11462

Availability of Glucose for Human Brain Oxidations.*

JOSEPH WORTIS AND WALTER GOLDFARB.

From the Division of Psychiatry, Bellevue Hospital, and the Department of Psychiatry, New York University Medical College, New York City.

The ready availability of glucose for brain tissue oxidations has been demonstrated both in the Warburg apparatus (Warburg, Posener and Negelein[1]) and in the intact organism (Himwich and Nahum,[2] Lennox[3]) Damashek, Myerson and Stephenson[4] have shown that when the human brain is deprived of this foodstuff during insulin hypoglycemia the oxygen uptake of the brain is correspondingly diminished, and Himwich, Bowman, Wortis and Fazekas[5] have shown that in the deep coma associated with therapeutic insulin shock brain metabolism approaches zero. Under these conditions in humans the brain potentials have been found to be diminished (Hoagland, Rubin and Cameron[6]) and typical neurologic signs appear. Clinical coma, neurologic signs and the characteristic brain potential changes all disappear after glucose administration. The increased oxygen uptake by the brain after glucose administration had already been demonstrated in dogs (Himwich, *et al.*,[7]), and in humans the neurological signs are alleviated by the administration of as little as 4 g of glucose (Himwich, Frostig, *et al.*[8])

In the course of our investigations of the availability of various food substrates for brain metabolism (Wortis and Goldfarb[9]) we have undertaken to establish the metabolic response of the brain to small doses of glucose administered intravenously to schizophrenic

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1 Warburg, O., Posener, K., and Negelein, E., *Biochem. Z.*, 1924, **152**, 309.

2 Himwich, H. E., and Nahum, L. H., *Am. J. Physiol.*, 1930, **90**, 389.

3 Lennox, W. G., *Arch. Neurol. Psych.*, 1931, **26**, 719.

4 Damashek, W., Myerson, A., and Stephenson, C., *Arch. Neurol. and Psychiat.*, 1935, **33**, 1.

5 Himwich, H. E., Bowman, K. M., Wortis, J., and Fazekas, J. F., *J. Nervous and Mental Disease*, 1939, 273.

6 Hoagland, H., Rubin, M. A., and Cameron, D. E., *Am. J. Physiol.*, 1937, **120**, 559.

7 Himwich, H. E., and Fazekas, J. F., *Endocrinol.*, 1937, **21**, 800.

8 Himwich, H. E., Frostig, J. P., Fazekas, J. F., and Hadidian, Z., *Am. J. Psychiat.*, 1939, **96**, 371.

9 Wortis, J., and Goldfarb, W., *Science*, 1940, **91**, 270.

subjects during therapeutic insulin shock, to serve as a basis of comparison for the availability of other substrates for brain oxidations.

Experimental. The cerebral metabolism was estimated from the arterio-venous differences of O_2, CO_2, and glucose. The arterial blood was obtained from either the brachial or femoral arteries, and the venous blood was sampled from the internal jugular vein using the technic described by Myerson, *et al.*[10] The blood samples were analyzed for O_2, CO_2 (Van Slyke and Neill[11]), and glucose (Folin and Wu[12]). The velocity of circulation in the peripheral vascular system was estimated with the method of Robb and Weiss.[13] The metabolism of the brain was estimated after the patients were in hypoglycemic coma, and again at various intervals after the administration of 4 g of glucose intravenously. The latter dose was chosen after some preliminary trial as the minimum amount required to rouse the patients. At the end of the experiment the patients were given the usual large amount of glucose to terminate the treatment.

The summary of data is presented in Table I. In 15 patients the administration of 4 g of glucose intravenously was sufficient to promptly rouse the patients from coma. In 13 experiments the

TABLE I.

Effect of 4 Grams of Glucose Intravenously on Cerebral Metabolism of Schizophrenic Patients in Coma.

Exp. No.	Min. after glucose	Volume % oxygen			Glucose		Circ. Time
		Art.	Ven.	Diff.	Art.	Ven.	
1	10	19.4	15.8	3.6			11
2	5	19.8	13.2	6.6			
3	5	17.9	15.1	2.8	57	57	10
4	9	21.4	13.1	8.3			14
5	5	18.1	8.4	9.6	48	40	12
6	4	19.0	12.3	6.7			
7	4	21.8	14.1	7.7	56	43	15
8	5	20.5	15.9	4.6	69	68	10
9	5	19.2	14.4	4.8	47	43	10
10	6	22.4	15.9	6.5	53	47	10
11	5	20.9	16.1	4.8			
12	5	19.6	14.4	5.2			
13	4	17.1	13.1	4.0	56	62	16
14	4	19.0	16.0	3.0	23	30	
15	4	20.9	17.2	3.7	42	49	
Avg		19.8	14.3	5.46	50	49	12.0
Avg of 60 cases in insulin coma		19.6	16.7	2.9	23	21	11.8

[10] Myerson, A., Halloran, R. D., Hirsch, H. L., *Arch. Neurol. and Psychiat.*, 1927, **17**, 807.

[11] Van Slyke, D. D., and Neill, J. M., *J. Biol. Chem.*, 1924, **51**, 523.

[12] Folin, O., and Wu, H., *J. Biol. Chem.*, 1920, **41**, 367.

