Reduction of locomotor activity in mice by dopamine-β-hydroxylase inhibitors — evidence against the involvement of non-specific irritation

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Dopamine-β-hydroxylase (DBH) inhibitors are widely used as research tools to distinguish between dopaminergic and noradrenergic mechanisms. However, it has been suggested (Moore, 1969; Thornburg & Moore, 1973) that the effects of DBH inhibitors on reducing spontaneous motor activity are not causally related to the depletion of brain noradrenaline which they produce, but to the stress provoked by local irritation which is reflected in the rise in blood glucose and plasma corticosterone which occurs after their intraperitoneal administration (Thornburg & Moore, 1971).

We have tested this hypothesis by comparing two DBH inhibitors with two known irritants, for their ability to produce irritation and their effect on motor activity. The two DBH inhibitors used were 1,1-dimethyl-3-phenyl-2-thiourea (U10,157) and bis(4-methyl - 1 - homopiperazinylthiocarbonyl)-disulphide (FLA-63) in doses which are known to inhibit cerebral DBH. The two irritants used were colloidal carrageenan and kaolin. Their effects were compared on the induction of mouse paw oedema after subplantar administration, and in stimulation of peritoneal exudation after intraperitoneal administration as measured by leakage of intravenous Evans' Blue dye into the peritoneal cavity. Their effects were also compared on apomorphine and L-DOPA-induced motor activity. The results show that although FLA-63 and carrageenan in the concentrations used have a similar ability to produce inflammation and intraperitoneal irritation, carrageenan has no effect on motor activity produced by L-DOPA; neither the irritants nor the DBH inhibitors affect apomorphine-induced locomotor activity.

We conclude that although the DBH inhibitors tested are irritants, they are producing their effect on motor activity by a more specific direct mechanism which we believe to be related to depletion of cerebral noradrenaline.

References

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A pithed rabbit preparation for stimulation of different segments of the autonomic outflow

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Gillespie, MacLaren & Pollock (1970) described a method of stimulating different segments of the autonomic outflow from the spinal cord to various organs in the pithed cat and rat. We have modified this method for use in the rabbit. Since the geometry of the rabbit skull does not permit pithing via the orbit as in the cat and rat, this has been accomplished through a trephine-hole.

New Zealand white rabbits (3.0-3.5 kg) were anaesthetized with halothane (3%) and were decerebrated following placement of cannulae in the trachea, both carotid arteries (left, for arterial and left ventricular pressure; right, for thermistor for cardiac output), and a jugular vein (for administration of drugs). Halothane was then discontinued, gallamine (1 mg/kg i.v.) was given and mechanical ventilation with 100% O_2 (Harvard Respirator) was adjusted to give an end-tidal CO_2 of 3-4% (Beckman Medical Gas Analyser LB-2). Pithing was carried out using a teflon covered stainless steel rod identical to that used for the cat by Gillespie *et al.* (1970). The resulting preparation had a resting arterial pressure of 48 ± 3 mmHg systolic and 26 ± 2 mmHg diastolic, and heart rate of 230 ± 4 min^{-1} ($n = 9$), which together with blood gas values remained stable over a period of at least 6 hours. As in the previous study in the rat and cat (Gillespie *et al.*, 1970), reproducible cardiovascular responses could be obtained to stimulation of the autonomic