Metiamide-treatment of brain oedema in animals exposed to ^{90}yttrium irradiation

F. JOÓ, A. SZÜCS*‡, E. CSANDA†, *Institute of Biophysics, Biological Research Center, Szeged, Hungary, *Department of Neurology, Medical University, Szeged and †Department of Neurology, Semmelweis Medical University, Budapest, Hungary*

The fact that, in brain capillaries, the regulation of permeability is cAMP-mediated has been evidenced (Joó, 1972). Histamine, which has long ago been found to be capable of increasing the permeability in brain capillaries (Földes & Kelentei, 1954), was shown recently to activate the adenylate cyclase in a subcellular fraction enriched by brain capillaries (Joó, Rakonczay & Wollemann, 1975). When the receptor properties of the adenylate cyclase were determined in the capillary-rich fraction, the presence of histamine H_1 and H_2 receptors were revealed. We have concluded that, in certain cases, histamine H_2 receptor blockers may be of use in the treatment of brain oedemas. To test the validity of our assumption, ^{90}yttrium (^{90}Y) irradiating β-electrons was chosen because it is frequently used in the neurosurgery, even though it induces, as an undesirable side effect, severe brain oedema in the white matter (Constans, Szikla & David, 1960).

^{90}Y cubes (approx. 4 mm^3) of varying strength (from 2·5 mCi to 0·1 mCi) were implanted on the right side to the surface of the parietal cortex in 4 adult dogs and 2 cats. After surgery, animals were treated either with metiamide (generous gift of Dr. R. W. Brimblecombe from The Research Institute, Smith Kline and French Laboratories Limited, Herts, England) or with saline (controls). Injections of metiamide were given intraperitoneally in a maintaining dose of 50 μg kg^{-1}. Animals being subjected to ^{90}Y irradiation were as a rule somnolent and apathic over the whole duration of observation, whereas those treated with metiamide did not show any sign characteristic of severe brain oedema. 24 or 72 h after implantation animals were killed in anaesthesia. To check the change in the permeability of brain capillaries to serum albumin, animals were given 2·5 ml kg^{-1} of 1 % Evans- blue 24 h before

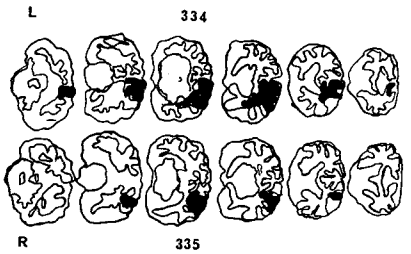

FIG. 1. Line drawing showing the extent of white matter and "blue-colorization". Planimetry was carried out. Dark areas represent the extent of brain oedema in control (334) and metiamide-treated (335) animals. L: left side; R: right side.

investigations. To express quantitatively the extent of oedema, the area of white matter and the "blue-colourization" was measured planimetrically on symmetrical coronal slices (approx. 5 mm thick) obtained from the hemispheres of different animals. Corresponding areas of the right and left hemispheres from 3 control and 3 metiamide-treated animals were averaged and the mean and s.d. were expressed. The extent of white matter in the control animals (right side: 15·8 s.d. 5·4 cm^2; left side: 14·8 s.d. 6·6 cm^2) was found to be similar to those of metiamide-treated animals

‡ On sabbatical leave with a Humboldt fellowship at the Psychiatrische und Nervenklinik, Universitäts-Krankenhaus Eppendorf, Hamburg, F.R.G.

(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

M. J. KIRBY, P. TURNER, *Clinical Pharmacology Department, St. Bartholomew's Hospital, London EC1A 7BE, U.K.*

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.