Blood composition in relation to food intake in the rat

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CHAPTER VII

CONCLUDING REMARKS

Concerning the possible role of nutrients circulating in the blood stream as factors in the regulation of food intake, no view has been put forward in as much detail so far as the glucostatic theory (Mayer, 1966). This theory holds that availability of blood glucose is one important determinant of mammalian feeding behaviour. In particular this hypothesis refers to availability of blood sugar to the peripheral tissues, in which glucose utilization is insulin dependent (for brevity this peripheral glucose availability is here called GAP). The theory assumes that GAP (and not simply blood glucose levels) is monitored directly by "glucreceptors" which activate the satiety mechanisms of the brain.

This theory has an a priori attractiveness: glucose is one of the main fuels in the body. Yet the glucose reserves are small. Insufficient GAP will be the first disturbance to arise when food intake is unduly postponed. What would be more efficient than to have a meal pattern governed by fluctuations in GAP?

Indeed experiments have been reported in which blood parameters affecting glucose utilization were found to be correlated with the meal pattern in a manner fully compatible with the gluco static theory (e.g., Stunkard et al. 1955, Stunkard and Wolff, 1954, 1958). However, none of those experiments fully proves this theory. Alternative explanations remain open. One reason why this is so, is that GAP values so far have been inferred only from arterio-venous glucose concentration differences. It has been argued in Chapter III that this is not a reliable procedure. Moreover, the possibility has not been excluded that other factors, not causally dependent on but merely correlated with GAP, were responsible for the observed meal patterns. It is worth while therefore to consider what support the present experiments may give the gluco static theory. The only true measure of GAP is the rate at which the peripheral tissues remove glucose from the blood. However, in the present experiments
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ess: glucose is oneucose reserves are disturbance to arise What would be more erned by fluctuations scribed in which blood n were found to be inner fully compatible ard et al. 1955, Stun one of those experi- ple explanations remain ; GAP values so far venous glucose con- gued in Chapter III Moreover, the pos- factors, not caus- ted with GAP, were nterns. It is worth the present experi- the only true measure eral tissues remove present experiments only concentrations of glucose, insulin, and FFA were measured. Unquestionably the former two rank high among the factors setting the GAP level. But, as GAP itself has not been directly determined, much caution is needed in dis- cussing the relevance of the present findings to the glucostatic theory.

We have seen in chapter V that a normal rat in the ad libitum situation has a normal blood glucose level, but low insulin level at the start of a meal. This suggests that GAP is poor just before the meal. Admittedly, due to limited facilities for insulin determinations, we do not know at what moment the insulin level has fallen to this low value from the higher level observed just after the foregoing meal. However, that the start of a meal may coincide with a cri- tical change in GAP is suggested by the decline of the glucose level when the meal is prevented. On the other hand in chapter VI it was shown that a meal is started each time hypoglycemia, induced by continuous infusion of insulin, reaches a critical level. Taken together these results in- dicate that feeding responses remain absent as long as both glucose and insulin are present in reasonable quantities, but that a meal is started as soon as either substance falls below a certain level (which level depends on the amount present of the other substance). Clearly this is what one would expect from the standpoint of the glucostatic theory. But again the question of possible alternative explanations arises.

Soon after the start of a carbohydrate containing meal glucose pours into the blood from the gut. The resulting incipient hyperglycemia is quickly curbed by insulin (chapter IV and V). It seems certain that GAP is excellent in this phase. Moreover, glucose absorbed in excess of immediate tissue needs is stored as glycogen and fat. As intestinal absorption comes to an end insulin release will diminish. However, it may be that about this time glucagon goes up (Tepperman, 1968), GAP will still be good therefore, now being maintained at the expense of the glycogen stores. At a still later time, the growth hormone level probably rises (Hunter, 1968). Its function may well be to supplement waning GAP by increased mobilization of reserve fats. It now be- comes important to recall the stability of the body weight.
This means that, on the average, a new meal is started just when the glycogen and fat stores derived from the foregoing meal have been used up. From this point of view the next meal might be triggered equally well, e.g., by monitors reporting the state of either store, or its rate of mobilization, as by GAP monitors.

To choose among these possibilities much further information will be needed. The sampling technique described in this paper will be useful for gathering this information. Radio immuno assays of glucagon and growth hormone will have to be performed on the samples. Turnover of glucose and FFA can be determined by radio active tracer methods. However, in the absence of such data it is worth while to consider the insulin infusion experiment once more. Here, the normal correlation between GAP and glycogen and fat stores undoubtedly is disrupted. It is a telling fact that under these conditions the meal pattern is clearly governed by glucose. Here a glucostatic explanation seems preferable.

So far we have considered only the initiation of meals. What about their termination? Here we have to face an even more complicated situation. In addition to the state of circulation and reserves, signals arising from the digestive tract may also play a role (see chapter I). That the latter are not alone responsible for the cessation of feeding follows from the fact that caloric dilution of the diet results in increased meal size already at the first meal taken of the diluted diet (Levitsky and Collier, 1968; Thomas, 1966, 1968). In the experiments here presented (chapter V) the glucose and insulin levels rise already during a meal; probably the same applies to GAP. Combining this with Anand's data already discussed in chapter I and V, we may conclude that the presumption is strong that increased GAP contributes to the termination of a meal.

After this discussion on the control of food intake in the intact rat, little needs to be said here about the results obtained in VMH lesioned subjects. These results confirm the currently accepted view as to the role of this area in feeding behaviour, which is to transmit satiety signals. Whatever signal may be responsible for starting or stopping meals, one would expect that higher levels of that signal are required for it to be effective when its transmission is im-
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paired by a VHM lesion. With respect to the glucostatic

theory, the insulin infusion experiment again is the most

informative for the reason already mentioned above. The

general pattern of the result of this experiment in the lesioned

subject is the same as in the intact one, but the meal starts

at a much higher glucose level in the former.

The discussion so far was concerned with a highly schematic­
tized individual under constant average conditions. To arrive

to a real understanding of food intake many complications

must be introduced. The data presented dealt only with meals

taken during the inactive phase of the diurnal rhythm. During

the active phase food intake is much higher, due to reduc­
tion of intermeal intervals, but not to increased meal size

(Le Magnen and Tallon, 1966). Preliminary experiments not

mentioned in the earlier chapters show that during this period

the glucose level is relatively high (about 130 mg%) and the

peaks caused by meals are less pronounced. Insulin data

are not yet available. Further, various stresses encountered

by animals in every day life have profound influence on the

docrine state, including many hormones that affect glucose

concentration and turnover (glucocorticoids, catecholamines,
thyroxin, growthhormone).

The method developed in the present investigation may well

prove valuable for the further analysis of these extremely

complex processes.