Effect of Glucose on the Activity of Hypothalamic "Feeding Centers"

Abstract. The unit activity of the neurons in the hypothalamic "satiety" and "feeding" centers and adjacent control regions was recorded before and after intravenous injection of glucose. Increase in blood glucose and arteriovenous glucose difference (glucose utilization) increases the activity of satiety center neurons and slightly decreases the activity of feeding center neurons, without producing any significant change in the activity of control regions.

There is enough experimental evidence available to demonstrate the presence of a dual mechanism in the hypothalamus for the regulation of food intake—a "feeding center" in the lateral hypothalamus and a "satiety center" in the medial hypothalamus (*1*). These centers provide the facilitatory and the inhibitory mechanisms respectively for feeding reflexes. The activity of the feeding center determines the state of "hunger." The satiety center is activated as a result of feeding, thus bringing about the state of "satiety." These mechanisms are further influenced in an integrative manner from the higher nervous levels.

It has been suggested that certain changes produced in the body as a result of taking a meal influence the activity of the satiety center, and when these changes disappear either in the form of stored energy, heat, or work, the satiety center is no longer stimulated (*2*). Various suggestions have been put forward regarding the nature of these changes, important ones being availability and utilization of glucose, concentration of circulating metabolites, concentration of serum amino acids, specific dynamic action of food, shifts of water among the compartments of the body, and sensory impulses from the alimentary tract.

Glucostatic regulation was proposed by Mayer (*3*), who suggested the presence of glucoreceptors in the hypothalamus which are sensitive to blood glucose in the measure that they can utilize it. He and his colleagues presented some evidence for the presence of this mechanism. This laboratory (*4*) has reported experimental evidence (obtained by recording the activity of hypothalamic centers electroencephalographically through implanted electrodes) that by changes in the blood glucose content and the arteriovenous glucose difference, produced either by intravenous injections or in the states of hunger and feeding, the activity of the satiety center significantly and selectively changes. Simultaneously the activity of the feeding center has a reverse effect, though not a marked one.

Studies have now been conducted to observe the effects of changes in blood glucose and glucose utilization on the "unit" activity of the single neurons of the hypothalamic centers and other regions. Steel microelectrodes with tips of 1 to 2 μ have been used for recording (*5*) and the unit activity (extracellular) has been recorded from neurons in the satiety center, feeding center, and adjacent hypothalamic regions, as well as the cerebral cortex, the two latter sites acting as controls. Dogs have been used for these acute experiments, carried out under Dial anesthesia. The skull was opened on one side, the temporal lobe was sucked out, the base of the brain was slightly lifted after cutting the third cranial nerve, and the microelectrode was guided visually with a micromanipulator to the appropriate sites. The activity picked up by the microelectrodes was fed into a Grass preamplifier through a cathode follower input probe and then recorded on a Dumont oscilloscope. After getting a stable unit, we gave an intravenous infusion of glucose.

Samples of arterial and venous blood were taken for estimation of glucose, once before glucose infusion and two or three times in the first hour after glucose infusion. During this period the unit activity was photographically recorded at frequent intervals. The arteriovenous glucose difference was calculated to provide a measure of glucose utilization. To determine the exact site of the electrode, at the end of the experiment current was passed through the electrode to make a small iron deposit, and the dog was killed by infusion of Formalin containing ferrocyanide, which would stain the iron deposit.

Successful experiments have been conducted so far in 41 animals. Twenty-two recordings have been taken from the satiety center, nine from the feeding center, and ten from the control

Table 1. The frequencies of unit activity of all the recordings during 15-minute periods (after intravenous administration of glucose) have been pooled to work out the mean change in frequency per second as compared with the mean frequency before giving glucose. The increase in the frequency of the satiety center and the decrease in the frequency of the feeding center are statistically significant, while no statistically significant change takes place in the activity of the control regions of the hypothalamus.

Time (min)	Change in frequency	t	p
	Satiety center		
15	+2.67	1.98	<.10 >.05
30	+3.37	2.84	<.02* >.01
45	+1.25	3.2	<.01† >.001
60	−0.785	1.509	<.20 >.10
	Feeding center		
15	−0.908	2.63	<.05* >.02
30	−1.053	3.05	<.05* >.02
45	−1.21	3.1	<.05* >.02
60	−1.36	3.1	<.05* >.02
	Control		
15	−0.442	0.832	<.40 >.30
30	−0.202	0.339	<.80 >.70
45	−0.534	0.58	<.60 >.30
60	+0.417	0.77	<.60 >.50

* Significant. † Highly significant.

