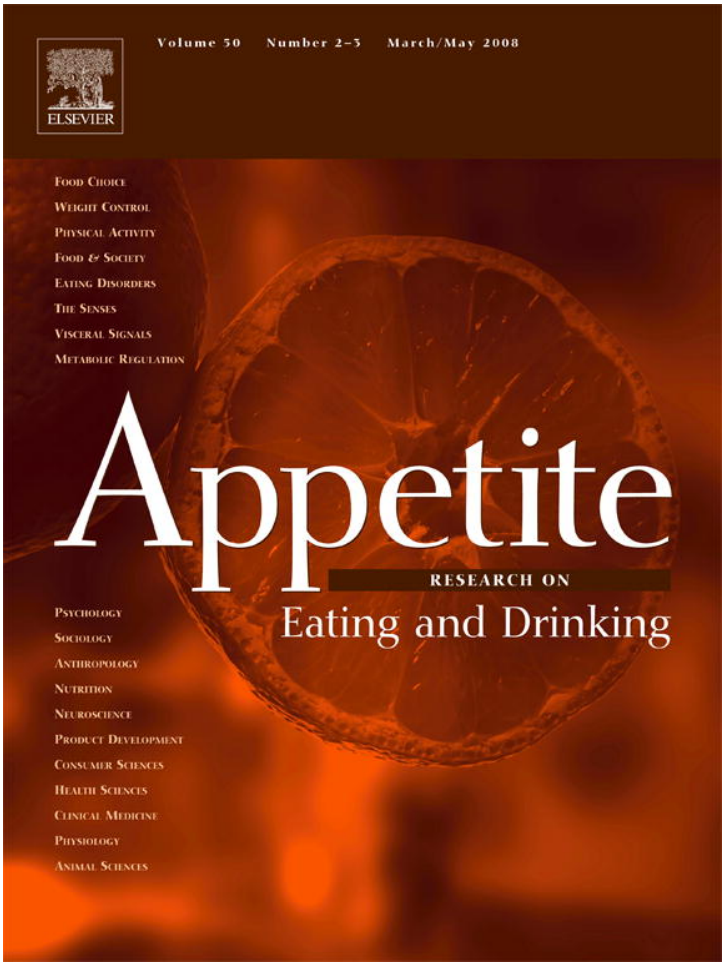

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Research Review

Anticipatory physiological regulation in feeding biology: Cephalic phase responses

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Abstract

Anticipatory physiological regulation is an adaptive strategy that enables animals to respond faster to physiologic and metabolic challenges. The cephalic phase responses are anticipatory responses that prepare animals to digest, absorb, and metabolize nutrients. They enable the sensory aspects of the food to interact with the metabolic state of the animal to influence feeding behavior. The anticipatory digestive secretions and metabolic adjustments in response to food cues are key adaptations that affect digestive and metabolic efficiency and aid in controlling the resulting elevation of metabolic fuels in the blood. Cephalic phase responses enable digestion, metabolism, and appetite to be regulated in a coordinated fashion. These responses have significant effects on meal size. For example, if the cephalic phase insulin response is blocked the result is poor glucose control and smaller meals. Cephalic phase responses also are linked to motivation to feed, and may play a more direct role in regulating meal size beyond the permissive one of ameliorating negative consequences of feeding. For example, the orexigenic peptide ghrelin appears to display a cephalic phase response, rising before expected meal times. This anticipatory ghrelin response increases appetite; interestingly it also enhances fat absorption, linking appetite with digestion and metabolism.

Keywords: Digestion; Appetite; Homeostasis; Insulin; Ghrelin; Evolution

Contents

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Introduction

Appetite, food preferences, and the regulation of food intake are key aspects of energy balance and weight homeostasis. There is an ever growing list of peptides, receptors, and other gene products associated with appetite and the regulation of food intake, and investigating their interrelated roles is an important process for understanding the proximate mechanisms by which people decide when and what to eat, and when to stop. In our opinion, a comparative, evolutionary perspective will also be important to understanding why the imbalance between food intake and energy expenditure appears to be so refractory.

The acquisition of food is a necessity for animals. Strong selective pressures have acted to produce the anatomy, physiology, and behavior that serve to enhance an animal's ability to ingest, digest, absorb, and ultimately metabolize the nutrients necessary for survival and reproduction. There are anticipatory physiological responses to feeding, the cephalic phase responses, that set in motion digestive and endocrine cascades that increase the efficiency of digestion and metabolism, but also directly and indirectly regulate meal size and duration. These cephalic phase responses can be conditioned, so experience, learning, and hence social and cultural factors, can and will play a role in their expression.

In this paper, we examine the role of cephalic phase responses in the regulation of food intake. The term cephalic phase response refers to anticipatory physiological regulation related to food and feeding; i.e. digestive and metabolic responses to food cues generated by the central nervous system that prepare the organism to ingest, digest, absorb, and metabolize food (Pavlov, 1902; Powley, 1977; Smith, 1995). These anticipatory physiological responses increase the efficiency with which an organism utilizes food. One result is an increase in the amount of food that can be processed at a given time; an advantage in our past evolutionary history, but possibly a source of our species' susceptibility to obesity in the modern milieu. Recent evidence suggests that physiological responses that serve to end feeding also can have a cephalic phase. Thus, by the first bite of food, or even before, physiological processes have been set in motion that will influence the duration of the meal and the amount of food eaten (Smith, 2000).

We will examine cephalic phase responses from an adaptive perspective. We focus on the functions of various cephalic phase responses, their effects on food intake, and the possible selective pressures that have influenced their evolution.

Importance of anticipatory responses in regulatory physiology

Animals anticipate. Behavior, physiology, and metabolism are not merely reactive. The senses convey information about the external environment to the central nervous system. The central nervous system interprets this information within the constraints of experience (knowledge), intrinsic, evolved tendencies (phylogeny), and current conditions (e.g. social setting, nutritional status, and so forth). Is there a threat? Is there an opportunity? The central nervous system sends messages to the appropriate peripheral organs to begin the physiological cascades that prepare the organism to respond to the anticipated challenge. The animal changes its state in advance of the potential need.

These anticipatory physiological changes can be in response to circumstances, or can reflect internal, clock-like rhythms. For example, there are circadian rhythms in the secretion of many hormones (e.g. cortisol, leptin, ghrelin), which allow an animal to be in the most appropriate physiological state at different time points. Moore-Ede (1986) suggested the term predictive homeostasis for these anticipatory changes in physiology. Anticipatory responses are associated with the central coordination of physiology, and the interplay of physiology and behavior. Some authors (e.g. Schulkin, 2003; Sterling, 2004) have emphasized how the central coordination of physiology, anticipatory physiological responses, and the interplay of physiology and behavior appear to be given short shrift by the classic homeostatic paradigm of physiological regulation. The concept of allostasis, defined as the "…process by which an organism achieves internal viability through bodily changes of state" has been proposed as an alternative (Schulkin, 2003, p. 21). Many of the examples of allostatic regulation provided by Schulkin (2003) involve the concept that the hormones that regulate peripheral physiology in response to a challenge are also involved in changing central motive states of the brain, and thus induce behaviours that aid the animal to meet the challenge (see also e.g. Epstein, 1982; Herbert, 1993; Smith, 2000). The regulation of food intake is a paradigmatic example of the linkage of peripheral physiology with central motive states, and the concept that behavior and physiology act together to preserve viability.

