(right side: 14·7 s.d. 4·7 cm^2; left side: 15·00 s.d. 6·7 cm^2). By contrast, the extent of "blue-colourization" in control animals was found to be significantly larger (5·2 s.d. 2·5 cm^2) than that of metiamide-treated animals (1·8 s.d. 1·0 cm^2).

Metiamide treatment proved to be effective for reducing the extent of brain oedema. For this reason, our results clearly indicate that, following ^{90}Y implantation, H_2 receptors were involved in the development of brain oedema. As metiamide is known to be unable of crossing the "blood-brain" barrier, it is conceivable that, in our experiments, the prevention of brain oedema was gained by the metiamide-provided insensitivity of brain capillaries to histamine released from ^{90}Y-irradiated brain tissue.

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Effect of mazindol on glucose uptake into human isolated skeletal muscle

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Previously Kirby (1974) and Kirby, Carageorgiou-Markomihelakis & Turner (1975) have examined the effects of various anorectic drugs on glucose uptake into human isolated skeletal muscle, and have shown that fenfluramine, its main metabolite norfenfluramine and flutiorex; all cause significant insulin-dependent increases in glucose uptake. That work was prompted by the observation of Butterfield & Whichelow (1968) that acute administration of fenfluramine increased glucose uptake into the muscle of the human forearm. In contrast, Kirby & Turner (1974a, b) found that amphetamine caused no significant alteration in glucose uptake into their isolated muscle preparation. Mazindol, a new anorectic agent (Smith, Innes & Munro, 1975), is chemically unrelated to amphetamine, fenfluramine and flutiorex, being an imidazo-isoindole, 5-hydroxy-5-*p*-chlorophenyl-2,3 dihydro-5H-imidazo (2,1-a)isoindole. The activity of this drug on the same *in vitro* preparation has been investigated.

The preparation of the muscle, incubation and estimation of glucose uptake were as described by Frayn, Adnitt & Turner (1973). Human skeletal muscle, gluteus maximus or gluteus medimus, was obtained at surgery for total hip joint replacement. Six or more parallel muscle strips of wet weight 80–155 mg were prepared from each muscle sample so that dose response curves could be determined. The concentrations of mazindol were 0, 10, 50, 100, 500 and 1000 ng ml.$^{-1}$ Mazindol is almost insoluble in water, but is fairly soluble in a weak acid. For the present purpose stock solutions of mazindol and insulin were prepared by dissolving them in N/30 HCl to give concentrations of 1 mg ml^{-1} and these stock solutions were subsequently diluted with Krebs-bicarbonate buffer as required.

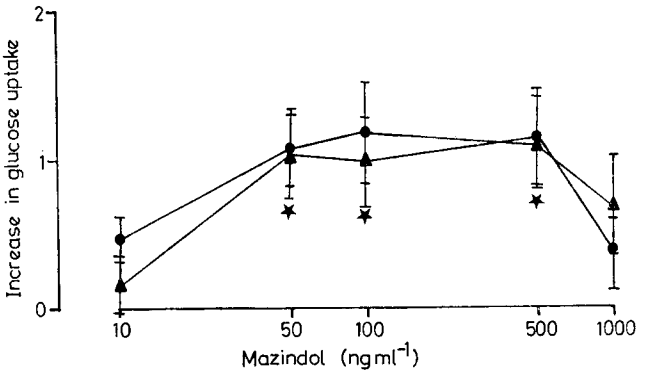

FIG. 1. Dose-response curves (mean ± s.e., n = 5) for mazindol on glucose uptake (mg g^{-1} wet weight tissue in 90 min) in the presence (▲) and absence (●) of insulin. ✱ indicates significant differences from control at the 5% level using a paired *t*-test.

Dose response curves, obtained in the presence and absence of insulin (100 μU ml^{-1}) are shown in Fig. 1, each point being the mean of five observations. It can be seen that mazindol caused a similar and significant increase in glucose uptake in both the presence and absence of insulin. The maximum response seen with mazindol is similar to that reported earlier with fenfluramine and norfenfluramine (Kirby, 1974) and flutiorex (Kirby & others, 1975). However, unlike the response seen with these drugs the response to mazindol was not dose-dependent above 50 ng ml^{-1} nor dependent upon the presence of added insulin.

The daily recommended dosage is only 1–3 mg and therefore the blood concentrations achieved will probably be much lower than 50 ng ml^{-1}, the concentration at which a significant increase in glucose uptake was demonstrated. This is in contrast to the previous work with fenfluramine, where the maximal effects seen on glucose uptake occurred with concentrations within the reported therapeutic drug concentrations and where the daily dose is 80–120 mg. Whether this finding has clinical relevance requires further study.

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