

6. SUMMARY

Hypothalamic glucose and food intake – a microdialysis study

Food intake is related to the nutritional state of the organism, which is characterized by the availability of energy, partly in form of glucose. It is known for decades that a fall in blood glucose level is a potent stimulus to initiate food intake, but little is known so far about feeding related changes in brain glucose concentrations. There are neurons in the hypothalamus and in the brain stem, which change their action potential frequency in response to changes in ambient extracellular glucose concentrations. Interestingly, these neurons are linked to other hypothalamic structures, which are involved in the control of food intake. The ability of neurons to respond to changing local glucose concentrations has been discussed recently with regard to the control of ingestive behavior.

The aim of the present *in vivo* microdialysis study was to describe the relation between feeding and changes in glucose concentrations in the VMH of rats. First, the method of ZNF microdialysis was used to evaluate interstitial glucose concentrations in VMH under baseline conditions, both in food deprived and non-deprived rats. The results demonstrate that in fed animals absolute glucose levels in the VMH are higher (1,43 mM) compared to rats after a 24-h food deprivation (0,94 mM). Additionally, a control group of non-deprived rats was used to measure blood glucose in order to compare VMH and blood glucose concentrations. As expected blood glucose concentration in control rats was significantly higher compared to interstitial glucose concentration observed in the VMH of non-deprived rats.

To examine whether feeding influences hypothalamic glucose, changes of glucose concentration over time were determined relative to a baseline. Experiments were conducted in relation to both, nutritional state (food deprived rats / non-deprived rats) and feeding conditions throughout the experiment (free feeding rats / rats without access to food). The experimental design took into account that rats are mainly nocturnal animals and start to feed shortly after beginning of the dark phase. Therefore, experiments enclosed light and dark phase. Sampling of microdialysates started 90 Minutes before and ended 120 Minutes after beginning of the dark phase of the experiment.

Whereas no significant alterations in VMH glucose concentration before meal initiation were observed in the light phase of the experiment, the results of this microdialysis study show clearly that glucose level in the VMH of rats increase significantly in relation to food intake. The data demonstrate that food intake following a 24-h food deprivation further augments

this increase as compared to non-deprived conditions. However, food related increase in VMH glucose does not correlate with the individual amount of food intake.

In addition, feeding related changes in VMH glucose and blood glucose over time have been compared. Whereas hypothalamic glucose increased significantly during feeding, blood glucose concentrations of free feeding control animals did not change significantly over the same experimental period.

Since lactate is closely linked to glucose metabolism, alterations in interstitial lactate concentrations in the VMH were examined. Independent of both, nutritional state and feeding conditions, hypothalamic lactate level in the VMH of rats increased significantly compared to baseline over the whole time of the experiment. As with glucose, the increase in interstitial lactate in the VMH of free feeding rats did not correlate with meal size. In contrast, lactate/pyruvate-ratio did not change significantly compared to baseline over the time of the experiment.

In conclusion, the present study shows for the first time that ventromedial hypothalamic glucose concentrations increase with food intake. After meal initiation a significant increase in glucose was observed, which could be intensified by a preceding food deprivation. Although numerous *in vitro* studies have demonstrated that changes in ambient extracellular glucose concentrations influence the action potential frequency of hypothalamic neurons, the present *in vivo* microdialysis study provides evidence that such changes actually occur under physiological conditions. Results further indicate that the feeding related increase in VMH glucose depends on the nutritional state of the organism.

Adaptive adjustments of brain glucose transporters to a changing nutritional status or/and compensatory responses of the brain, e.g. mobilization of brain glycogen reserves to sustain cerebral function, may possibly be involved.

The data further indicate that feeding related alterations in cerebral glucose concentration over time do not parallel changes in blood glucose level. This is evidence to suggest that mechanisms regulating glucose supply in the brain are dissociated from that in the periphery, possibly to ensure predominantly glucose supply of the brain when energy levels are diminished.

The nature of the relation between food intake, hypothalamic glucose concentrations and involved regulatory mechanisms as well as their physiological importance appears to be

complex. The present study demonstrates that changes in hypothalamic glucose concentrations occur in relation to food intake. One of the mechanisms by which brain glucose acts on feeding behavior could be by inducing gene expression of both, orexigenic and anorexigenic peptides, as suggested by *in vitro* studies. It was important, therefore, to demonstrate with the present study that hypothalamic glucose changes in relation to feeding under *in vivo* conditions.