Chem. Senses 30 (suppl 1): i182–i183, 2005 doi:10.1093/chemse/bjh174

Peripheral Signals in the Control of Feeding Behavior

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Key words: ATP, energy metabolism, liver, obesity, vagus

Introduction

Eating requires at least two basic decisions: what to eat, which is a decision about food choice, and how much to eat, which is a decision about food intake. This distinction is important because food choice and intake involve different behaviors, different controlling signals and different physiological mechanisms.

Feeding behavior is controlled by a variety of signals. 'Cephalic' signals, such as the taste, smell, sound and sight of food, control food choice and can influence the amount of food consumed in the short-term. Gastrointestinal signals resulting from changes in distention or the release of gut peptides may play a role in the control of short-term intake within a meal or across several meals. Metabolic signals generated by the supply and utilization of metabolic fuels not only influence food choice, but also how much food is consumed in the short-term. Metabolic signals also determine food intake in the long-term and are important in maintaining energy balance over a nutritionally significant interval.

Traditionally, research emphasized separate signals associated with glucose and fat metabolism. 'Glucostatic' hypotheses about these signals have focused on either changes in the circulating level of glucose or on intracellular glucose utilization, whereas 'lipostatic' hypotheses have targeted the amount of body fat or, more recently, the adipose hormone, leptin. A less well known line of research has looked to metabolic processes common to the metabolism of both glucose and fat for metabolic signals controlling food intake. This perspective was initially proposed by Ugolev and Kassil (1961), who investigated the tricarboxylic acid cycle as a source of a common, 'oxidative' metabolic signal. More recently, research in this area has focused on aspects of ATP production.

Our approach to the study of the metabolic controls of food intake addresses questions that are usually associated with the study of sensory systems: Where are receptors/detectors that monitor metabolic events to control food intake? What stimulus is adequate to activate the receptor? How is this stimulus transduced into a neural signal? And how is this signal transmitted to and within the central nervous system? Here, we review our laboratory's work on each of these issues in turn.

Receptor site

Russek (1963) first proposed the liver as a site where changes in metabolism are detected to control feeding behavior. Although his hypothesis was initially ignored for many years, it is now generally accepted that information about hepatic metabolism is communicated to the brain and contributes to the control of food intake.

Work in our laboratory on the role of the liver in feeding behavior has taken a number of different directions, although perhaps the most compelling evidence stems from comparing the effects on food intake of hepatic portal and jugular vein infusion of nutrients and metabolic inhibitors. In one series of experiments, taking a cue from Russek's studies, we compared the effects of hepatic portal and jugular (i.e. systemic) infusions of glucose on satiety in rats. These studies showed that, under relatively normal feeding conditions, glucose infusions within the physiological range suppressed food intake more effectively when delivered into the hepatic portal vein than when given by a jugular route (see Friedman *et al.*, 1996). In other experiments, we studied the role of the liver in hunger by comparing hepatic portal and jugular infusions of the fructose analogue, 2,5-anhydro-D-mannitol (2,5-AM), which we had shown triggered feeding in rats when given by gastric gavage or an intraperitoneal route. The results showed clearly that portal infusion of 2,5-AM elicited food intake more rapidly and at lower doses than did infusions into the jugular vein (see Tordoff *et al.*, 1991).

Nature of the stimulus

Since studies in our laboratory first demonstrated an inverse relationship between hepatocyte ATP concentration and food intake, we have been focused on testing the role of changes in hepatic energy status as a stimulus for hunger and satiety. Under a variety of conditions, eating behavior triggered by injection of 2,5-AM was associated with the analogue's effect of reducing liver ATP (e.g. Friedman *et al.*, 2002). The decrease in ATP was due largely to trapping of phosphate in phosphorylated forms of 2,5-AM (Rawson *et al.*, 1994). Most telling therefore was the observation that preventing the decrease in ATP by administration of exogenous phosphate also prevented the eating response (Rawson and Friedman, 1994). Subsequently, we found that eating behavior stimulated by administration of other metabolic inhibitors, including fatty acid oxidation inhibitors, was also associated with lowered hepatic ATP levels (e.g. Ji *et al.*, 2000).

