Gluconeogenesis following Hypothalamic Stimulation

In previous experiments[1,2], a rise in serum glucose, and increased endogenous gluconeogenesis in liver slices, was found 5 min after the injection of 50–100 mg of 2-deoxyglucose (2 DG), an inhibitor of glucose utilization, into fasting rats. 2 h after administration of 2 DG, an accumulation of liver glycogen was observed. There was a constant rise in urea excretion during the first 24 h. Adrenalectomy inhibited the response to 2 DG, and no effect was observed when 2 DG was injected together with glucose or insulin.

The changes due to 2 DG were not observed in animals anaesthetized with ether or pentobarbital. This suggested that stimulation of gluconeogenesis at least in these experiments originated in the central nervous sytem, possibly in the hypothalamus. The actual stimulus in the hypothalamus may be cellular glucopenia due to inhibition of glucose utilization caused by 2 DG. Previous observations in both experimental animals[1] and man[3] support the concept that 2 DG acts on the hypothalamus. If this hypothesis is correct an electrical stimulation of the hypothalamus may induce gluconeogenesis, and the present communication reports the results of such experiments. The stimulation was carried out in the following manner.

A bipolar stainless steel electrode—insulated except for its tip—was implanted, with the aid of a 'Krieg' stereotaxic instrument, into the posterior hypothalamus or caudate nucleus of male albino rats weighing between 200 and 300 g. One week after the surgical procedure the rats were deprived of food overnight and then stimulated with a 'Grass' stimulator with pulses of 10 msec duration and at a frequency of 20/sec. The current and duration of stimulation are shown in Table 1. Other animals which were similarly treated on the same day and kept exactly under the same conditions served as controls. Within 30 min of the end of the stimulation the animals were anaesthetized and killed by bleeding. Hepatic gluconeogenesis and glycogen content were determined. The brains were removed, fixed in formalin, cut at 80μ and examined for confirmation of the position of the stimulating electrodes (Fig. 1).

It was found that electrical stimulation of the hypothalamus increased the serum glucose level and the rate of hepatic gluconeogenesis. After 3 h, a 10–20-fold rise in liver glycogen was found. The stimulation was effective with a current as low as 0·06 m.amp.

Electrical stimulation at a different area in the central nervous system, namely, the caudate nucleus, had no effect on the measured parameters.

As in the case of 2 DG, adrenalectomized rats did not show an increased rate of gluconeogenesis after electrical stimulation.

These results and our earlier observation that anaesthesia inhibits the onset of gluconeogenesis indicate the important role of the central nervous system in the regulation of gluconeogenesis and consequently of the blood glucose level. It seems that both electrical stimulation and 2 DG cause a discharge of adrenocorticotrophic hormone releasing factor, thus activating the adrenal cortex.

Table 1. Effect of Electrical Stimulation of the Hypothalamus on Gluconeogenesis in Rats

Implantation	Current (m. amp)	Duration of stimulus (h)	Serum glucose (mg%)		Gluconeogenesis in liver slices (μmole glucose/100 mg wet tissue/2 h)		Glycogen in liver (γ/100 mg wet tissue)	
			E	*C*	*E*	*C*	*E*	*C*
Posterior hypothalamus	1·80	3	175 ± 14·7 (7)*	101 ± 13·0 (5)	2·96 ± 0·01	1·32 ± 0·03	300 ± 36	24 ± 2
	1·80	1/2	150 ± 13·6 (3)	95 ± 12·8 (2)	3·40 ± 0·08	1·90 ± 0·09	34 ± 4	30 ± 4
	0·20	3	150 ± 9·1 (4)	103 ± 9·5 (4)	2·50 ± 0·06	1·10 ± 0·08	600 ± 53	35 ± 2
	0·20	1/2	180 ± 15·8 (3)	105 ± 9·3 (2)	2·40 ± 0·03	1·70 ± 0·05	20 ± 3	20 ± 3
	0·06	3	135 ± 23·0 (3)	105 ± 8·1 (2)	2·00 ± 0·09	1·30 ± 0·04	55 ± 6	50 ± 3
	0·06	1/2	125 ± 14·1 (3)	100 ± 9·8 (2)	2·10 ± 0·02	1·40 ± 0·06	35 ± 5	46 ± 8
Caudate nucleus	1·80	3	98 ± 5·1 (6)	97 ± 4·7 (4)	1·00 ± 0·01	1·10 ± 0·02	100 ± 12	81 ± 11

* No. of animals indicated in brackets.