Importance of anticipatory responses in feeding biology

Human beings feed in discrete meals. In consequence, food enters our bodies in pulses, and presents our digestive and metabolic systems with challenges to accommodate a discontinuous supply of nutrients (Storlien, Oakes, & Kelley, 2004). Our internal milieu is not strictly constant. The state of the digestive system and numerous other organ systems (e.g. liver, kidney, adipose tissue) constantly change to accommodate conditions of nutrient excess (feeding) followed by potential nutrient deficits (between meals). Nutrients continually flow into and out of storage pools.

This differs from the feeding strategies of other primates. Our closest relatives do not routinely feed in meals, except in captivity where we give them little choice. Rather, they are more likely to graze. Our pattern of feeding is more

similar to that of many carnivores than it is to nonhuman primates.

Meals result in perturbations of the internal milieu that must be accommodated (Woods, 1991); the nutrients that enter the blood in pulses from the digestive tract during feeding must be metabolized or transported to and sequestered in the appropriate storage pools. Later, when the gastrointestinal tract is largely empty, nutrients re-enter the blood from nutrient stores. Or to be more precise, the secretory responses that regulate absorption, storage, and mobilization of nutrients constantly change over the day, sometimes favoring a net deposit into storage pools and sometimes favoring a net mobilization into extracellular fluid.

These changes take time. Cephalic phase responses, anticipatory digestive, and metabolic responses to cues that feeding is imminent, allow organisms to get "ahead of the curve". They improve the efficiency with which animals digest food, and absorb and metabolize the liberated nutrients. They also prime the organism to meet the resulting homeostatic challenges presented by the influx of nutrients, such as changes in blood pH and electrolytes.

Cephalic phase responses

The concept was first introduced by Pavlov in his work on the alimentary tract and its secretions. The phrase originally used by Pavlov was "psychic secretions" (see Powley, 1977; Smith, 1995; Todes, 2002). For Pavlov, salivary secretions were digestive secretions, serving the same intrinsic function as gastric and intestinal secretions—enabling the animal to utilize food for bodily needs. He demonstrated in dogs that salivation varied with the food ingested. For example that ingesting dry food stimulated greater salivation than ingesting wet food (Todes, 2002). He also, famously, demonstrated that salivation can occur in anticipation of feeding (Pavlov, 1902). He extended the work to gastric secretions, and showed that they too could be stimulated by the sight, smell, and taste of food. Anticipatory secretion of other digestive fluids (e.g. pancreatic) has been demonstrated as well (e.g. Farrell, 1928; Preshaw, Cooke, & Grossman, 1966). Thus, digestive secretions are anticipatory as well as reactive. The gut and the brain are intimately linked, working together to acquire and utilize the nutrients necessary for life.

The general concept of cephalic phase responses has changed little since the original demonstrations. It was revitalized by Powley (1977), with special emphasis on the cephalic phase insulin response. In functional terms cephalic phase responses are anticipatory changes in physiology and metabolism that serve to prepare the digestive tract to digest food and absorb nutrients, and to prepare other organ systems (e.g. liver, adipose tissue) to metabolize and store the absorbed nutrients. What has changed is that the list of secretions and other responses that appear to have a cephalic phase has continued to expand (Table 1). In addition to gastric and pancreatic secretions there are cephalic phase responses in gastric emptying and gut motility (Powley, 1977), gall bladder secretions (Mattes, 2005), and thermogenesis (Soucy & LeBlanc, 1999). Recent evidence suggests that cephalic phase responses not only prepare an animal to digest, absorb and metabolize food, but they may also play a role in appetite and satiety, and thus in the beginning and ending of a meal. For example, both ghrelin (Drazen, Vahl, D'Alessio, Seeley, & Woods, 2006) and leptin (Bado, Levasseur, & Attoub, 1998) secreted by the stomach appear to exhibit a cephalic phase.

The mouth is the "clearinghouse of the organism" (Pavlov quoted in Smith, 1995). It is the proximal end of the alimentary tract, and the first stage of digestion. Food is masticated and mixed with saliva, which begins the digestive process. Food is also tasted.

Taste has two main functions: to promote or inhibit ingestion, and to prepare the body to utilize or metabolically respond to ingested materials. Cephalic phase responses generally prepare an animal to digest, absorb and then store nutrients that enter the body through feeding. However, cephalic phase responses can also serve to inhibit feeding and prepare an animal to deal with toxic or tainted food. For example, a bitter tasting substance can decrease gastric motility (Wicks, Wright, Rayment, & Spiller, 2005).

Table 1
Selected known cephalic phase responses

Cephalic phase response	Organ(s)	Function(s)
Salivation	Mouth	Lubricate food, begin digestion of starch, dissolves food particles (essential for taste)
Gastric acid secretion	Stomach	Hydrolysis of food
Gastrin	Stomach	Stimulates gastric acid secretion
Lipase	Stomach; pancreas	Fat digestion
Gastric emptying	Stomach	Regulate food passage
Intestinal motility	Intestine	Regulate food passage
Bicarbonate	Intestine	Neutralizes stomach acid
Cholecystokinin (CCK)	Small intestine	Terminate feeding
Insulin	Pancreas	Regulates glucose and fat storage
Pancreatic polypeptide	Pancreas	Biological role uncertain
Digestive enzymes	Pancreas	Digestion of protein, carbohydrates and fat
Bile	Gall bladder	Fat emulsification
Leptin	Adipose tissue; stomach	Reduce appetite
Ghrelin	Stomach	Stimulate appetite; stimulate GH secretion, fat absorption
Thermogenesis	Adipose	Raises body temperature

Evidence for cephalic phase responses

There is a considerable literature on cephalic phase responses, going back to Pavlov (Todes, 2002). Cephalic phase responses have been demonstrated in a wide range of birds and mammals, including humans, nonhuman primates, dogs, cats, sheep, rabbits, and rats (Powley, 1977). Their origin would appear to be quite ancient; for example striped bass display cephalic phase insulin and glucagon responses (Papatryphon, Capilla, Navarro, & Soares, 2001). Some of these cephalic phase responses are general, and some appear to be specific to the nutritional properties of the tastant, i.e. responses to sweet substances differ from those to bitter substances or to high-fat substances. It has long been established that sensory contact with food stimulates cephalic phase digestive responses that result in increased secretion of saliva (Pavlov, 1902), gastric acid (Farrell, 1928; Pavlov, 1902), and pancreatic secretions, including enzymes, proteins, and bicarbonate (Pavlov, 1902; Preshaw et al., 1966). Even the sight of food within sealed plastic containers stimulates gastric secretions in humans (Feldman & Richardson, 1986). Adding smell and taste to the sensory experience increases the response (Feldman & Richardson, 1986).

