The effect of metiamide on protracted anaphylaxis in the guinea-pig

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The intravenous injection of antigen in actively sensitized guinea-pigs results in death due to respiratory failure which occurs within a few minutes of injection. However, the injection of antigen by intraperitoneal or subcutaneous route usually results in protracted anaphylactic shock a major effect of which is congestion and/or haemorrhaging of the gastrointestinal tract (Stone, 1959). In the present experiments we have studied the effect of the histamine H_2-receptor antagonist, metiamide (Black, Duncan, Emmett, Ganellin, Hesselbo, Parsons & Wyllie, 1973) upon the reaction.

Guinea-pigs (500–700 g), sensitized to egg albumen at least 3 weeks previously, were pretreated with mepyramine (2 mg/kg) 1 h before challenge by the i.p. administration of egg albumen (40 mg). The animals showed some respiratory distress but did not die as a result of respiratory failure. After 30 min they became lethargic and showed piloerection. Those animals that died (7/15) did so between 30 and 120 min after the antigen injection and the remainder were killed after 3 hours.

Upon examination, little evidence of lung damage was seen, but the stomach and large intestine showed signs of hyperaemia and localised haemorrhagic patches were apparent. The volume and pH of the contents were measured and the mucosa examined for damage using a dissection microscope. Mucosal damage varied in extent from small petechiae to larger haemorrhagic lesions located in the main body of the stomach. Rarely were lesions seen in the fundus or pyloric antrum. Pretreatment with metiamide (10 mg/kg s.c.) 30 min before challenge reduced the severity of the lesions but did not prevent them.

In the anaesthetized guinea-pig, histamine infusions (0.5–20 $\mu g\ kg^{-1}\ min^{-1}$ i.v.) caused an increase in gastric acid secretion but the introduction of egg albumen, i.p. or i.v. in sensitized animals failed to increase gastric acid secretion. Thus protracted anaphylaxis following i.p. egg albumen results in gastric mucosal damage that is not associated with an increase in gastric acid secretion.

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Evidence *in vivo* for a 5-hydroxytryptamine link in dopamine-receptor-mediated hypothermia in the rat

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In rats, intrahypothalamic injection of dopamine agonists causes a fall in core temperature which appears to be mediated through tail skin vasodilation (Cox & Lee, 1977). An involvement of 5-hydroxytryptamine (5-HT) in this response has been suggested (Maj & Przewlocka, 1975; Przewlocki, 1977), but there is no general agreement (Grabowska, Michaluk & Antkiewicz, 1973). Therefore in this study, we have investigated the possibility of a 5-HT link.

Male Sprague–Dawley rats were used at the ambient temperature of 17°C. Drugs were injected into the preoptic anterior hypothalamus through previously implanted guide cannulae in a dose volume of 1 µl. Core temperature was measured by means of a rectal probe and tail skin temperature by a small strap-on thermistor.

Intrahypothalamic injection of either dopamine or 5-HT caused a fall in core temperature which was blocked by intrahypothalamic pretreatment with either methysergide or cyproheptadine (Figure 1). Oxotremorine-induced hypothermia was unaffected by these antagonists. Haloperidol antagonized dopamine but not 5-HT (Figure 1). These findings support the suggestion of a 5-HT link.

Further evidence for 5-HT involvement came from studies with 5,6-dihydroxytryptamine (5,6-DHT), which was injected bilaterally into the preoptic area two weeks prior to the experiment in a dose of 8 µg in 2 µl and which significantly depleted hypothalamic 5-HT ($P < 0.01$) without affecting hypothalamic dopamine. This pretreatment antagonized dopamine, but was without effect on intrahypothalamic 5-HT (Figure 1). Furthermore, 5,6-DHT treated rats sub-

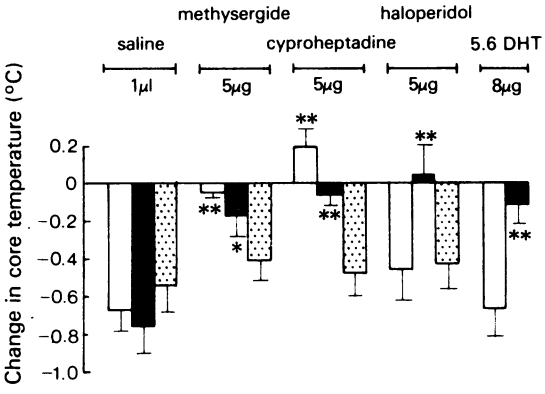

Figure 1 Change in core temperature after intrahypothalamic injection of 5-hydroxytryptamine (20 μg, open column), dopamine (10 μg, closed column) or oxotremorine (1.25 μg, dotted column) in saline or drug pretreated rats. Each column represents the mean maximum change in core temperature ±s.e. mean ($n = 4$ to 18). Significance of difference from appropriate agonist control, $*P < 0.05$, $**P < 0.01$ (Mann-Whitney U test, two tailed).

jected to a heat load were incapable of initiating heat loss in a manner analogous to that following blockade of hypothalamic dopamine receptors (Cox & Lee, 1977). These results support the hypothesis of a dopamine-5-HT link in the central thermoregulatory pathways of the rat.

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Does 5-hydroxytryptamine influence the facilitating effect of fenfluramine on glucose uptake into rat isolated hemidiaphragm?

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Fenfluramine, a clinically useful anti obesity drug, will, in the presence of insulin, increase glucose uptake into rat isolated hemidiaphragm (Bajaj & Vallance-Owen, 1974; Frayn, Hedges & Kirby, 1974) and human gluteus maximus (Kirby & Turner, 1974). Of a series of drugs known to be antagonists of various types of pharmacological receptors, only methysergide appeared to inhibit this effect (Kirby & Turner, 1974), suggesting that 5-hydroxytryptamine may play a role in this phenomenon.

Using the methods described by Frayn *et al.* (1974) on groups of ten rats of the Wistar breed, 5 to 6 weeks old and starved for 24 h prior to sacrifice, we have confirmed that fenfluramine facilitates glucose uptake into rat isolated hemidiaphragm in the presence of insulin 100 μu/ml (mean % glucose uptake increase 77.69, $P < 0.001$).

5-HT (1 μg/ml) in the presence of insulin (100 μu/ml) had no effect on glucose uptake. When 5-HT (1 μg/ml) was added to fenfluramine (100 ng/ml) in the presence of insulin (100 μu/ml), glucose uptake was not significantly different from that with fenfluramine alone. 5-HT (10 μg/ml) also had no effect. However, 5-HT (100 μg/ml) added to fenfluramine (100 ng/ml) in the presence of insulin (100 μu/ml) increased glucose uptake by 26.71% compared to fenfluramine (100 ng/ml) alone ($P < 0.05$). 5-HT (1 μg/ml) added to fenfluramine (50 ng/ml) did not significantly increase glucose uptake compared to fenfluramine (50 ng/ml) alone. 5-HT (100 μg/ml) added to similar fenfluramine concentration in the presence of insulin (100 μu/ml) significantly increased glucose uptake (mean % increase 54.50, $P < 0.025$) when compared to fenfluramine (50 ng/ml) alone in the presence of insulin (100 μu/ml).

The results show that the facilitating effect on glucose uptake seen with fenfluramine in rat isolated hemidiaphragm is significantly increased by 5-HT and are consistent with the hypothesis that the influence of methysergide on the action of fenfluramine on isolated skeletal muscle uptake is mediated by 5-HT receptor blockade.

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