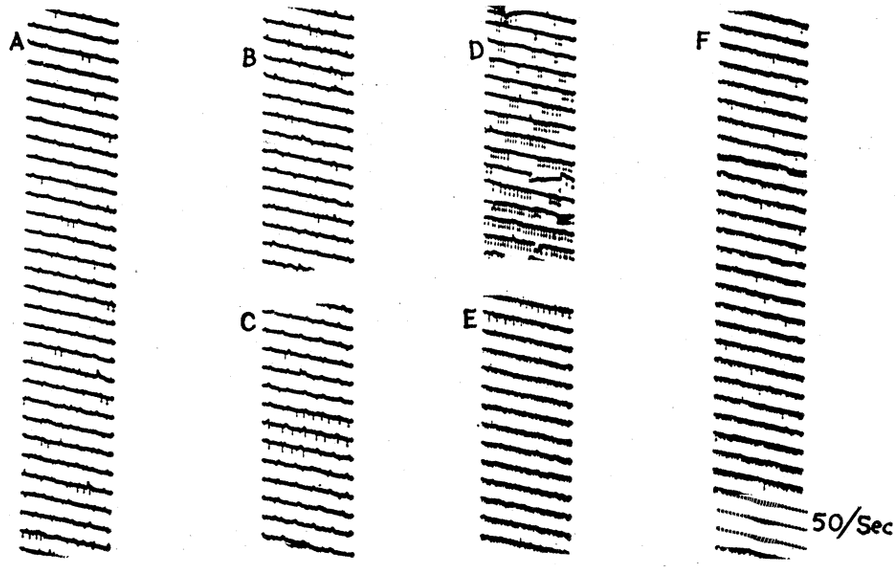

Fig. 1. The unit activity recorded from the satiety center before giving glucose (*A*), and at frequent intervals after intravenous glucose infusion. (*B*) After 5 minutes; (*C*) after 15 minutes; (*D*) after 30 minutes; (*E*) after 45 minutes; (*F*) after 60 minutes.

regions. These studies have demonstrated that the frequency of the unit activity of satiety center neurons increases significantly, while the unit activity of feeding center neurons decreases, after glucose transfusion. No significant change is observed in the unit activity recorded from other hypothalamic regions, nor from the cerebral cortex after glucose infusion. A sample of the recorded unit activity from the satiety center and the changes produced in its frequency by glucose infusion are shown in Fig. 1. The frequency of the activity increases within 5 to 10 minutes of giving glucose and is quite marked up to about 30 to 45 minutes, after which it starts decreasing. Usually within 1 hour it falls back to its level before the injection of glucose. Similarly the activity of the neurons from the feeding center is decreased during approximately the same periods. The averages of change in the frequencies from all the experiments have been statistically analyzed (Table 1), and it is apparent that the changes in the activities of the satiety and feeding centers are statistically significant, while the control regions do not show any statistically significant change.

In Fig. 2 the averages of frequencies of the unit activity from these three regions have been correlated with the averages of blood glucose and the arteriovenous glucose difference in these animals. There is a distinct correlation between the increase and decrease in the frequency of the activity of the satiety and feeding centers respectively, with the rise in blood glucose and the increase of glucose utilization. This correlation appears to be more intimate with the increase in glucose utilization, in view of the observation that after about 45 minutes, when the blood glucose is still high but the glucose utilization is returning to its original level, the frequency of the activities of these two centers also starts returning to its original level. More studies are required to finally establish this point.

Sufficient evidence, therefore, has been provided for the presence of glucose-sensitive cells in the satiety center of the hypothalamus. It is not clear whether the less marked inhibition in the activity of feeding center neurons is a direct influence of glucose or whether this is due to their inhibition as a result of activation of satiety center cells (lateral projection). It also appears probable that it is the concentration of glucose within the satiety center cells (glucose utilization) that activates them, although this needs further confirmation (*6*).