In humans, dogs, and rats it has been repeatedly shown that the palatability of the offered food is positively correlated with the extent and magnitude of the cephalic salivary and gastric secretions (reviewed in Powley, 1977). Perceived palatability of the food influences the cephalic phase of thermogenesis; there was a greater initial increase in oxygen consumption when human subjects ate a protein meal they rated as highly palatable (Soucy & LeBlanc, 1999). Thus appetite, or the psychological state of wanting food, directly affects the physiological processes of digestion and metabolism (Pavlov, 1902; Powley, 1977; Soucy & LeBlanc, 1999).

Cephalic phase responses can be demonstrated using the technique of sham feeding. In humans, this consists of masticating the test diet or tastant, but not swallowing it. In animal models, the use of fistulas at different parts of the GI tract allows an animal to masticate and swallow, but keeps the food from the GI tract below the fistula. Thus food sensory cues can be restricted to sections of the alimentary canal. Pavlov (1902) used esophogeal fistulas, restricting sensory input to the mouth and tongue. He showed that the gastric secretions stimulated by sham feeding exceeded those stimulated by the sight of food. Many experimenters have preferred gastric fistulas, which means that potential effects of the exposure of food to the stomach must be considered. In both cases metabolic changes due to absorbed nutrients are minimal if not nonexistent.

Sham feeding stimulates a number of changes in the gastrointestinal tract, the blood stream, and in behavior. For example, sham feeding increases gastric acid secretion in dogs (e.g. Pavlov, 1902), rats (e.g. Martínez, Barrachina, Ohning, & Taché, 2002), and humans (e.g. Goldschmidt, Redfern, & Feldman, 1990). Sham feeding induces the secretion of peptides from the pancreas, resulting in an anticipatory rise in blood insulin and pancreatic polypeptide concentration (Fig. 1).

Pavlov (1902) demonstrated that food placed directly into the stomach of dogs was poorly digested; however, if sham feeding preceded the intragastric intubation, then digestion was enhanced. Several clinicians in the 1800s and early 1900s independently discovered that patients with fistulas that were by necessity fed by gastric intubation fared much better if they were allowed to chew and taste food prior to the actual meal being delivered to their gastrointestinal tract. One patient insisted on swallowing the masticated food, even though it was shortly regurgitated from his esophogeal pouch. Appetite was much better, and patients were better able to maintain body weight (reviewed in Powley, 1977).

Another method to demonstrate cephalic phase versus reactive responses is by showing that the physiological changes occur before postingestional effects. For example, an initial pulse of insulin secretion in response to food ingestion occurs within 10 min (peak value at 4 min postingestion) in normal weight men, and this is before

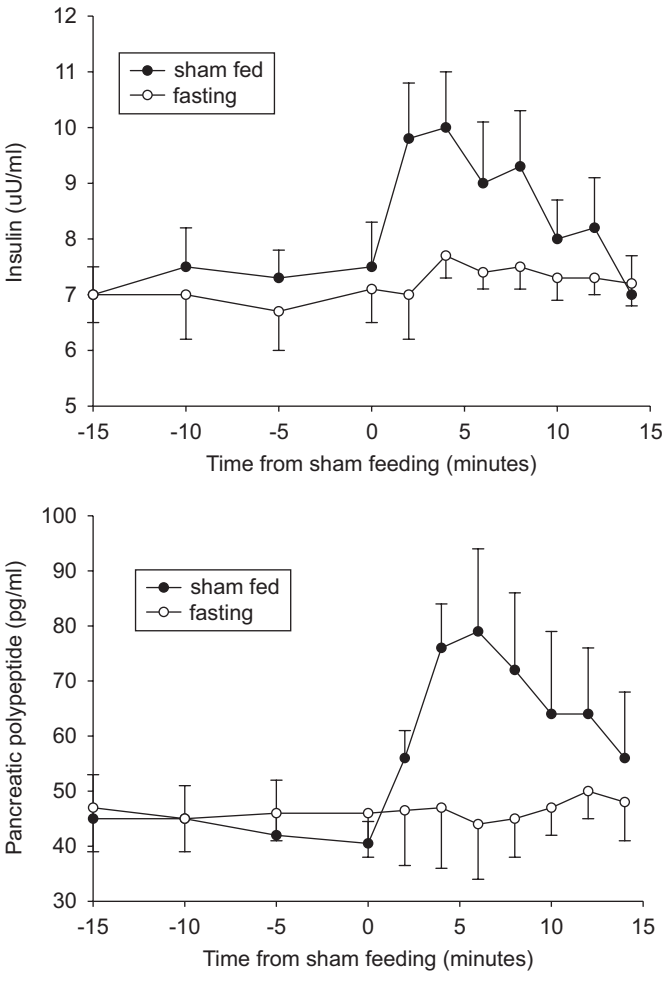

Fig. 1. Cephalic phase insulin and pancreatic polypeptide response in humans in response to sham feeding (data from Teff, 2000).

any change in blood glucose concentration due to absorption of nutrients could occur (Teff, Mattes, & Engelman, 1991). The cephalic phase insulin response can also be triggered by non-nutritive sweet tasting substances, such as saccharin (Powley & Berthoud, 1985).

Cephalic phase insulin response

Insulin is the primary peptide regulating glucose metabolism. Insulin increases glucose storage (in the form of glycogen) in liver and muscle, decreases lipolysis and gluconeogenesis, and increases fatty acid synthesis by adipose tissue (Porte, Baskin, & Schwartz, 2005). The net result is to lower blood glucose concentration by increasing the conversion of glucose to other energy storage molecules (glycogen and fat) and decreasing the production of glucose from the liver.

In humans and rats there is a robust cephalic phase insulin response (reviewed in Powley, 1977; Powley & Berthoud, 1985; Teff, 2000). In response to masticating and tasting food, the pancreas rapidly begins to secrete insulin. This initial pulse of insulin secretion is followed by a larger, more sustained insulin secretion in response to the absorption of digested nutrients (Fig. 2; Teff, 2000). The cephalic phase insulin response thus anticipates and mimics, at an attenuated level, the postabsorptive insulin response to changes in blood glucose concentration (Teff, 2000). Direct vagal stimulation also influences an insulin response (Powley, 1977; Powley & Berthoud, 1985).

Although the magnitude of the cephalic phase insulin response is lower than the postprandial response, it appears to have significant physiological effects (Ahren & Holst, 2001). The cephalic phase insulin response has been shown in rats to be sufficient to increase lipoprotein lipase activity in adipose tissue and decrease it in muscle (Picard, Naïmi, Richard, & Deshaies, 1999). Preventing the cephalic insulin phase response, for example through infusion of trimethaphan, which inhibits neurotransmission across autonomic ganglia results in both significantly higher peak blood glucose concentration and impaired reduction of glucose within the first hour postprandial (Fig. 3; Ahren & Holst, 2001). Thus the absence of a cephalic phase insulin response compromises glucose control and can even lead to hyperinsulinemia (Berthoud, Trimble, Siegal, Bereiter, & Jeanrenaud, 1980). Administration of insulin immediately prior to or at the beginning of a meal, i.e. during the preabsorptive period, improves glucose control in obese humans (Teff & Townsend, 1999) and type 2 diabetics (Bruttomesso et al., 1999).

