Carbohydrate and Fat-Based Appetite Control Mechanisms

Wolfgang Langhans

Physiology and Animal Husbandry, Institute of Animal Sciences, Swiss Federal Institute of Technology (ETH), Zürich, Switzerland

Introduction

Any physiological mechanism that controls appetite must influence the size and/or frequency of individual meals through positive or negative feedback. Positive feedback initiates and maintains eating; it is mainly provided by the sensory properties of food and their hedonic evaluation, which changes based on experience and physiological state. Negative feedback builds up during the meal and eventually stops ingestion; it is derived from the bulk of the food as well as from digestion, absorption and metabolism of ingested nutrients. Carbohydrates (CHO) and fat account for more than 80% of the daily energy intake in industrialized countries. Energy intake often increases with the fat content of the diet, suggesting that the appetite-suppressive effect of fat is rather weak. This is presumably related to the high palatability and high energy density of most high fat foods, which, together with the moderate postingestive oxidation of fat, allows excess energy intake. Despite that, it is clear that fat as well as CHO potently affect appetite through various mechanisms, which are reviewed below. The first part of the article deals with the direct feedback effects of CHO and fat on meal size based on these nutrients’ chemical and secretagogue properties. The second part deals with the usually more delayed feedback effects of CHO and fat metabolism on appetite.

Direct Preabsorptive Feedback

Intestinal CHO and Fat Suppress Appetite

The presence of CHO and fat in the small intestine inhibits eating. Intraintestinal infusions of long-chain fatty acids and oligosaccharides, such as
maltose and maltotriose, lead to a dose-dependent reduction of food intake [1]. This effect is due to an intestinal action because it occurs prior to significant nutrient absorption and because isocaloric intravenous (IV) nutrient infusions usually inhibit eating less effectively. The magnitude of the appetite suppression by intestinal CHO and fat depends on specific chemical properties rather than energy content [1]. Thus, highly unsaturated fatty acids reduce food intake more than saturated fatty acids [2], and preventing hydrolysis blocks the satiating effect of intestinal fat.

Electrophysiological data suggest that vagal sensory fibers, which are abundant in the proximal small intestine [3], can respond specifically to CHO and fats [4]. Intestinal CHO- and fat-induced satiation in fact depends mainly on such afferents [1]. It is still largely unknown how intestinal fat and CHO trigger vagal afferent signals that suppress appetite. For CHO, mucosal transport or some related process appears to be crucial because blockade of sodium/glucose symport with phlorizin attenuated the satiation induced by intestinal oligosaccharides [1]. Fat-induced activation of vagal afferents most likely depends on an endocrine intermediate (see below) [4].

Intestinal fat and CHO acutely reduce meal size [1]. Fat may also prolong the inter-meal interval, but this effect is unlikely to be due to preabsorptive feedback [1]. Intraintestinal fat infusion was more satiating during a meal than prior to meal onset, suggesting that interaction of intestinal signals with pregastric or gastric signals is important for the appetite suppression by intestinal fat [1]. Recent evidence indicates that mechanical feedback signals from the stomach may be enhanced by intestinal nutrient-derived signals [5]. This functional synergism is reflected on the electrophysiological level and based on the convergence of intestinal and gastric vagal sensory afferent pathways [3].

Peptides produced in the gastrointestinal (GI) tract during a meal can directly or indirectly activate vagal sensory afferents [4] and mediate many of the nutrients’ effects on appetite, gut functions and metabolism. Peptides that fit this description include cholecystokinin (CCK), bombesin-like peptides, the pancreatic hormones insulin, glucagon, amylin, and somatostatin, neurotensin, enterostatin, apolipoprotein A-IV (apo A-IV), glucagon-like peptide 1 (GLP-1), and even cytokines. The role of some of these peptides in CHO and fat-based appetite control mechanisms is addressed below and schematically depicted in Figure 1.

**Role of CCK**

CCK-producing cells (termed I cells) are mainly located in the proximal small intestine, where fat and protein are major stimuli for CCK release [6]. Parenteral administration of CCK-8, the biologically most potent form of CCK, reduces food intake, in particular meal size [7]. CCK also stimulates pancreatic secretion and gallbladder contraction, and inhibits gastric emptying. The satiating effect of CCK is physiologically relevant because CCK receptor
Carbohydrate and Fat-Based Appetite Control Mechanisms

Fig. 1. Schematic diagram of the carbohydrate (CHO) and fat-based preabsorptive feedback control of appetite. Apo A-IV = apolipoprotein A-IV, CCK = cholecystokinin, GLP-1 = glucagon-like peptide 1, 5-HT = serotonin. Note that enterostatin has not yet been reported to suppress appetite in humans, whereas an appetite-suppressive effect of circulating GLP-1 has only been shown for humans but not for rats. Furthermore, the stimuli for central CCK and GLP-1 release or transmission are presently unknown.

