Hyperphagia caused by Cerebral Ventricular Infusion of Phloridzin

WE report here an experiment which seems to provide definite proof that the hypothalamic feeding mechanism contains glucoreceptors controlling satiety. That such glucoreceptors exist, and are different metabolically from other brain tissue, had been suggested indirectly by studies relating hunger and gastric contractions to the utilization of glucose¹ and by work on goldthioglucose. Single injections of this compound cause lesions in the ventromedial area of the hypothalamus². The action is specific chemically: glucose and not similar metabolites has to be a part of the molecule³. It is specific anatomically: induced weakness of the blood-brain barrier in other cerebral areas does not increase permeability to this compound⁴. Goldthioglucose destroys cells the axons of which connect the ventromedial area to the lateral area⁵, and cells at the origin of Schultze's bundle—a structure which links the hypothalamus to the roots of the vagus⁴. The former gives an anatomical basis for the known physiological relation between the "satiety" area and the "feeding" area, the latter for the physiological role of the ventromedial area in inhibition of gastric contractions by glucagon⁶ and stimulation of gastric secretion by insulin⁷. The action of goldthioglucose is blocked by analogues of glucose⁸ and by alloxan diabetes⁹, the latter confirming the postulated dependency of the glucoreceptors on insulin. Anand has also shown that the electrical activity of the ventromedial area is increased when the utilization of glucose is increased and vice versa, while the lateral area shows the opposite pattern¹⁰.

In our experiment, phloridzin, a known inhibitor of glucose uptake in a wide variety of tissues (though not known, until now, to inhibit any neural tissue), was tested for similar effects in hypothalamic glucoreceptors in rats. A cerebral lateral, ventricular infusion of a 1×10^{-3} M solution at a rate of 1 to 2 μ l./min for 50 to 90 min resulted in marked hyperphagia (up to 30 g of Purina chow a day for 250 g females—double the normal intake) and gain in weight (up to 15 g/day).

The hyperphagic effect was transient (approximately 48 h) when the rate of infusion was 1 μ l./min and the animals gained 15 to 30 g during this interval. It lasted for at least 2 weeks when the rate was 2 μ l./min and the animals gained up to 5 g/day. Intraperitoneal injections of doses of phloridzin, two to four times greater than those injected into the ventricle, had no effect on food intake. (The amount of phloridzin infused is too small to have any detectable systemic effect.) The data confirm the existence of cerebral glucoreceptors which are involved in the regulation of food intake. The presumption that they are identical to the hypothalamic receptors previously identified is being tested experimentally.

ZVI GLICK
JEAN MAYER

Department of Nutrition,
School of Public Health,
Harvard University,
Boston, Massachusetts.

Received July 18, 1968.

- ¹ Mayer, J., *Ann. NY Acad. Sci.*, **63**, 15 (1955).
- ² Marshall, N. B., Barnnett, R. J., and Mayer, J., *Proc. Soc. Exp. Biol. and Med.*, **90**, 240 (1955).
- ³ Mayer, J., and Marshall, N. B., *Nature*, **178**, 1399 (1956).
- ⁴ Mayer, J., and Arees, E. A., *Fed. Proc.* (in the press).
- ⁵ Arees, E. A., and Mayer, J., *Science*, **157**, 1574 (1967).
- ⁶ Mayer, J., and Sudsaneh, S., *Amer. J. Physiol.*, **197**, 274 (1959).
- ⁷ Ridley, P. T., and Brooks, F. B., *Amer. J. Physiol.*, **209**, 319 (1965).
- ⁸ Likuski, H. J., Debons, A. F., and Cloutier, R. J., *Amer. J. Physiol.*, **212**, 669 (1967).
- ⁹ Debons, A. J., Krinsky, I., Likuski, H. J., From, A., and Cloutier, R. J., *Amer. J. Physiol.*, **214**, 652 (1968).
- ¹⁰ Anand, B. K., Chhina, G. S., Sharma, K. N., Dua, S., and Singh, B., *Amer. J. Physiol.*, **207**, 1146 (1964).