Not all experiments have been able to demonstrate a cephalic phase insulin response. For example, humans differ from rats in that merely tasting a sweet substance does not appear to be sufficient to generate the cephalic phase insulin response in humans. Oral infusion of a glucose solution stimulates a cephalic phase insulin response in rats (e.g. Berthoud et al., 1980). Rats that ingested saccharine solutions displayed a reliable and dose-dependent cephalic phase insulin response (Fig. 4; Powley & Berthoud, 1985); ingesting sweetened solutions or sucking on sweetened tablets do not reliably initiate insulin secretion in human subjects (Abdallah, Chabert, & Lois-Sylvestre, 1997; Bruce, Storlien, Furler, & Chisolm, 1987). A study in which human subjects tasted but did not swallow sweet tasting liquids found no cephalic phase insulin response or effects on blood glucose (Teff, Devine, & Engelman, 1995). However, in the same study sham feeding on apple pie produced a reliable insulin response.

Most studies using the sham feeding paradigm with human subjects have reliably found a cephalic phase insulin response, although there have been studies which did not (e.g. Taylor & Feldman, 1982). The complexity of the food stimulus appears to affect the cephalic responses in humans; the more modalities involved the greater the

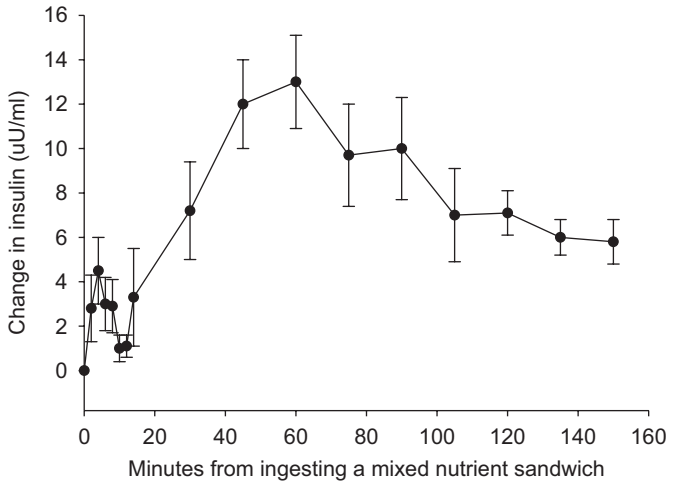

Fig. 2. Plasma insulin concentration following ingestion of a mixed nutrient sandwich (data from Teff, 2000).

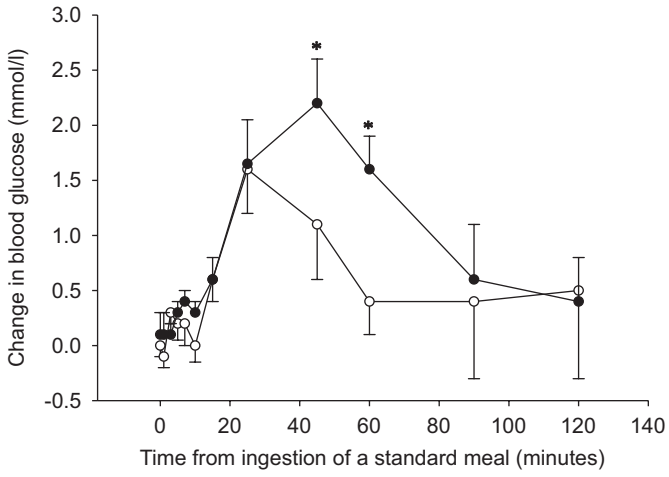

Fig. 3. There were no significant differences in blood glucose between saline (open circles) and trimethaphan (filled circles) infused women for the first 25 min after beginning the meal. In both groups blood glucose was not significantly different from baseline until 15 min. At 45 and 60 min saline infused women had significantly lower blood glucose concentrations (indicated by *). Data from Ahren and Holst (2001).

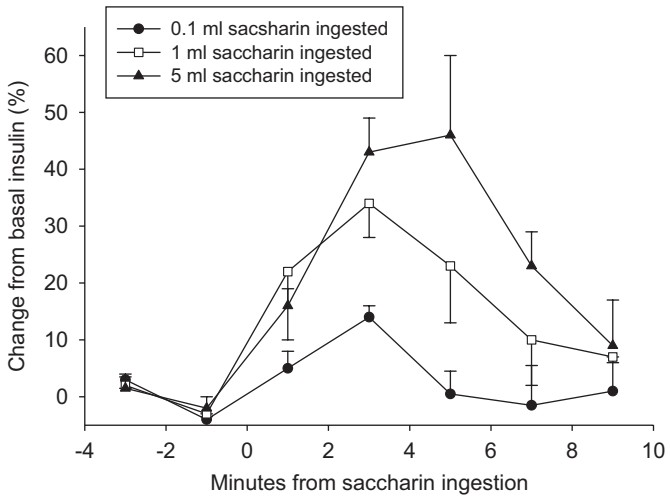

Fig. 4. Cephalic phase insulin response to the ingestion of different volumes of 0.15% sodium-saccharin solution in rats. Data from Powley and Berthoud (1985). Plasma glucose levels did not change.

response (Feldman & Richardson, 1986). Perhaps the stimulation of taste alone, without the associated motor and other secretory involvement involved in eating (e.g. chewing, salivation) is not sufficient to cue the full cephalic metabolic responses in humans. A sweet taste alone may not ensure the expectation that food is to be ingested, and it is that expectation that underlies the functional aspect of the cephalic insulin response.

There are a number of reasons for the variability in results of experiments examining cephalic phase insulin secretion in humans. There appears to be significant individual variation in the insulin response and even variability among tests for the same individual (Bellisle, Lous-Sylvestre, Demozay, Blazy, & Le Magnen, 1983; Powley & Berthoud, 1985). Obese individuals often have a blunted or even absent cephalic phase insulin response (e.g. Teff & Townsend, 1999). The insulin response in humans is associated with palatability judgments more so than with food composition. For example, a cephalic phase insulin response was generated by feeding human subjects a palatable high fat (whipped cream) meal, even though the high fat meal did not result in a postprandial increase in insulin. Palatable high carbohydrate and high protein meals generated both a cephalic and a postprandial insulin response (LeBlanc, Soucy, & Nadeau, 1996).

Evidence for central nervous system contribution

Responses to food cues can be both intrinsic and learned (Booth, 1972; Rozin, 1976). Conditioned taste preferences and conditioned taste aversions provide strong proof that responses to food cues can be learned and modified. For example, most animals readily learn to avoid foods that render them ill; a special visceral learning linked to food ingestion (Garcia, Hankins, & Rusiniak, 1974; Rozin, 1976). Bait shyness linked to poison is well known and is an important adaptation (Richter, 1953).