Antagonists have often been shown to stimulate food intake after parenteral administration and to block the appetite-suppressive effect of exogenous CCK [8, 9]. Moreover, rats and perhaps also humans with a genetic deficiency in functional CCK_A receptors become obese [9], suggesting that a deficit of the CCK satiating action affects body weight. Endogenous CCK is a mediator of
the satiating effect of intestinal nutrients because CCK_A receptor antagonists attenuate the appetite suppression after intestinal nutrient infusions [1, 9]. Moreover, rats lacking functional CCK_A receptors are less sensitive to the satiating effect of intestinal fat, and are more sensitive to overfeeding with high fat diets [1].

Peripheral CCK’s satiating effect is mediated by vagal afferents and appears to be primarily based on a paracrine action of CCK on CCK_A receptors at sensory vagal afferents in the pyloric area [10]. High doses of CCK presumably suppress appetite also by inhibiting gastric emptying [10]. Peripherally injected CCK induces c-fos-like activity in the nucleus of the solitary tract (NST), the area postrema (AP), and the paraventricular nucleus (PVN) [9]. Intraintestinal fat and glucose infusions reproduced similar activation patterns, which could be attenuated by CCK_A receptor antagonists, indicating that these CHO and fat-derived effects were both mediated via CCK_A receptors [1, 11]. CCK is also expressed by central neurons projecting to the ventromedial hypothalamus (VMH). A role for brain CCK in satiation is suggested by the release of hypothalamic CCK in response to eating [8], and by the stimulation of eating after ICV administration of CCK receptor antagonists [9]. The satiating effect of CCK is mediated at least in part by the central serotonergic system because serotonergic antagonists, primarily of the 5-HT_1 subtypes, attenuated CCK’s inhibitory effect on ingestion [7].

**Role of Enterostatin**

Enterostatin is the aminoterminal pentapeptide of pancreatic procolipase that is released during fat digestion. Enterostatin specifically inhibits fat intake after peripheral or central administration in food-deprived rats [12, 13]. The appetite-suppressive effect of enterostatin requires adaptation to high fat intake and can last up to 24 h after a single intraperitoneal (IP) injection [13]. To date there are still no reports of an appetite suppression by enterostatin in man. The experimental design in these studies, however, may have prevented such a result [13]. A critical examination of the physiological role of enterostatin in appetite control is also hampered because an enterostatin receptor has not yet been identified.

Apparently enterostatin suppresses appetite by acting at a peripheral site, presumably located in the GI area, and/or a central site, in the amygdala or the PVN [13]. Capsaicin-sensitive afferent vagal fibers are essential for the appetite-suppressive effect of peripheral enterostatin because sectioning the hepatic branch of the vagus and capsaicin treatment abolished the suppression of high fat diet intake by IP enterostatin in overnight fasted rats [13]. It is not clear how enterostatin activates the vagal afferents; lumenal enterostatin may be transported across the mucosal layer to activate the nerve terminals directly, or enterostatin could activate a paracrine system and thus stimulate the sensory afferents indirectly.
Procolipase could not be detected in the CNS, but enterostatin-like immunoreactivity is present there at high levels [13]. Thus, circulating enterostatin must gain access to the CNS either through circumventricular organs or through a specific transport system. The fat intake reducing effect of enterostatin also appears to be mediated through the serotonergic system (presumably through 5-HT\textsubscript{1} receptors) because it was attenuated by the serotonin antagonist metergoline but not by the specific 5-HT\textsubscript{2} receptor antagonist ketanserin [13].

**Role of Apo A-IV**

For a long time, the physiological role of apo A-IV was largely unknown. Recently, evidence is accumulating that apo A-IV contributes to appetite control after fat ingestion, which markedly stimulates apo A-IV production [14, 15]. In rats, intravenous (IV) infusion of purified apo A-IV and apo A-IV-containing mesenteric lymph collected during lipid absorption suppressed food intake compared to fasting lymph. Equivalent IV intralipid infusions did not suppress food intake, indicating that the appetite-suppressive effect of mesenteric lymph was not due to the absorbed lipid [15]. Apo A-IV production is associated with chylomicron formation, and mesenteric lymph did not suppress eating when chylomicron formation was inhibited pharmacologically [15]. Mesenteric lymph treated with apo A-IV antiserum did also not suppress food intake. Together, these data indicate that apo A-IV is a circulating signal released by the small intestine after fat ingestion, and is a likely contributor to the appetite-suppressive effect of a fat meal [14, 15].

