

## Hypoglycaemic action of L-DOPA in nialamide treated mice

SUZAN A.E. DARWISH & B.L. FURMAN\*

*Department of Physiology & Pharmacology, University of Strathclyde, George Street, Glasgow G1 1XW*

5-Hydroxytryptamine, dopamine and their precursors have various effects on blood glucose depending upon the route of injection and whether or not the animals have been fasted or fed. The hyperglycaemic action of L-DOPA and dopamine is well documented (Hakansson, Lundquist & Rerup, 1967). 5-Hydroxytryptophan (5-HTP) injected intravenously (i.v.) or intracerebroventricularly (i.c.v.) and 5-HT injected i.c.v. but not i.v. have been reported to produce hypoglycaemia in mice pretreated with monoamine oxidase inhibitors (MAOI) (Darwish & Furman, 1974). In fed mice pretreated with a monoamine oxidase inhibitor (nialamide 80 mg/kg 20 h and 2 h before blood sampling) both L-DOPA and dopamine produced a dose-dependent elevation in plasma glucose confirming the results of Hakansson *et al.* (1967). However, in fasted, nialamide-treated mice L-DOPA, but not dopamine produced a dose-dependent hypoglycaemic response at 1 h and 2 h after i.v. injection. This response could only be obtained in mice treated with nialamide. DOPA (10 µg) or dopamine (10 µg) each produced hypoglycaemia when injected intracerebroventricularly. This suggested a possible central site of action for L-DOPA. The hypoglycaemic response to L-DOPA was prevented by the dopamine receptor blocking drug haloperidol (0.2 mg/kg s.c. 30 min before injecting L-DOPA). Haloperidol itself had no

effect on plasma glucose and did not prevent the hypoglycaemic response to 5-HTP (4 mg/kg i.v.). Cyproheptadine (0.1 mg/kg) or methysergide (0.1 mg/kg) known to block the hypoglycaemic action of 5-HTP (Furman, 1974) each injected 30 min prior to L-DOPA also blocked the response to L-DOPA (20 mg/kg).

Parachlorophenylalanine (PCPA) (300 mg/kg daily for three days p.o.) prevented the hypoglycaemic response to L-DOPA (20 mg/kg or 80 mg/kg) PCPA itself produced an increase in the plasma glucose concentration. Prevention of the response by the 5-HT receptor blocking drugs methysergide and cyproheptadine and by the 5-HT synthesis inhibitor PCPA suggested that the response to L-DOPA might be mediated by 5-HT. However, it was found that PCPA pretreatment also prevented the hypoglycaemic response to 5-HTP (4 mg/kg i.v.) or to 5-HT (10 µg by intracerebroventricular injection). The mechanism of the hypoglycaemic response to L-DOPA in MAOI pretreated mice remains to be determined as does the role of 5-HT in the production of the response.

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### References

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## The relation between the plasma concentration of edrophonium, inhibition of erythrocyte acetylcholinesterase, and the facilitation of neuromuscular function in the rat.

H.E. BARBER, T.N. CALVEY, K.T. MUIR\* & K. TAYLOR

*Dept. of Pharmacology & Therapeutics, University of Liverpool*

Although both the biological effects and the pharmacokinetics of edrophonium have been investigated (Randall, 1950; Back & Calvey, 1972a, 1974) little is known of the correlation

between them. We have therefore studied the relation between the plasma concentration and the pharmacological activity of the short-acting quaternary amine.

Male Wistar rats (body weight: 250-350 g) were anaesthetized with urethane (1.4 g/kg, i.p.). The contraction of the tibialis anterior muscle evoked by supra-maximal sciatic nerve stimulation (0.33 Hz, 0.5 ms) was measured from both hind limbs. [<sup>14</sup>C]-edrophonium (dose: 4 or 10 µmol/kg) was rapidly administered via the jugular vein. Blood samples were collected at intervals for up to 3 hours. Part of the sample was analysed for acetylcholinesterase inhibition by radiometric assay (Potter, 1967; Smith, 1974). (This method abolishes the effects of dilution and