Rats can be conditioned to react aversively to sweet solutions by rendering them ill after ingestion. They will decrease their intake of the sweet solutions when they are exposed to them again; they also emit species-specific oral/facial rejection responses as opposed to the normal positive oral/facial responses associated with ingestion (Berridge, Grill, & Norgren, 1981). Importantly, the cephalic-mediated insulin response is now decreased to orally infused sweet solution (Fig. 5; Berridge et al., 1981).

Cephalic phase responses can also be stimulated by Pavlovian conditioning; i.e. animals can learn to associate arbitrary sensory stimuli with the availability of food, and then will react as if the food itself has been perceived. For example, insulin secretion in anticipation of feeding can be associated with other environmental stimuli, such as time of day, sounds, visual cues, or tastes (e.g. Woods et al., 1977). Rats fed at a certain time everyday begin to secrete insulin time locked to a circadian clock (Dallman et al., 1993l; Woods, Hutton, & Makous, 1970).

The vagus nerve is thought to be a main pathway for cephalic phase responses (Powley 2000a, 2000b; Zafra, Molina, & Puerto, 2006). The vagus nerve innervates the gastrointestinal tract from the esophagus to the colon. Vagal afferents below the diaphragm integrate meal-related gastrointestinal signaling (Schwartz & Moran, 1996). Truncal vagotomy largely eliminates gastric acid secretions (Powley, 2000a) and pancreatic enzyme and bicarbonate secretions (Powley, 2000a) induced by tasting food. This includes elimination of the insulin cephalic phase response (Powley, 2000a). Blocking cholinergic inputs also block cephalic phase responses. For example, infusion of atropine eliminates the increase in gastric acid secretion due to sham feeding in humans (Fig. 6; Katschinski et al., 1992).

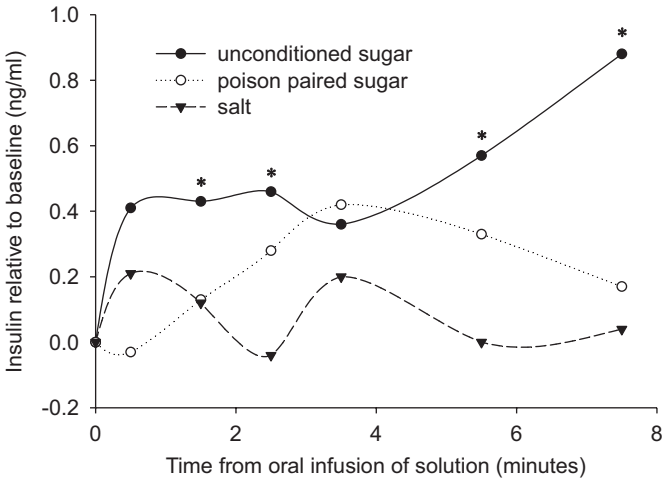

Fig. 5. The cephalic phase insulin response to an orally infused sugar solution was significantly attenuated in rats that had been conditioned by pairing the sugar solution with a poison that caused gastrointestinal upset. There was no consistent insulin response to a sodium chloride solution. Data from Berridge et al. (1981).

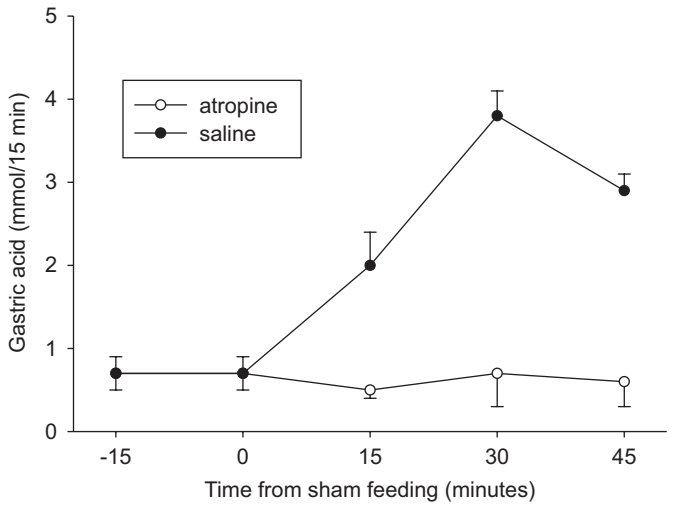

Fig. 6. Infusion of atropine blocks the increased secretion of gastric acid due to sham feeding in humans. Data from Katschinski et al. (1992).

Bypassing the mouth and placing food directly into the stomach also eliminates most cephalic phase responses (reviewed in Powley, 1977). Finally, in rodent models in which the pancreatic β cells have been destroyed, and new β cells transplanted such that they lack innervation by the vagus nerve, the reactive insulin secretion to increases in blood glucose is still intact, but the cephalic phase insulin secretion is absent (e.g. Berthoud et al., 1980).

Many cephalic phase responses are intrinsic, and appear to require only brain stem function and are not dependent on forebrain structures. Decerebrate rats and rabbits obviously are incapable of forming learned associations; however, they have been shown to produce competent cephalic phase insulin responses to glucose infused into the oral cavity (e.g. Flynn, Berridge, & Grill, 1986). The neural networks that underlie cephalic phase responses and the regulation of ingestive behavior have been recently reviewed (Zafra et al., 2006).

The paradox of feeding

Cephalic phase responses serve postabsorptive metabolism and physiology as well as digestion. They prepare the organism to assimilate the ingested nutrients. This is a key adaptation, as although feeding is necessary for survival, it also presents a significant challenge to homeostasis, in what has been termed the paradox of feeding (Woods, 1991).

The homeostatic paradigm has guided thought and research on physiology for over one hundred years. Starting from the work of Bernard (1865) to Cannon (1935) to modern physiology, the concept that stability of the internal milieu is required for health and survival has been a central tenet. Woods (1991) presented the fundamental paradox of feeding from this physiological perspective. Organisms must consume food in order to survive. However the act of consumption brings exogenous substances into the body, and presents a challenge to the stability of the internal milieu. Nutrients are required, but many nutrients are also toxic; they have both minimal and maximal levels for concentration in the blood. The influx of nutrients from feeding can have negative as well as positive effects, and requires metabolic adaptations to return the intercellular fluid to its homeostatic set points.

Although both of us have questioned the primacy of the homeostatic paradigm (Power, 2004; Schulkin, 2003), neither of us denies the importance of homeostasis in understanding functional and adaptive aspects of physiology. We have merely argued that homeostasis does not represent all of physiological regulation, and that often animals are required to abandon homeostasis to serve the goal of being a viable organism (defined in the evolutionary sense as capable of passing on its genetics to future generations). Viability, not stability, is the parameter of evolutionary importance (see Power, 2004). In the case of the challenges presented by digesting, absorbing, and metabolizing nutrients, however, the homeostatic paradigm provides insight into the selective pressures driving the evolution of complementary digestive and metabolic adaptations. In particular it highlights the inherent contradictions between adaptive changes that enhance the efficiency of digestion and absorption of nutrients with the necessity of maintaining the blood stream within critical parameters for many of the absorbed nutrients.

