Cephalic Reflexes: Their Role in Digestion and Possible Roles in Absorption and Metabolism

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ABSTRACT Stimulation of the oral cavity immediately elicits salivation, gastric acid secretion and pancreatic exocrine and endocrine secretions that serve to prepare the alimentary canal for digestion, transport and utilization of ingested nutrients. Oropharyngeal-stimulated responses are reliably initiated by the taste and smell of food. These gastrointestinal reflexes, often referred to as anticipatory or cephalic phase responses, are mediated by the autonomic nervous system and are believed to be independent of the postabsorptive effects of ingested nutrients. A common pathway used by cephalic phase responses to trigger gastrointestinal secretions is the vagus. Several studies have also demonstrated that cephalic stimulation activates both the sympathetic and parasympathetic nervous systems and thus, many cephalic-metabolic reflexes may arise indirectly from more general physiological changes that accompany oropharyngeal stimulation. The present studies suggest that oral stimulation results in alterations in intestinal function. Specifically, oropharyngeal stimulation of conscious, unrestrained rats with sucrose increases the uptake of radioactive glucose from the small intestine into the hepatic portal blood. J. Nutr. 117: 1191-1196, 1987.

INDEXING KEY WORDS:
• cephalic reflexes • oropharyngeal stimulation • digestion • absorption • chemosensory • taste

The role of taste and smell in food selection and in motivating an organism to consume a meal is obvious. Not as widely recognized is the impact on gastrointestinal secretory function by the chemical senses and other oropharyngeal stimuli. Pavlov (1) was the first to document quantitatively that sensory and mechanical input at the level of the oropharyngeal cavity can reflexively stimulate secretions at several locations along the gastrointestinal tract. These gut reflexes, which are activated by the stimulation of receptors located in the head and neck, are collectively known as cephalic phase responses (1-3). Powley (4) has defined cephalic responses of digestion as “autonomic and endocrine reflexes involved in the metabolism of food that are triggered by sensory contact with foodstuffs rather than by post-ingestional consequences of food.” Nicolaidis (2) suggested that these cephalic responses play an important role in the regulation of both digestive and metabolic processes and act to optimize the utilization of the ingested nutrients.

Cephalic responses can arise from the taste, smell or merely the sight and sound of food (1-3, 5, 6-9). Stimulation of receptors, including chemoreceptors and mechanoreceptors (activated by chewing and swallowing), can initiate the gut responses. Once cephalic components have been activated, the gut anticipatory response is mediated by the vagus nerve, which can be reflexively stimulated either by the central nervous system or by visceral efferents (5, 10). An intact vagus is necessary for these gastrointestinal anticipatory reflexes to occur (11-14). Powley (4) has suggested that cephalic responses have three defining traits: a) afferent limbs that originate in the head and neck region; b) integration and relay pathways within the central nervous system; and c) efferent limbs consisting of neural and neuroendocrine pathways that control gastrointestinal function.

Classically, the cephalic phase is contrasted with the gastric and intestinal phases of digestion; the latter two phases are related to the post-ingestional consequences of food, whereas the former is associated with the preabsorptive consequences of food. The responses triggered by the cephalic phase are anticipatory in the sense that they are in the same direction as those that occur during the gastric and intestinal phases (13, 15-19). However, they are more rapid in onset, of shorter duration and usually lower in magnitude than secretions stimulated during the gastric and intestinal phases.
Nevertheless, cephalic phase events appear to influence the magnitude of subsequent postigestional gastrointestinal responses (1, 2, 5, 6, 13, 15–20).

Although the existence of cephalic-gut reflexes has been repeatedly demonstrated, the physiological significance of these responses remains undefined. A major function that these cephalic responses probably serve is to “prime” the gut and modulate metabolic processes so that optimal digestion, absorption and utilization of the ingested nutrients occur (2–5). This is supported by reports in which rats denied oropharyngeal stimulation by means of intragastric (21, 22) or intravenous feeding (2) generally had lower body weight gains than those fed orally at similar energy intakes. Moreover, cephalic phase responses may function to modulate the influx of the ingested nutrients as suggested by Nicolaidis (2) so that large deviations in absorption and utilization of the nutrient do not occur. For example, when the cephalic release of insulin is prevented by intragastric feeding (18, 23) or pharmacological vagotomy (24), the resulting hyperglycemia is much greater in magnitude than that which results from oral feeding.

The role of taste and smell thus extends beyond its obvious involvement in food selection to the modulation of digestive function. The following discussion will focus upon the interrelationship between cephalic components and gastrointestinal function. The effects of oropharyngeal stimulation on digestive (i.e., gastric and pancreatic secretions) and metabolic reflexes will be emphasized in a recent review. The discussion of metabolic reflexes will focus on physiological changes that directly and/or indirectly affect digestion. Finally, new data will be presented to support the concept of a cephalic-intestinal absorption reflex.