ICV administration of apo A-IV inhibited eating more potently than IV infusion, and ICV administration of apo A-IV antibodies stimulated eating. This suggests that apo A-IV inhibits eating through an action in the CNS. Interestingly, ICV administered apo A-IV also affects gastric motor and secretory functions [15]. Fat intake increases the apo A-IV concentration in the cerebrospinal fluid (CSF). Yet, as \textit{de novo} synthesis of apo A-IV in the CNS is unlikely [15], apo A-IV presumably somehow crosses the blood-brain barrier. Immunohistochemistry revealed apo A-IV staining in astrocytes throughout the brain, indicating uptake of apo A-IV at least by these cells.

Whether the production of apo A-IV during a meal is fast enough and sufficient for an acute effect on meal termination is open to discussion, and studies are still missing in which apo A-IV is administered in relation to spontaneous meals in order to critically examine a possible acute effect. Apo A-IV may, however, mediate several of the inhibitory effects of ileal fat on gastric emptying, intestinal motility and pancreatic secretion. These mechanisms, collectively termed the ‘ileal break’, have traditionally been invoked mainly during the delivery of abnormal amounts of undigested nutrients into the distal intestine [16]. Yet, because of the rapid gastric emptying early in the
meal, nutrients may reach the distal gut also under normal conditions [15]. All in all, the exact mechanism of apo A-IV-induced suppression of appetite needs to be identified, but it certainly fits the general pattern of the intestinal fat-derived feedback on ingestion and processing of nutrients.

Role of Glucagon-Like Peptide 1

The truncated (i.e. 7–36) amidated form of glucagon-like peptide-1 (GLP-1) has received much attention because of its insulinotropic effect and because it has been shown to potently inhibit eating in man and animals [17, 18]. GLP-1 is cleaved from proglucagon in mucosal L cells of the distal portion of the ileum, and in the A cells of the pancreas. CHO ingestion stimulates GLP-1 secretion. The paradox that GLP-1 secretion starts within minutes after meal onset although the L cells are located primarily in the lower GI tract has not yet been resolved conclusively, but neural signaling from the upper to the lower intestine may be involved [16]. GLP-1 stimulates insulin and inhibits pancreatic glucagon secretion and thus prepares the organism for the arrival of glucose. There may also be some direct effect of GLP-1 on glucose utilization in various tissues. In addition to effects on pancreatic endocrine secretion, GLP-1 has also remarkable feedback effects on upper GI motor and secretory functions (‘ileal brake’) [16].

There appear to be species differences with respect to the appetite-suppressive effect of GLP-1. Thus, IV administration of GLP-1 reduces food intake in humans [18] but not in rats, in which so far only ICV GLP-1 administration suppressed appetite [17, 19]. Several possible explanations for this discrepancy are discussed. In man, peripheral GLP-1 may mediate the satiating effect of intestinal glucose infusions. A close association between the suppression of appetite by intestinal glucose and the increase in plasma GLP-1 was observed, whereas no such correlation between appetite suppression and plasma insulin or GIP was found. In one experiment, the suppression of GI peptide release by co-infusion of octreotide blocked the satiating effect of intraduodenal glucose [20].

GLP-1 and its receptors can be detected by immunohistochemistry in several brain areas [19, 21]. The central appetite-suppressive effect of GLP-1 appears to be physiologically relevant because ICV administration of the specific GLP-1 receptor antagonist exendin 9–39 increased food intake and blocked the appetite-suppressive effect of exogenous GLP-1 in rats [17]. Again, the stimulus for central GLP-1 release or transmission is open to discussion. One possibility is that peripheral GLP-1 stimulates central GLP-1 neurotransmission by acting through afferent vagal fibers. In addition, at least GLP-1 receptors in circumventricular organs, which lack a blood brain barrier, are accessible to circulating GLP-1 [16].

GLP-1 has aversive properties in rats, and this has sometimes been implicated in its appetite-suppressive effect. Recent data, however, indicate that both effects can be dissociated [19]. Thus, central infusion of GLP-1 directly
into the hypothalamic PVN reduced short-term food intake at doses that did not induce a conditioned taste aversion. Moreover, rats with PVN lesions did not reduce food intake in response to ICV GLP-1, but were still able to form a conditioned taste aversion [19]. Finally, no side effects of GLP-1 accompanied the marked appetite suppression in humans [18].

**Postabsorptive Metabolic Feedback**

*Metabolic Signals Contribute to Appetite Control*

Consistent with the assumption that metabolic signals contribute to appetite control, parenteral administration of various fuels or pharmacological manipulation of fuel utilization have often been shown to alter food intake. Chronic administration of metabolic fuels usually reduces food intake equivalent to about 40–70% of the infused energy, depending on the timing of the infusion and on the composition of the infusate [22]. Metabolic inhibitors attenuate the appetite-suppressive effects of IV nutrient infusions. These and other findings suggest that parenterally administered fuels must be utilized to affect food intake [22].