Different foods require different digestive and absorptive responses. Animals, or at least omnivorous ones (e.g. humans and rats), appear to have developed mechanisms to detect these constituents in ingested food, and thus anticipate the required digestive and other exocrine and endocrine secretions. Our digestive tract is not continuously in the same state. Digestive secretions are not constant, but rather change in accord with feeding, and with the anticipation of feeding. Cephalic phase responses account for a significant portion of the secretions induced by feeding (Katschinski, 2000).

These anticipatory digestive responses to food cues increase the rapidity and efficiency with which food is transformed into nutrients, and thus can be absorbed through the intestinal walls. This increased efficiency in absorption presents both advantages and challenges to the organism. The main advantage is obvious; the digestive tract can process a greater amount of food per unit time, and thus the rate of nutrient transfer from the environment to the animal is greater. This allows, among other possible effects, greater total food intake, shorter latency time between meals, shorter total feeding/foraging time to meet requirements, an increased ability to meet requirements on foods of lower quality or that are scarce in the environment, or combinations of these effects. However, the more quickly and efficiently an organism can digest and absorb ingested food, the greater the potential disruption to the homeostatic conditions of the internal milieu. This requires correspondingly rapid and efficient metabolic responses in order to accommodate the pulse of nutrients entering the blood stream, keep the concentrations within tolerable

limits, and eventually return the intercellular fluid to the "normal" range.

Digestive and metabolic cephalic phase responses likely would have evolved in concert. The advantages of rapid and efficient digestion and assimilation of nutrients are tempered by the subsequent greater perturbation of homeostasis due to the rapid influx of these efficiently acquired nutrients. Anticipatory, cephalic phase metabolic responses serve to ameliorate the challenge to homeostasis, and thus allow increases in digestive and absorptive efficiency. The net effect of the coordination of these processes establishes many of the constraints on feeding, such as maximal meal size and frequency, types of foods that can be eaten, the efficiency with which nutrients can be incorporated into the body, and so forth.

There are tradeoffs and interrelated constraints among these phases of feeding. A foraging strategy that provides more food than the digestive system can process may not be adaptive (unless food caching is possible). A rapid and efficient digestive strategy that routinely delivers pulses of nutrients above the rates that metabolic adaptations can process may present greater selective disadvantages than advantages.

Consider the example of a snake and a small mustelid mammal (e.g. a weasel) that both feed on small mammals (e.g. mice). The weasel will, of necessity, catch many more mice per day than will the snake. The weasel will also digest ingested mice more rapidly. However, the snake will incorporate mouse nutrients into its body more efficiently than will the weasel. Snakes will put on more mass per gram of eaten mouse than will the weasel.

There would be no advantage to the snake to have the weasel's foraging and digestive strategies. Its metabolism does not require that rate of nutrient input, and likely could not maintain homeostasis if faced with such a high rate of nutrient input. The weasel, of course, would die if it had to maintain its metabolic rate using the snake's foraging and digestive strategies. The relatively slow feeding strategy of the snake is efficient at turning food into growth. The relatively fast feeding strategy of the weasel includes using a much higher proportion of ingested food for metabolism. These two strategies represent very different, but equally successful, solutions to the ultimate problem: surviving and reproducing.

The fact that mammalian physiology requires that a high proportion of ingested food fuel metabolism generates interesting ideas regarding cephalic phase responses and the concept of satiety. Cephalic phase responses that increase the rate of nutrient absorption may be both required by the generally high mammalian metabolic rate, but also might contribute to it as well. There might be a necessary "inefficiency" in the mammalian feeding strategy in which some proportion of ingested nutrients is "burned off" in defense of homeostasis. Thermogenesis, the increase in metabolism and body temperature induced by feeding, may in part be an adaptation to defend homeostasis by metabolically removing glucose and fatty acids from circulation. Thermogenesis appears to have a cephalic phase (Diamond & LeBlanc, 1988). Short-term satiety signals likely serve the same ultimate purpose; to aid the animal to ameliorate the perturbation to the internal milieu due to the flow of nutrients from feeding by limiting meal size. An interesting question is to what extent are satiety signals reflective of longer term energy balance as opposed to shorter term considerations of defending homeostasis?

A role for cephalic phase responses in appetite and satiety?

Cephalic phase responses have been suggested to play a role in appetite and satiety (Powley, 1977; Woods, 1991). Palatable foods generally result in more robust cephalic phase responses than do less preferred foods. Preventing cephalic phase responses results in animals and humans eating smaller meals (reviewed in Woods, 1991). This is an example of the short-term effects of cephalic phase responses and the role of defense of homeostasis in appetite and satiety. Cephalic phase responses would appear to allow larger meals, presumably due to their ability both to stimulate digestive processes and to address the challenge to homeostasis of the subsequent absorbed nutrients.

It has also been suggested that cephalic phase responses are linked to motivation to feed, and thus may actually play a more direct role in determining meal size and total daily food intake beyond the permissive one of ameliorating negative consequences of feeding. For example, the cephalic phase insulin response biases metabolism towards directing metabolic fuels into storage, preparing the organism for ingested nutrients. The fuel oxidation theory of appetite (Friedman & Stricker, 1976) predicts that one result is that fuel available for oxidation by the liver is reduced, and this aids in development of an appetite. Saccharin ingestion has been shown to increase subsequent food ingestion in rats, a response abolished by hepatic vagotomy (Tordoff & Friedman, 1989).

Time scale is an important consideration. The above hypothesis focuses on short-term, peripheral effects of insulin that appear to lead to an increased appetite. Insulin also has longer term, central effects on appetite that act to limit food intake (Porte et al., 2005). It is interesting that ingesting fructose produces a much less robust insulin response than does an isocaloric dose of glucose (Teff et al., 2004). Of course the absorption of fructose into cells is not insulin dependent, relying on GLUT5 as opposed to GLUT4 transporters. However, if insulin plays a significant role in satiety, then foods high in fructose, such as foods sweetened with high-fructose corn syrup, potentially will have a low satiety-to-calories response. Such foods are believed to play a significant role in weight gain among some people. For example, women who self-reported to be restrained eaters (e.g. consciously refrain from eating certain foods for health and weight reasons) reported higher hunger scores on the day that they were given a high fructose beverage for breakfast compared with days when

they were give an isocaloric high glucose beverage. The day following the high fructose beverage condition, when offered food ad lib, they consumed more fat than they had consumed the day after the high glucose condition. This supports the hypothesis that a lower insulin response leads to increased food intake over the long term. However, unrestrained eaters showed no differences in either hunger scores or fat intake the following day (Teff et al., 2004), so there is variability among people in this response. Quite likely there are additional endocrine and metabolic signals that influence the response.

So far only one gut peptide has been identified to have orexigenic activity. Ghrelin is secreted into the bloodstream by the stomach and intestines. Exogenous ghrelin rapidly increases food intake in rats (Wren et al., 2001a) and humans (Wren et al., 2001b). Indeed, ghrelin is as potent at stimulating feeding as neuropeptide Y. Starvation increases ghrelin plasma concentration and refeeding rapidly decreases circulating ghrelin (Ariyasu et al., 2001). Ghrelin has been suggested to act to initiate feeding (Cummings, Purnell, Frayo, Schmidova, & Wisse, 2001).