[13] Robb, G. P., and Weiss, S., *Am. Heart J.*, 1932-3, **8**, 650.

oxygen uptake of the brain was increased significantly above the average of a large control series, the average changing from 2.9 volumes % to 5.46 volumes % after glucose administrations. During coma the arterial glucose averaged 23 mg % and the venous sugar 21 mg %. After glucose administration the values were 50 and 49 mg % respectively. The circulation time revealed no change.

The estimation of brain metabolism in these experiments was based on the differences between the concentrations of various substances in the arterial and venous blood. We are in agreement with other investigators that this method does not measure the total metabolism of the brain, and that the observations are affected by changes in blood flow; Abramson, *et al.*,[14] have observed an increased blood flow in the extremities of patients receiving insulin therapy for schizophrenia, and the authors concluded that the evidence strongly suggested that there was an increased blood flow through the brain. They believe that the reduced oxygen uptake found in insulin hypoglycemic coma may be attributable to this possibly increased blood flow through the brain. Abramson's observations, however, in contrast to ours, were made less than 2 hours after insulin injection, preceding the onset of coma. Moreover, it is well known that blood flow through the brain may vary independently of the blood flow in the periphery, and is principally controlled by the arterial blood pressure. The latter gradually falls if the hypoglycemia is not associated with convulsive seizures. Direct observation of blood flow during insulin hypoglycemia in rabbits reveals no significant changes unless convulsions occur (Leibel and Hall[15]). In humans a gradual decrease in brain blood flow occurs during insulin hypoglycemia (Loman and Myerson[16]). Such a decrease in blood flow indicates that there is probably an even greater diminution of brain metabolism than the diminished arterio-venous oxygen differences recorded by Himwich, Bowman, Wortis and Fazekas[17] would indicate. It will be noted that the arterio-venous difference for glucose did not return to normal values with the return to a normal oxygen difference. This apparent discrepancy can probably be explained on the assumption that the glucose administered is rapidly absorbed by the tissues, including the brain tissue, and that its subsequent utilization within the cell is not accompanied by any further removal of glucose from the

14 Abramson, D. I., Schesloven, N., Margolis, M. N., and Mirsky, I. A., *Am. J. Physiol.*, 1939, **128**, 124.

15 Leibel, B. S., and Hall, G. E., PROC. SOC. EXP. BIOL. AND MED., 1938, **38**, 894.

16 Loman, J., and Myerson, A., *Am. J. Psychiat.*, 1936, **92**, 791.

17 Wortis, J., Bowman, K. M., Goldfarb, W., Fazekas, J. F., and Himwich, H. E., *Am. J. Physiol.*, 1940, in press.

blood. Since there is no comparable intracellular storage of oxygen the increased oxygen uptake continues. This supposition is supported by reference to blood sugar curves after the administration of 4 g of glucose intravenously to patients in insulin coma. These show a rapid removal of glucose from the blood, preceding clinical arousal (Fig. 1) with a persistence of clinical recovery long after the blood glucose ceases to show any further considerable drop.

The rapid clinical arousal and the rapid increase in oxygen uptake, however, again confirm the ready availability of glucose as a metabolic substrate for the human brain, and affords a convenient yardstick for comparison with the availability of other foodstuffs for brain metabolism during hypoglycemic insulin coma.

Summary and Conclusions. The availability of glucose for brain oxidations in hypoglycemic insulin coma was studied in human patients. The intravenous administration of 4 g (in 50% solution) invariably aroused the patients and approximately doubled the oxygen uptake of the brain.

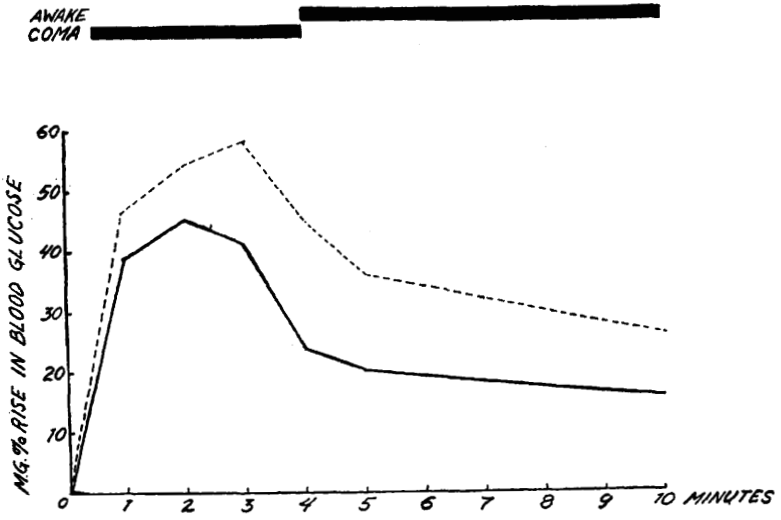

FIG. 1.

The solid line shows the amount of increase of blood glucose (antebrachial vein) following intravenous administration of 4 g of glucose during insulin coma. The dotted line shows the amount of rise above fasting levels in the same patients on non-treatment days. The comatose patients almost invariably roused in about 4 minutes. The curves are based on averages of 13 experiments in coma, and 7 experiments outside of coma.