*Metabolic Feedback from CHO Glucose Utilization (see Fig. 2)*

Blood glucose concentration and glucose utilization increase in response to CHO meals. Ingested glucose is readily utilized because of the limited glycogen storage capacity [23]. Consistent with an appetite-suppressive effect of increases in glucose availability and utilization, IV glucose infusions have often, but not always, been shown to inhibit eating [22]. The timing or route of glucose application, the composition of the test diet and the duration of the feeding test determine the satiating potency of parenterally administered glucose. In some studies the satiating potency of glucose increased when insulin was infused simultaneously [22], suggesting that the involved glucose sensors are partly sensitive to insulin.

In rat and man, spontaneous meals are preceded by a small (6–11%) decline in blood glucose [24, 25], which appears to be causally related to meal onset. A rapid decline in blood glucose – as in the dynamic decline phase after a high CHO load – may be a particularly strong signal for meal initiation. It is still unclear whether a change in glucose utilization accompanies the pre-meal decline in blood glucose. It could just be related to the cessation of intestinal glucose absorption at some point after the previous meal, necessitating a metabolic switch to endogenous glucose production in order to maintain blood glucose at a certain level. Cellular glucoprivation induced by glucose antimetabolites (e.g. 2-deoxyglucose [2-DG]) also triggers a meal (glucoprivic eating) [22]. This is consistent with a role of glucose utilization in the maintenance of postprandial satiety.
Carbohydrate and Fat-Based Appetite Control Mechanisms

Fig. 2. Schematic diagram of the postabsorptive feedback control of appetite based on carbohydrate (CHO) and fat metabolism. LCFA = long-chain fatty acids, MCFA = medium-chain fatty acids, NE = norepinephrine, NPY = neuropeptide Y, SCFA = short-chain fatty acids. For the sake of consistency with Figure 1, the diagram depicts a negative feedback. It therefore shows a decrease in the release or transmission of orexigenic neurochemicals, although so far mainly an increase in the expression or transmission of these substances has been shown in response to decreases in fuel availability or utilization. A clear picture has yet to emerge for the exact role of galanin. Note also that the signal transduction pathway for hepatic fatty acid oxidation is still unknown.
Carbohydrate and Fat-Based Appetite Control Mechanisms

Fig. 3. Effect of remotely controlled hepatic portal vein infusions of glucose on spontaneous meal size in *ad libitum* fed rats. The infusions (0.1 ml/min) were started at 2 min into the first spontaneous dark phase meal and lasted for 5 min. Values are means (SE. N: number of animals used in individual crossover tests. *Significantly (paired t-test, p < 0.05) different from corresponding control (isoosmotic saline) value.

Hepatic Monitoring of Glucose Utilization and Signaling Pathways

The liver is an ideal location for a glucose sensor in the control of eating, GI functions, and metabolism because of its key role in glucose homeostasis. Infusion of physiological amounts of glucose into the hepatic portal vein reduces food intake more effectively than equivalent infusions into the jugular vein [26]. Usually, there is no clear relationship between the amount of glucose infused into the portal vein and the observed appetite suppression. In our hands, remotely controlled hepatic portal vein infusions of 1 mmol of glucose during the first spontaneous nocturnal meal acutely decreased meal size in the rat, whereas lower and higher glucose doses did not (Fig. 3). This suggests that circulating glucose can immediately suppress appetite, but this effect appears to be situationally variable. Moreover, intraportal glucose infusions sometimes suppressed oral intake only when the infusions began 60 or 45 min prior to meal onset [22].

Hepatic glucose sensors play a role in the reliable translation of the transient pre-meal decline in blood glucose into meal initiation because complete subdiaphragmatic as well as hepatic branch vagotomy disrupted the otherwise reliable coupling between the glucose decline and meal initiation in the rat [24]. Some studies with 2-DG also suggest a contribution of hepatic glucose sensors to meal initiation. In rabbits, hepatic portal vein infusion of 2-DG caused a more rapid and greater increase in food intake than jugular vein infusion, and the effect was reduced by subdiaphragmatic vagotomy. In rats, hepatic branch vagotomy attenuated glucoprivic eating when 2-DG was injected in the early dark phase of the lighting cycle or after consumption of a test meal [27].
Glucose is readily utilized by peripheral nerves, and the available electrophysiological data indicate that hepatic vagal afferents function as hepatic glucose sensors as originally suggested by Niijima [28]. Hepatic vagal afferents appear to react directly to glucose utilization, and the coding mechanism presumably involves changes in ATP and sodium pump activity [28]. As many of the vagal afferents terminate in the wall of the hepatic portal vein, hepatic glucose sensors are well suited to monitor the incoming supply of glucose and to feed this information into the CNS circuitry that controls feeding. Yet, as glucose infusions into the hepatic portal vein affect hepatic vagal afferent nerve activity faster than food intake, an additional stimulus appears to be required to suppress appetite. Candidates include hepatic glucose uptake and glycogen formation, but the exact nature and the mechanism of this additional stimulus remains to be identified [22].