In human volunteers provided meals on a fixed schedule, plasma ghrelin concentration displayed a consistent pattern of being low immediately after a meal, slowly increasing, and then having a rapid increase in concentration immediately prior to the next meal (Cummings et al., 2001; Fig. 7). The pattern of ghrelin concentration was roughly opposite to the pattern of insulin concentration, but in phase with the circadian cycle of leptin concentration, though much more variable than leptin concentration. Both ghrelin and leptin were lowest immediately after breakfast. Leptin concentration gradually rose throughout the day, with small declines immediately after each meal, and reached a zenith roughly during the middle of the sleep period. Ghrelin followed the same pattern (Fig. 7), except for the pronounced surges immediately prior to a meal, followed by equally dramatic declines immediately after the meal (Cummings et al., 2001). Because the meals were provided at known, fixed times, this evidence supports the hypothesis that the surge in ghrelin secretion prior to meals is a cephalic phase response that serves to initiate feeding and/or to prepare the person to digest and metabolize food.

In a study of real and sham feeding in human volunteers, serum ghrelin concentration increased prior to the meal, in identical fashion. After both real and sham feeding serum ghrelin concentration initially declined; the decline continued for the real feeding condition, but serum ghrelin concentration began to rise 60 min after sham feeding (Arosio et al., 2004). Thus ghrelin secretion appears to have a cephalic phase for both the anticipatory rise before a meal, and the decline with the initiation of feeding.

Further evidence for a cephalic phase component to ghrelin secretion patterns comes from a recent study involving rats fed either ad lib or at a fixed time. Freely feeding rats had a peak of ghrelin secretion just before the dark phase of their light cycle; meal-trained rats had a significantly higher peak of ghrelin secretion at the start of the 4 h period of the light phase during which they had become accustomed to have access to food (Drazen et al., 2006).

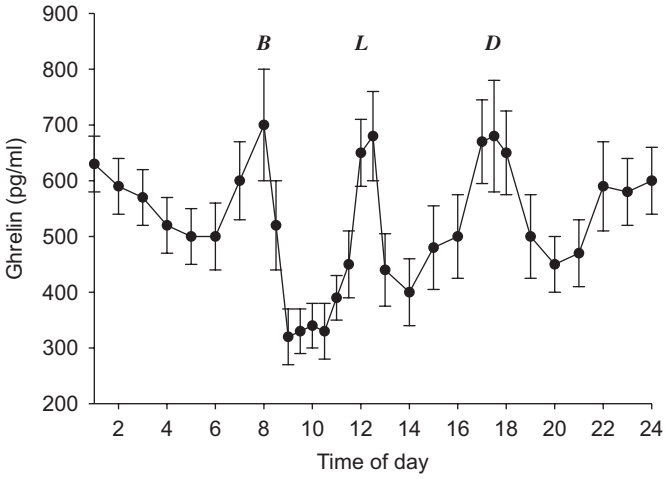

Fig. 7. Mean plasma ghrelin in 10 human subjects (9 women and 1 man) over a 24 h period consuming breakfast (B), lunch (L), and dinner (D) at set times (8:00, 12:00, and 17:30). Subjects were aware of when meals were to be provided and the time. Data from Cummings et al. (2001).

These results are consistent with the pattern of plasma ghrelin in 6 humans (3 men and 3 women) accustomed to eating three meals per day who fasted over a 33 h period. Plasma ghrelin increased on both mornings (around 8:00), the middle of the day (12:00–13:00) and in the early evening (17:00–19:00), consistent with the expected meal times. These increases were followed by a spontaneous decline in plasma ghrelin despite the fact that the subjects were fasting (Natalucci, Reidl, Gleiss, Zidek, & Frisch, 2005).

These results in rats and humans suggest that appetite can be trained to a circadian clock. It suggests that hunger can occur in anticipation of food being available, but if the food is not delivered, then the system reverts to a ''nonfeeding'' state. Perhaps the readers are familiar with the phenomenon of being hungry, but not able to eat; after several hours the feelings of hunger recede. Of course the scent and sight of food can bring them back intensified, but otherwise, a person will no longer be ''hungry'' despite having not fed.

In addition to affecting feelings of hunger and the propensity to feed, ghrelin also appears to affect parameters of digestion, absorption, and metabolism. Exogenous ghrelin stimulates insulin and gastrin secretion (Lee, Wang, Englander, Kojima, & Greeley, 2002), as well as secretion of gastric acid (Masuda et al., 2000), possibly via gastrin (Lee et al., 2002). Exogenous ghrelin increases gastric motility (Masuda et al., 2000). Vagotomy increases plasma ghrelin concentration (Lee et al., 2002), and abolishes the effect of exogenous ghrelin on gastric acid secretion and gastric motility (Masuda et al., 2000). A cephalic ghrelin response is associated with increased fat absorption (Heath, Jones, Frayn, & Robertson, 2004).

Modified sham feeding in healthy human subjects resulted in a higher ghrelin serum concentration at the time of an oral ^{13}C labeled fat load, a more rapid decline in ghrelin after the ingested fat load, as well as a higher and more rapid peak in serum triglyceride concentration. Recovered ^{13}C from respired CO_2 was greater when fat ingestion was preceded by modified sham feeding, indicating that cephalic responses, possibly associated with the ghrelin response, increase the rapidity with which fat is absorbed and metabolized.

Leptin has been suggested to regulate food intake. Leptin is secreted by adipose tissue; plasma leptin concentration is highly correlated with fat mass. Leptin acts on neurons in the hypothalamus and arcuate nucleus, and appears to act in opposition to neuropeptide Y, and in concert with insulin and corticotropin-releasing hormone (CRH) to reduce food intake. Leptin and insulin are thought to influence the hedonic perception of food, both centrally (reviewed in Isganaitis & Lustig, 2005), and via taste receptors. Leptin modulates sweet taste sensation via actions on sweet taste receptor cells via the leptin receptor. Increased leptin decreases firing of sweet taste cells in mice (Kawai, Sugimoto, Nakashima, Miura, & Ninomiya, 2000).

Leptin also is synthesized and secreted by the gastric mucosa, and appears to be secreted during meals (Bado et al., 1998). Vagal stimulation results in gastric mucosal leptin secretion, but no increase in plasma leptin concentration (Sobhani et al., 2002), suggesting that gastric leptin is secreted during the cephalic phase of gastric secretions, and acts in a paracrine fashion. Leptin receptor mRNA is present in vagal afferent neurons that innervate the gastric fundus, suggesting that leptin may have direct stimulatory effects on vagal afferents (Peters, McKay, Simasko, & Ritter, 2005). Infusions of leptin into the celiac artery, but not the jugular vein, significantly reduced intake of a sucrose solution by rats (Peters et al., 2005).

