EFFECTS UPON PLASMA GLUCOSE OF INHIBITORS OF 5HT UPTAKE AND THEIR INTERACTION WITH 5-HYDROXYTRYPTOPHAN IN PRODUCING HYPOGLYCAEMIA

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5-Hydroxytryptophan (5HTP) has been shown to produce hypoglycaemia in mice pre-treated with monoamine oxidase inhibitors (MAOI) but not in normal mice (Lundquist & others 1971, Furman, 1974). This effect may be mediated at least partly through some central nervous system action of 5HT (Darwish & Furman, 1974). In the present work we have examined the effect upon plasma glucose of 5HTP in normal mice and the interaction between 5HTP and some drugs reported to inhibit the neuronal uptake of 5HT. Other effects of 5HTP believed to be mediated through central 5HT mechanisms have been shown to be augmented by drugs of this type (Sinclair, 1972). Additionally we have examined the effects of inhibitors of 5HT uptake on plasma glucose in mice pretreated with MAOI since 5HT uptake inhibitors may mimic the effects of 5HTP under these conditions (Sinclair, 1972).

All experiments were carried out using male albino mice (20-30g) fasted for 18h beforehand.

5HTP (100-400mg/kg i.v.) produced a dose-dependent hypoglycaemic response which was augmented by MAOI pre-treatment. In normal mice chlorimipramine (1-25mg/kg) fenfluramine (5-20mg/kg) ORG6582* (10-25mg/kg) and mazindol (10-20mg/kg) did not modify the plasma glucose concentration at 1h after i.v. injection although a small hyperglycaemic response was seen at 30 min after the injection of chlorimipramine or ORG6582. However these drugs, when combined with a dose of 5HTP which did not itself alter significantly the plasma glucose concentration, each produced a marked and significant hypoglycaemic effect. Dexamphetamine (5mg/kg) which has not been shown to inhibit 5HT uptake had no effect upon plasma glucose itself but produced a very marked fall in the plasma glucose concentration when combined with 5HTP.

In mice pre-treated with either nialamide (80mg/kg i.p. 18h and 2h previously) or pargyline (100mg/kg i.p. 24, 16 and 2h previously) chlorimipramine, fenfluramine, ORG6582 or mazindol each produced a statistically significant fall in the plasma glucose concentration compared with appropriate controls. Neither nialamide nor pargyline modified the plasma glucose concentration of fasted mice. Dexamphetamine had no effect on the plasma glucose concentration of MAOI pre-treated animals. The effects of chlorimipramine, fenfluramine, ORG6582 and mazindol in producing hypoglycaemia in MAOI pre-treated mice and in augmenting the hypoglycaemic effect of 5HTP in normal animals may be explained by their reported ability to inhibit the uptake of 5HT. However the augmentation of 5HTP induced hypoglycaemia by dexamphetamine probably requires some different explanation and may involve inhibition of MAO (Renson 1971) or the release of 5HT (Fuxe & Ungerstedt, 1970).

* ORG6582 is dl-8-chloro-11-antiamino-benzo-(b)-bicyclo [3.3.1] nona-3,6a(10a) diene hydrochloride.

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