CNS Monitoring of Glucose Utilization

The reliable appetite-stimulating effect of ICV administered glucose antimitabolites implicates central glucosensitive neurons [29] in glucoprivic eating. In fact, eating in response to central and peripheral glucoprivation appears to require glucosensitive neurons in the AP/NST region [30]. Intravenously infused 2-DG also induced \textit{fos}-like immunoreactivity in the AP/NST region of the rat [30]. The neurophysiological data at hand indicate that the glucosensitive neurons in liver, NST and lateral hypothalamus are anatomically and functionally related. They represent a network that senses the availability of glucose and is probably involved in gut function, glucose homeostasis and food intake control [31].

Norepinephrine (NE), neuropeptide Y (NPY) and the recently discovered orexin peptide family appear to be among the central mediators of the appetite-stimulating effect of a decrease in circulating glucose and/or glucoprivation. All three neurochemicals potently stimulate eating after central administration, and their expression and/or turnover is increased by a decrease in blood glucose and/or pharmacological glucoprivation [32, 33].

Other CHO Metabolites

The plasma level of lactate increases in response to CHO ingestion, and lactate reduces food intake after parenteral administration in animals [22]. In our hands, meal-contingent hepatic portal vein and vena cava lactate infusions reduced meal size (Fig. 4), suggesting that an increase in circulating lactate can prematurely end a meal. Only hepatic portal vein lactate increased the duration of the subsequent inter-meal interval relative to meal size (satiety ratio), and peripherally injected lactate’s appetite-suppressive effect was blocked by hepatic branch vagotomy [22]. Thus, part of lactate’s appetite-suppressive effect is probably due to a hepatic action. A central mechanism may also contribute to the acute meal size effect of IV infused lactate because lactate is rapidly taken up into neurons by a saturable transport system.
Carbohydrate and Fat-Based Appetite Control Mechanisms

**Fig. 4.** Effect of remotely controlled hepatic portal vein infusions of sodium L-lactate on spontaneous meal size in *ad libitum* fed rats. The infusions (0.1–0.15 ml/min) were started at 2 min into the first spontaneous dark phase meal and lasted for 5 min. Values are means (SE; N: number of animals used in individual crossover tests. *Significantly (paired t-test, *p* < 0.05) smaller than corresponding control (iso-osmotic saline) value.

Like glucose, fructose also potently reduced food intake after hepatic portal infusion, and this effect appeared to depend on hepatic fructose utilization [34]. Yet, unlike glucose, hepatic portal infusion of fructose did not affect hepatic vagal afferent activity in the isolated guinea pig liver preparation [35] leaving the mechanism of the fructose-induced appetite suppression open to discussion.

**Metabolic Feedback from Fat (see Fig. 2)**

**Fatty Acid Oxidation**

The fact that only a small proportion of ingested fat is metabolized after a meal is often misinterpreted as suggesting that fat metabolism does not affect appetite. Several lines of evidence, however, strongly indicate that fatty acid oxidation suppresses hunger. IV infusions of lipid emulsions from which fatty acids are released by lipoprotein lipase reduce food intake [22, 36], although usually less than isocaloric CHO or protein infusions. Long-term lipid infusions increase oxygen consumption and decrease the respiratory quotient, indicating that the infused lipids enhance fatty acid oxidation. The feeding-suppressive effect of parenteral nutrition is attenuated by the fatty acid oxidation inhibitor mercaptoacetate (MA) [37] and is therefore in part due to oxidation of the infused fatty acids. More importantly, a pharmacological inhibition of fatty acid oxidation is associated with a stimulation of food intake (lipoprivic eating) in animals and man [36, 38]. Fatty acid oxidation inhibitors, such as MA or the carnitine palmitoyltransferase-1 (CPT-1) inhibitors etomoxir (ETO) and methylpalmoxirate (MP), stimulate appetite when fat-rich diets are consumed.
Carbohydrate and Fat-Based Appetite Control Mechanisms

Fig. 5. Effect of the fatty acid oxidation inhibitor etomoxir (150 mg, oral administration) on the plasma concentration of (β-hydroxybutyrate (BHB) and on meal size in humans selected for habitually high fat intake (mean: 44% of energy intake). Etomoxir or placebo was administered after an overnight fast, 2.5 h before an oversized high fat breakfast (6,960 kJ, 72% from fat) was offered. Control meal size was 1,044–5,919 kJ. BHB values refer to the area under the curve calculated from all 4 measurements in response to BHB or placebo administration. Values are given as mean percent change (±SE) of the 10 subjects’ individual control values. *Significantly (paired t-test, \( p < 0.05 \)) different from corresponding control value.