Some of the leptin secreted by the gastric mucosa appears to survive the gastric acid and travels intact to the intestine where it is thought to perform multiple functions regulating the absorption of lipid, carbohydrate, and protein (reviewed in Picó, Oliver, Sánchez, & Palou, 2003). The functional form of the leptin receptor (Ob-Rb) is expressed in human jejunum and ileum (Morton, Emilsson, Liu, & Cawthorne, 1998). Leptin has been shown to inhibit D-galactose absorption (Lostao, Urdaneta, Martinez-Anso, Barber, & Martinez, 1998) and increase the intestinal absorption of small peptides (Morton et al., 1998). Leptin also stimulates cholecystokinin (CCK) secretion (Guilmeau, Buyse, Tsocas, Laigneau, & Bado, 2003). Leptin and CCK appear to form a positive feedback loop; plasma CCK stimulates gastric leptin secretion (Bado et al., 1998) and duodenal infusion of leptin in rats increased plasma CCK comparable to the effects of feeding (Guilmeau et al., 2003). Leptin and CCK appear to act synergistically to activate vagal afferent neurons (Peters, Karpiel, Ritter, & Simasko, 2004).

CCK has direct effects on meal size. Giving exogenous CCK to rats results in meals that are shorter on average than the meal duration of control rats. However, the treated rats ate a greater number of meals per day, and total daily food intake did not differ between treated and control rats (West, Fey, & Woods, 1984). In rats without expression of CCK receptor type A, meals were of greater duration and consisted of greater amounts ingested. The number of meals per day decreased, however, the net effect was an overall greater daily food intake, and eventual obesity (Moran & Kinzig, 2004).

Thus, in addition to its role in long-term energy balance, leptin has been suggested to play a role in short-term satiety signals, either directly via vagal afferents or indirectly through stimulation of CCK secretion. Indeed, leptin and CCK appear to act synergistically to reduce both long- and short-term food intake (Barrachina, Martinez, Wang, Wei, & Tache, 1997; Matson & Ritter, 1999).

Diverse actions in diverse tissues

Leptin provides an example of a key concept we believe needs emphasizing in regulatory physiology. More and more, physiologically important peptides, steroids, and other information molecules are being shown to have multiple functions in diverse tissues. Their actions and regulation can be tissue and context specific. Leptin, for example, is secreted by placenta and appears to have important functions in fetal development (Bajari, Nimpf, & Schneider, 2004; Henson & Castracane, 2006). Leptin also acts on the gonads, and acts to regulate sexual maturity and fertility, especially in females (Bajari et al., 2004). In many ways leptin serves as much as a reproductive hormone as it does a hormone of energy balance.

Ghrelin also appears to be an ancient regulatory molecule. Its structure is highly conserved among mammals, and it has been detected in chickens, fish, and bullfrogs (Tritos & Kokkotou, 2006). Ghrelin is a potent secretogue of growth hormone from the pituitary through binding to the GHS receptor (Takaya, Ariyasu, & Kanamoto, 2000). Circulating ghrelin exists in both an acylated and nonacylated form. The nonacylated form does not activate the GHS receptor, but does appear to have effects on glucose homeostasis, lipolysis, adipogenesis, cell apoptosis, and cardiovascular function, suggesting that an additional, as yet undetected, receptor might exist (Tritos & Kokkotou, 2006). Ghrelin is produced by posttranslational cleavage of a prepropeptide of 117 residues; an alternative cleavage of this prepropeptide produces obestatin (Zhang et al., 2005). Intriguingly, obestatin suppresses food intake (Zhang et al., 2005). Thus the ghrelin gene appears to produce two distinct peptide hormones with opposing actions. These facts highlight the importance of posttranslational mechanisms in understanding gene effects.

The processes that affect evolutionary change are limited in that they can only work on existing variation. There are

many examples of ancient regulatory molecules, like leptin and ghrelin, which, over time, became adapted and co-opted to serve multiple, diverse functions. These regulatory molecules serve as "information molecules", transmitting information among organ systems and coordinating the responses of peripheral organs and the central nervous system to external and internal challenges to an organism's viability. An evolutionary perspective predicts that these molecules will have multiple and diverse functions and that their regulation, function and mode of action will vary among different taxa, and among different tissues within taxa.

Evolutionary considerations

Physiological and metabolic systems serve the survival and reproductive capabilities of the organism (fitness). Anticipatory physiological regulation is an adaptive strategy that enables animals to respond faster to physiologic and metabolic challenges. The cephalic phase responses are anticipatory responses that prepare animals to digest, absorb and metabolize nutrients. They enable the sensory aspects of the food to interact with the metabolic state of the animal to influence feeding behavior, including the size of the meal. Cephalic phase responses increase digestive efficiency and aid in controlling the resulting elevation of metabolic fuels in the blood due to feeding (Woods, 2002). Thus digestion, metabolism and appetite are regulated in a coordinated fashion.

In real-world situations animals are constantly balancing competing imperatives. It can be argued that coordinating responses to and in anticipation of challenges and resolving and prioritizing competing imperatives are principle functions of the central nervous system. The central nervous system is intimately involved in physiological regulation, and has evolved a variety of responses and mechanisms that enhance feeding efficiency, but also balance other considerations, such as homeostasis. This includes signals to both start and stop feeding.

Why have we emphasized cephalic phase responses in this paper? Anticipatory, feedforward systems are vital to regulatory physiology. Physiology is not merely reactive. Cephalic phase responses represent a fundamental concept in regulatory physiology: anticipatory changes in state to meet expected needs. They are a paradigmatic example of anticipatory physiological responses. They need to be integrated across the diverse regulatory information molecules that are being discovered. They need to be viewed in an adaptive, evolutionary perspective. They represent, in our opinion, the results of feedforward evolutionary pressures; an "arms race", if you will, between the imperatives of increasing the rate of nutrient acquisition and of defending the internal milieu.

A principal function of satiety is meal termination. Cephalic phase responses serve to increase meal size/duration (efficiency of digestive and metabolic responses) and thus increase food intake per meal. They also begin endocrine cascades to terminate a meal. There are multiple reasons, in addition to energy balance and adipose tissue homeostasis, to terminate a meal. Defense of homeostasis (sensu Woods, 1991) is an important consideration; elevated levels of blood glucose, amino acids, and insulin contribute to a loss of appetite.

Another simple, and perhaps little considered factor, is that animals have many necessary functions to perform to be viable. There are strong incentives and redundant neural circuits reinforcing feeding behavior. There have to be equally strong mechanisms to stop feeding in the presence of available food or animals would be constantly feeding, regardless of other imperatives. There are many constraints on animals, but time is a universal one. Animals, to be viable, must apportion their time among the various activities necessary for survival and reproduction.

To what extent is the adaptive value of terminating feeding related to conserving time for other activities? And to what extent does the current human obesity epidemic relate to the fact that the amount of time needed in the past to acquire sufficient calories far exceeds the amount of time today needed to acquire a gross surfeit of calories? The evolution to regulate meal size and the evolution to regulate energy balance have independent aspects. Therefore the regulation of food intake on the time scale of the meal can be decoupled from the regulation of energy balance; and this has significant implications for understanding the pathogenesis of obesity.

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