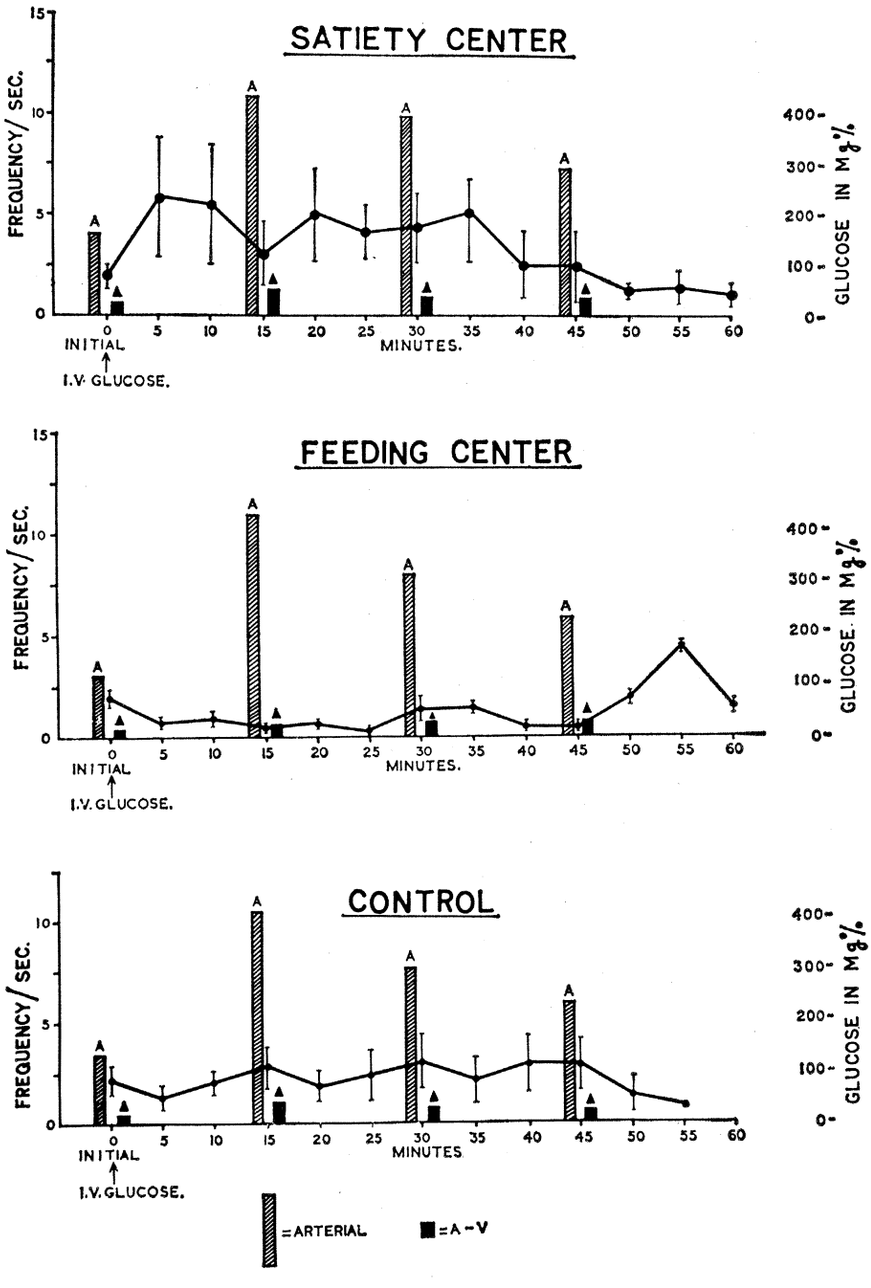

Fig. 2. Graphs showing separately the mean of the frequencies of unit discharges recorded from the satiety center, the feeding center, and the control hypothalamic regions, and correlating these with the arterial blood glucose levels and the amount of glucose utilization (A — V difference).

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References and Notes

1. B. K. Anand and J. R. Brobeck, *Yale J. Biol. Med.* **24**, 123 (1951); B. K. Anand, S. Dua, K. Shoenberg, *J. Physiol. London* **127**, 143 (1955); B. K. Anand, *Physiol. Rev.* **41**, 677 (1961).
2. J. R. Brobeck, *Ann. N.Y. Acad. Sci.* **63**, 44 (1955).
3. J. Mayer, *Physiol. Rev.* **33**, 472 (1953); ——— and M. W. Bates, *Am. J. Physiol.* **168**, 812 (1952); N. B. Marshall and J. Mayer, *ibid.* **178**, 271 (1954).
4. B. K. Anand, S. Dua, B. Singh, *Electroencephalog. Clin. Neurophysiol.* **13**, 54 (1961); B. K. Anand, U. Subberwal, S. K. Manchanda, B. Singh, *Indian J. Med. Res.* **49**, 725 (1961).
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