Implications of Hyperglycaemia and Cataract in a Colony of Tuco-tucos (*Ctenomys talarum*)

SPONTANEOUS diabetes mellitus occurs rarely in domestic animals¹⁻². It has been found in more than 10 per cent of individuals in captive colonies of the Egyptian sand rat (*Psammomys obesus*)³, the Israeli spiny mouse (*Acomys cahirinus*)⁴, the Philippines tree shrew (*Urogale everetti*)⁵ and the squirrel monkey (*Saimiri sciureus*)⁶.

A colony of tuco-tucos of unknown age from a restricted locality in the province of Buenos Aires, Argentina, was established at the Wellcome Institute of Comparative Physiology. The tuco-tuco (*Ctenomys talarum*) is a small (120 mm) burrowing hystricomorph rodent. The forty males weighed 85–210 g (mean 166 g). Many of the seventy-six females (95–190 g, mean 127 g) were pregnant. After pregnancies lasting at least 3 months, twenty-seven litters of one to six young were born. This F_1 generation was weaned when 4 weeks old, and housed like the parent colony, one male to three females, in 0.25 in. wire mesh cages, 22 in. long, 17 in. wide and 8 in. deep. Room temperature was maintained at 20°C; room lights were on from 08.00 h to 20.00 h and skylights provided natural daylight. Initially, each animal consumed approximately 5 g of compound diet pellets (Dixon, Diet 86), 10 g of hay, 10 g of carrot, 5 g of cabbage and 2 g of sunflower seeds daily.

Dense lens opacities were first observed in members of the F_1 generation at the age of 3 months and some animals appeared to be obese. The first complete eye and blood sugar assessments were carried out on all members of this generation after 2–5 months on the diet. The animals were then subdivided randomly into two groups: two-thirds received hay, sunflower seeds and pellets daily, together with cabbage and carrot three times weekly (diet A), and the remaining one-third were fed similarly, but were deprived of pellets (diet B). One month later, the eyes and blood sugar concentrations of the parent colony were assessed.

Qualitative and quantitative reagent strips and tablets (Ames: 'Clinitest', 'Albustix' and 'Acetest') were used for analysis of urine. A retro-orbital bleeding technique⁷ was used to obtain 50 μ l. aliquots of blood which were analysed by a modified microferriocyanide method with a Technicon autoanalyser⁸. Bleeding was carried out under brief, light halothane anaesthesia by a "bell-jar" technique which has been shown not to produce transient hyperglycaemia⁹. Blood samples were all collected between 11.00 h and 13.00 h without food withdrawal. Both eyes of each animal were examined by direct ophthalmoscopy with or without mydriasis, using 1 per cent tropicamide ('Mydriacyl'). The observer (J. M. H.) was unaware of the blood sugar status of the animals. Representative lesions were photographed with a Kowa II medical camera.

A change of refractive index at the lens equator, seen only after mydriasis, was the most minor sign of lens abnormality. Other changes included vacuolation (Fig. 1a and b), discrete opacities (Fig. 1c) and complete opacification of the lens (Fig. 1d). In some animals, the changes appeared sequentially. One to two months later, regressive changes were seen in some lenses (Fig. 1e).

In the F_1 generation of forty-seven animals, nineteen (40 per cent) had one or more of these lens changes, and the distribution of blood sugar values according to lens appearance in the least affected eye of each animal is shown in Fig. 2. The blood sugar concentration (mean $\pm$ S.D.) for the group with the normal lenses was 101 ± 34 mg per cent, compared with 150 ± 30 mg per cent for the group showing vacuoles ($t = 2.79$, $0.001 < P < 0.01$) and 174 ± 58 mg per cent for the group with more advanced cataractous changes ($t = 5.79$, $P = 0.001$). There was a highly significant correlation between blood sugar level and weight at the time of sampling ($r = 0.61$, $P = 0.001$),