and when the rate of fatty acid oxidation is high [36]. In rats, an inhibition of fatty acid oxidation increased food intake primarily through an acute effect on the duration of the inter-meal interval [22], implicating fatty acid oxidation in the maintenance of satiety. In man, ETO acutely increased meal size (Fig. 5), suggesting that hepatic fatty acid oxidation can also contribute to meal termination [38]. This difference is probably due to differences in the experimental conditions. In rats maintained on a macronutrient self-selection diet, MA increased intake of carbohydrate and protein and decreased intake of fat [30], i.e., the rats appear to avoid the nutrient they cannot oxidize in response to MA, and overconsume the nutrients they can utilize. It is still unproven whether physiological changes in fatty acid oxidation affect appetite. This is possible, however, because the plasma concentration of free fatty acids and fatty acid oxidation increase after a fat-rich meal [22].

Hepatic Monitoring of Fatty Acid Oxidation and Signaling Pathways

Hepatic branch vagotomy blocked the appetite-suppressive effect of continuous low dose (25 nmol/min) hepatic portal vein oleate infusion [Benthem et al., unpubl. results]. Similarly, the stimulation of eating by MA was markedly attenuated by hepatic branch vagotomy [37, 39] and blocked by capsaicin pretreatment, subdiaphragmatic vagotomy, and lesions of the vagal sensory terminal fields in the AP/NST. Further, MA increased multiunit hepatic vagal
afferent nerve activity [36] similar to 2-DG. Thus, metabolic sensors involved in lipoprivic eating are presumably located in the liver, and are connected to the brain through sensory afferents. Consistent with an effect of hepatic fatty acid oxidation on appetite, ETO increased appetite and decreased the plasma concentration of β-hydroxybutyrate (Fig. 5), i.e. inhibited hepatic, but not the whole body fatty acid oxidation in man. Finally, we observed recently that hepatic portal vein infusion of a low MA dose (50 µmol/kg BW) increased cumulative food intake in rats.

The coding mechanism of portal-hepatic sensors for fatty acid oxidation is unknown. Whereas afferent nerves readily utilize glucose, it is very unlikely that they oxidize fatty acids. As hepatocytes rely primarily on fatty acid oxidation for ATP generation, they are probably involved in the monitoring of fatty acid oxidation by hepatic vagal afferents. Yet, how the signal is relayed from hepatocytes to sensory fibers must still be clarified. The often observed inhibition of eating in response to ingestion or intragastric administration of medium-chain triglycerides [31] provides indirect evidence for a role of hepatic fatty acid oxidation in appetite control because dietary medium-chain fatty acids are efficiently oxidized in the liver. Finally, it is worth mentioning that β-hydroxybutyrate also reduces food intake after peripheral and central administration [36]. (β-Hydroxybutyrate increases in plasma as a result of an increase in hepatic fatty acid oxidation after ingestion of medium-chain triglycerides or a fat meal).

Central Pathways

Induction of fos-like immunoreactivity in response to oral MP administration has been observed in the NST/AP, the lateral parabrachial nucleus, the central lateral nucleus of the amygdala, the dorsal lateral bed nucleus of the stria terminalis, and in the hypothalamic PVN [36]. Subdiaphragmatic vagotomy abolished the c-fos expression in the brain induced by peripheral administration of MA. On the other hand, lesions of the lateral parabrachial nucleus but not of the hypothalamic PVN blocked lipoprivic eating, and eating could not be elicited by ICV injection of MA [30]. Thus, inhibition of hepatic fatty acid oxidation activates an afferent pathway projecting from the hindbrain to the forebrain. Neurons in the brain do not detect the signal derived from fatty acid oxidation, but are involved in the processing of the signal generated in the periphery.

Food deprivation and MA affect the hypothalamic expression and immunoreactivity of the neuropeptide galanin, which potently stimulates fat intake [32, 40]. Whereas food deprivation increased PVN galanin and stimulated fat ingestion, MA decreased galanin and reduced fat ingestion. These results suggest a relationship between peripheral fatty acid oxidation, PVN galanin activity, and fat ingestion. Yet, the interactions appear to be complicated because central administration of a galanin antagonist has also been shown to attenuate the feeding response to peripheral MA [30]. The final central feeding pathway
activated by inhibitors of fatty acid oxidation can be blocked by serotonergic drugs [41].