Additional experiments investigated the relationship between liver energy status and food intake under other conditions. Confirming earlier studies, we found that fasting reduced hepatic energy status and that the time course of compensatory hyperphagia during refeeding paralleled that in the restoration in liver energy status (Ji and Friedman, 1999). The dramatic increase in food intake in rats with experimental diabetes and its prevention with fat feeding were also found to be associated with, respectively, lower and normalized liver energy status (unpublished data). Most recently, we have examined the role of hepatic energy status in dietary, genetic and neurological rat models of overeating and obesity (unpublished data). In all three models, obese rats showed lowered hepatic energy status than controls, in some cases despite marked hyperphagia.

Transduction mechanism

Little is known about how changes in hepatocyte energy metabolism are transduced into a signal the nervous system can interpret. We have begun to investigate this question along two tracks. In one set of studies (Rawson *et al.*, 2003), we studied the effects of 2,5-AM on intracellular Ca^{2+} concentration in hepatocytes as such changes are well known to be involved in cellular signaling in a variety of tissues. The results showed that 2,5-AM produced an increase in intracellular Ca^{2+} in ~50% of hepatocytes and that the rise was due to release of intracellular calcium stores. In another set of experiments (Friedman *et al.*, 2003), we tested a hypothesis that changes in

hepatocyte ATP levels generate a signal by lowering activity of the sodium pump, causing cellular depolarization (Langhans and Scharrer, 1987). Using nuclear magnetic spectroscopy, we showed that 2,5-AM increased intracellular sodium with a latency consistent with that of the eating response, a finding supporting Langhans and Scharrer's conjecture. These intriguing results require considerable follow-up before the effects of 2,5-AM seen *in vitro* can be understood and directly related to the behavioral response seen *in vivo*.

Transmission of the signal

Theoretically, changes in hepatic energy status could be transmitted to the brain via a neural or humoral route; at present, however, there is evidence only for a neural connection, specifically via vagal afferent neurons. Evidence that vagal sensory fibers carry the metabolic signals from liver that control food intake stem from a variety of studies (see Langhans, 1998; Horn *et al.*, 2001) showing that interruption of vagal afferent transmission can alter *ad libitum* food intake and prevent the eating response to metabolic inhibitors that act in liver. Other studies using the immunocytohistochemical expression of Fos as a marker for neural activity have demonstrated that metabolic inhibitors that stimulate feeding behavior activate areas in the brain known to receive and process vagal afferent input.

Electrophysiological experiments provide the most direct demonstration that metabolic perturbations trigger hepatic vagal sensory neurons. Niijima (this volume) was the first to show that infusion of glucose can decrease activity in the hepatic branch of the vagus. Subsequently, Niijima and his colleagues reported that these fibers respond to a range of nutrients, hormones and other agents. Using techniques that allow for measurement of single unit activity in the hepatic branch of the vagus, we recently found (Horn and Friedman, 2004) afferent responses to infusion of serotonin (5-HT) and cholesystokinin (CCK). By comparing the effects of hepatic portal and jugular infusions of these agents it was possible to identify 'portal' and 'jugular' responsive units. In keeping with the anatomical observation that fibers in the hepatic branch also innervate the stomach and intestine, we found that cutting the gastroduodenal sub-branch (GDB) of the hepatic vagus eliminated ~75% of the spontaneous activity in the hepatic branch as well as most of the response to 5-HT and CCK. These and other findings indicate that only a small proportion of afferents in the hepatic branch innervate the liver and that afferents of hepatic origin have a different pharmacology than those from the gastrointestinal tract.

Summary

Our results and those of others indicate that sensors in liver detect changes in hepatocellular energy status and communicate this information to the brain via vagal sensory neurons to control food intake. The mechanisms involved in this sensory function of the liver have yet to be elucidated in detail and many questions remain.

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