mg kg^{-1} (immediately)	(7) Atropine 75 mg kg^{-1} (immediately)	(8) Reserpine*
Blood glucose (mg/100 ml) mean ± s.e.	97·33 ± 3·46	212·83[a] ± 11·36	188·93[a] ± 6·59	111·16[b,c] ± 3·24	197·88[a] ± 6·33	106·37[b,c] ±3·90	111·63[b,c,d] ±1·41	209·75[a] ± 13·75
Glycogen (mg/100 g) mean ± s.e.	100·53 ± 3·51	74·83[a] ± 3·81	80·39[a] ± 4·26	99·61[b,c] ± 4·05	75·61[a] ± 4·53	104·06[b,c,d] ± 5·05	99·94[b,c] ± 3·37	78·08[a] ± 3·79

* Reserpine (1 mg kg^{-1} i.p.) was given daily for 3 days before the administration of malathion.
[a] Significantly different from the control values (group 1), $P < 0·01$.
[b] Significantly different from the values in malathion treated animals (group 2), $P < 0·01$.
[c] Significantly different from the values in group 3, $P < 0·01$.
[d] Significantly different from the values in group 5, $P < 0·05$.

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