**Integration**

The presence of nutrients in the intestine inhibits eating and gastric emptying, and intestinal nutrients or GI peptides and stomach fill suppress appetite synergistically. Metabolic feedback signals also interact: Combined treatment with glucose antimetabolites and fatty acid oxidation inhibitors increased food intake of rats synergistically [22]. It is unclear how much of this synergism is based on an integration of the metabolic feedback signals on the biochemical level. It has been proposed that hepatocellular ATP might provide such an integrative signal and might link hepatic oxidative metabolism to afferent neural activity [42]. This is an attractive hypothesis, but some findings are hard to reconcile with it [22]. Hepatic metabolic feedback signals apparently also interact with GI feedback signals in appetite control. Thus, parenteral fuel administration inhibits eating most potently when the infusion times coincide with the animals’ usual feeding time.

The adequate postabsorptive handling of nutrients requires their recognition and the subsequent initiation of specific endocrine and metabolic responses. It is reasonable to assume that this information feeds back into the mechanisms of nutrient selection. Signals from hepatic sensors for glucose and fructose utilization and fatty acid oxidation apparently influence taste processing and nutrient selection. Rats given hepatic portal glucose or fructose infusions developed a preference for the flavor that had been paired with the infusion. In turn, pre- and postabsorptive feedback signals may have to be associated with familiar oral cues to effectively suppress appetite [43].

Finally, the CHO and fat-based short-term appetite control mechanisms are integrated in the long-term control of energy balance. Available evidence suggests that adiposity signals such as leptin and insulin influence feeding mainly through changes in meal size, i.e. by modulating the direct feedback control of meal size [9]. Appetite control is part of a complex regulatory system that consists of several intertwined feedback loops which ensure adequate energy intake and nutrient selection, prepare the organism for the arrival of particular nutrients, facilitate their metabolic handling, and control energy storage.

**References**


Discussion

Dr. Ritz: You’ve shown that CCK antagonists and etomoxir both work in healthy humans. Do they also work in disease? We are short of products that can promote appetite or increase energy intake in diseased patients. That is a really big issue.

Dr. Langhans: There are not many studies that have investigated CCK in relation to disease. As far as I remember, there have been one or two that have looked at whether CCKA antagonists would block the feeding suppression effect of cytokines, and they showed there may be some contribution of CCK. But I would like to raise a note of caution here, because we know from other studies that the CCK effect is almost fully mediated by vagal afferents, and the cytokine effect is not. Under exactly the same conditions, the CCK picture I presented to you was a functional control in a cytokine study that we did, where we tested whether subdiaphragmatic vagal deafferentation would reduce the feeding-suppressive effect of cytokines or bacterial products, and it did not.
**Dr. Holm:** In relation to disease, cancer patients have increased levels of \( \beta \)-hydroxybutyrate and increased fatty acid oxidation with reduced appetite, while cirrhotic patients have increased levels of lactate, so they should have reduced appetite but they have normal appetite. Also, in the cirrhotic liver the sensors may be at least partly destroyed, and blood tends not to flow into the liver in the portal circulation but comes out of the liver through the portal vein, so the situation is very complicated. Is there any experimental work on that?

**Dr. Langhans:** I fully agree with you that this is a very complicated issue, and one of the characteristics of the whole food intake control system is that there are many redundancies – if you take one factor out, you can almost be sure that you won’t affect food intake in the long term. In disease, the situation is even more complicated. There are a few studies that have looked at whether the metabolic changes occurring in cancer or other diseases have something to do with food intake suppression. Lactate was one early candidate, for obvious reasons because of the metabolic characteristics of cancer tissue and so on, but the results were not very clear. Those studies have not been continued very intensively after the advent of cytokines, because everybody jumped on the cytokine bandwagon. So this is still an open question. I can very well imagine that metabolic factors could contribute to disease anorexia, but it needs to be sorted out how much and under what circumstances.

Concerning the liver question, there are so far no detailed studies, but we are currently undertaking an investigation in cooperation with the liver transplant unit of the University Edinburgh (Prof. Garden and coworkers) to see whether any of these mechanisms change after transplantation. There is some circumstantial evidence that liver transplant patients have more problems with maintaining a stable body weight after surgery than, for instance, kidney transplant patients, although the immunosuppressive therapy is similar.

**Dr. Fernstrom:** You said that the CCK effect on food intake was lost when you cut the afferent vagus. So the appetite effects of peripherally released CCK are all peripherally mediated, presumably on the afferent vagus?

**Dr. Langhans:** Yes.

**Dr. Fernstrom:** Very interesting. Is the increase in \( \beta \)-hydroxybutyrate that you see with feeding high fat sufficient to affect the fuel mix in the brain?