The livers were removed, chilled in cold saline, sliced with a 'Stadie Riggs' slicer and weighed. 100-mg liver slices were suspended in 1 ml. Krebs Ringer bicarbonate medium (ref. 4), aerated with 95 per cent oxygen and 5 per cent carbon dioxide. Incubation was carried out in a metabolic incubator at 37° C for 2 h. The glycogen content of the liver was determined by the anthrone method (ref. 5) and glucose after deproteinization (ref. 6) by the glucose oxidase method (ref. 7).

Endogenous gluconeogenesis was estimated by subtracting the amount of glycogen that disappeared from the liver slices during incubation from the amount of glucose found in the medium at the end of the incubation.

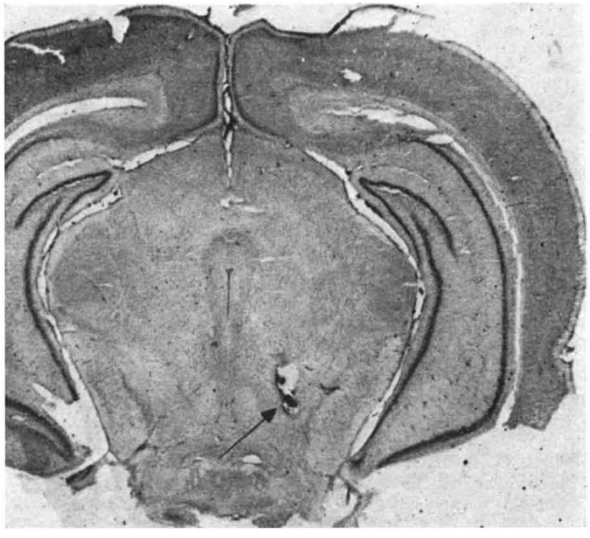

Fig. 1. Histological section of the posterior hypothalamus showing position of stimulating electrode

The fact that the hormones of the adrenal cortex are essential for the normal gluconeogenetic response is well known[8]. But it is probable that their effect in this process of gluconeogenesis is permissive. This problem is discussed elsewhere[1].

To sum up, electrical stimulation of the posterior hypothalamus in rats fasted overnight resulted in increased endogenous hepatic gluconeogenesis, hyperglycaemia and accumulation of liver glycogen. These changes did not occur in animals stimulated in the caudate nucleus. In adrenalectomized rats the effect could not be observed.

S. Feldman

Department of Nervous Diseases,
Hadassah University Hospital,
Jerusalem.

N. Friedman
H. E. Wertheimer

Department of Biochemistry,
The Hebrew University-Hadassah Medical School,
Jerusalem.

[1] Friedman, N., and Wertheimer, E., *Metabolism*, **15**, 222 (1966).
[2] Friedman, N., thesis, Hebrew Univ., Jerusalem.
[3] Landau, B. R., Laszlo, J., Stengle, J., and Burke, D., *J. Nat. Cancer Inst.*, **21**, 485 (1958).
[4] Umbreit, W. W., Burris, R. H., and Stauffer, J. F., *Manometric Techniques*, 149 (Burgess Publishing Co., 1959).
[5] Roe, J. H., *J. Biol. Chem.*, **208**, 889 (1954).
[6] Somogyi, M., *J. Biol. Chem.*, **117**, 771 (1937).
[7] Hestrin-Lerner, S., and Ben-Jonah, S., *Proc. Microbiol. Chem. Assoc. Israel*, 27 (1962).
[8] Long, C. N. H., Katzkin, B., and Fry, Edith G., *Endocrinology*, **26**, 309 (1950).