**Dr. Langhans:** That’s an interesting question. We know from previous studies that if you inject \( \beta \)-hydroxybutyrate peripherally in rats, you can eliminate or block its effect by hepatic branch vagotomy, but I could well imagine that, as with lactate, there might also be a central component to the \( \beta \)-hydroxybutyrate effect. What I left out here are the data showing that lactate has a similar effect on meal size when it is infused into the vena cava under exactly the same conditions. There are subtle differences which point to the liver, but there is certainly also something else operative apart from the liver.

**Dr. Vandewoude:** You talked about the appetite-suppressing effects of carbohydrates and fats. Do you have any data on the effect of fiber in the diet?

**Dr. Langhans:** Fiber in the diet can have suppressive effects on appetite. There are several studies showing that dietary fiber can, at least under certain conditions, have a short-term effect on food intake. There are various possible mechanisms. One is slowing down of gastric emptying and gastrointestinal transit. Another is the prevention of postprandial reactive hypoglycemia.

**Dr. Bourdel-Marchasson:** Do you have information about the control of meal initiation and the inter-meal interval?

**Dr. Langhans:** I would suggest that there is a kind of ebb and flow. Obviously during a meal, gastrointestinal or preabsorptive signals will have priority and primarily affect meal size, but that doesn’t mean that they have no effect on the inter-meal interval. As I showed you, I think metabolic signals can also have an effect on meal
size, and of course they will affect the inter-meal interval too. I left out studies that we did with fatty acid oxidation inhibitors; these show that in rats inhibition of fatty acid oxidation does not affect meal size, but it does affect the inter-meal interval. The basic outcome is the same – you get stimulation of food intake, but in humans there is an increase in meal size while in the rat there is an increase in meal frequency. I believe that the signals I discussed in my talk will affect meal size and meal frequency, but with different potencies.

**Dr. Holm:** Excuse me, but I have still difficulties with the β-hydroxybutyrate. With TPN, and also when you start enteral nutrition, the level of ketone bodies falls dramatically and they stay very low unless you give about 44% of the total energy in the form of fat. Were you really giving as much as that? Normally we give about 30%.

**Dr. Langhans:** This was not parenteral or enteral nutrition; it was just normal food intake. There was no infusion whatever. We selected these subjects for their habitual high fat intake. The average European and North American now eats something like 38% fat energy, so they were only a little higher than the average for industrialized countries. The only additional factor was that these subjects received etomoxir orally to inhibit fatty acid oxidation.

**Dr. Holm:** There can only have been a very slight increase in fatty acid oxidation because the uptake of fatty acids by the liver is very small after feeding, and the body changes from fatty acid oxidation to carbohydrate oxidation after a meal.

**Dr. Langhans:** I showed you the RQ data. Even in the high fat condition during a meal, the RQ increased, which of course indicates increased carbohydrate utilization. About 1 hour or 90 minutes after a high fat meal, the RQ was lower in the high fat than in the high carbohydrate condition, indicating that there was some fatty acid oxidation going on. I agree with you on this point. Basically you confirm what I tried to show, that the postprandial oxidation of fatty acids is not particularly impressive.

**Dr. Uauy:** Are there any specific effects on food preference for carbohydrate or fat that are specific to the regulators?

**Dr. Langhans:** Fatty acid oxidation inhibitors tend to stimulate protein and carbohydrate intake and not fat intake. It looks as if the organism realizes that it cannot utilize the fat and so it switches to other nutrients, but this is a superficial explanation. As far as other signals are concerned, glucose has a stronger effect on food intake in animals that are adapted to a high fat diet, while CCK or intraintestinal fat is less effective in animals adapted to a high fat diet. So there are all kinds of interactions that await further investigation.

**Dr. Kaye:** I’d be interested in your speculation on why there’s so much redundancy in these systems. What do you think that means?

**Dr. Langhans:** Well, this may be a superficial explanation but I think it would be stupid of Nature to make a system that is as important for survival as food intake dependent on just one factor, or to link it to just a single controlling factor. There has to be plasticity to allow adaptation to changes in the environment.

**Dr. Rosenberg:** I’m reminded of the exquisite systems that we have to protect our blood osmolality and to maintain satisfactory hydration. It seems to me that whoever designed the food intake system must have taken some cues from that redundancy which obviously occurred when our predecessors emerged from water onto land. But I think there is a certain parallelism in the use of nervous mechanisms, humoral mechanisms, direct sensing of distension in luminal tissues, and so forth; there are some very interesting parallels here.
Dr. Langhans: Food intake regulation is a tricky issue, because on one hand the organism obviously needs food for survival, but on the other hand, food intake also poses a threat to homeostasis, so it needs to be very well regulated so that the system doesn’t get out of control. It is also known now that high protein intakes trigger immune reactions in the gut, because they constitute a large antigen load; this also relates to this issue of homeostatic mechanisms that need to be well controlled.