CEPHALIC-GASTROINTESTINAL SECRETORY REFLEXES

Salivary secretion. Saliva is the first secretion to be directly stimulated by the presence of food in the mouth (25). In addition to lubricating foods for swallowing, saliva contains the enzymes amylase and lipase, which initiate the digestion of starch and fats. The classic studies of Pavlov (1) with dogs included a demonstration that salivary output increased upon the presentation of food. Visual and olfactory stimulation can also increase saliva output in animals (26) and humans (27) but not to the extent that occurs when food is tasted or chewed. When human subjects chewed on plastic tubing for 30 min saliva flow approximately doubled, indicating that the mechanical act of chewing alone can also stimulate flow (27).

Alterations in salivary flow may be influenced more by the physical and chemical nature of foods than by the palatability. For example, strong acids such as lemon juice are potent stimuli for salivation and produce a saliva rich in protein (25). Interestingly, when saliva output was measured in humans in response to only the sight of various foods, the highest saliva output occurred in response to foods that contain irritants such as acids or spices that provide potent stimulation when ingested (28). This suggests that prior learning may also be important in influencing the cephalic phase of salivary secretion.

Gastric secretions. The secretion of pepsinogen and hydrochloric acid from the fundic glands and the secretion of gastrin from the neuroendocrine glands in the antrum of the stomach occur in response to cephalic stimulation and are mediated by the vagus nerve (11, 12, 29). Moreover, vagal stimulation arising from cephalic events potentiates the responsiveness of the parietal cell to gastrin (11). The cephalic phase of gastric secretion was first documented by Pavlov (1) using the technique of sham feeding. This technique eliminates the gastric and intestinal phases of digestive secretions by diverting the ingested food directly to the exterior via an esophageal fistula (1). When dogs with esophageal fistulas and Pavlov pouches (innervated) were sham fed, acid and pepsinogen were secreted from both the main body of the stomach and the pouch. However, if the vagi were cut, then sham feeding no longer resulted in secretion. Pavlov inferred from his studies that the magnitude of the gastric response to sham feeding was dependent on the palatability of the food (1). Similarly, in human subjects, it has been demonstrated that the magnitude of gastric acid secretion during the cephalic phase is directly related to the acceptability of the meal (30–33). Feldman and Richardson (33) recently reported that olfactory stimulation by food is relatively poor at eliciting gastric secretions as compared to taste or sight of food.

Pancreatic secretions. A cephalic phase of pancreatic exocrine secretion has been reported in many species (14, 34–39). However, its importance has been questioned because it is difficult to separate the stimulatory effects of hormones such as gastrin and secretin from direct cephalic effects. Preshaw, Cooke and Grossman (37) reported that when gastrin secretion was inhibited by acidification of the Pavlov pouch in the dog, the increase in pancreatic exocrine secretion upon sham feeding was reduced. However, damage to vagal fibers innervating the pancreas may have occurred during surgical preparation of the pouch in these studies. Novis, Banks and Marks (38) later authenticated a cephalic phase of pancreatic exocrine secretion in humans with achlorhydria; chewing and masticating followed by expectoration of the food resulted in a pancreatic juice rich in chymotrypsinogen, trypsinogen and lipase without an effect on the volume or bicarbonate levels. It has been demonstrated that electrical stimulation of the vagus nerve rather than sham feeding also results in moderate increases in pancreatic enzyme secretion in the cat (40) and dog (41) and a copious secretion of water, bicarbonate and amylase in the pig even after removal of the stomach and intestines (42).
As with gastric secretion, the nature of the taste stimulus influences the magnitude of the pancreatic response. Behrmann and Kare [43], using conscious dogs equipped with gastric and duodenal fistulas, observed that water or sucrose mixed with a basal diet produced higher pancreatic flow rates and protein outputs than did citric acid- or quinine-adulterated diets. Furthermore, Naim, Kare and Merritt [34] quantitated this with respect to time and reported that palatable sucrose solutions and nonpurified diets (commercial dog food) also produced greater pancreatic exocrine secretions than purified diets or a cellulose-water mix.

In addition to pancreatic exocrine secretions, activation of cephalic receptors leads to preabsorptive changes in pancreatic endocrine secretions. Animals sham fed various solutions such as glucose and tap water exhibit immediate increases in insulin secretion that are produced without any change in blood glucose concentration [23; see also 7, 13, 44]. Furthermore, it has been demonstrated that oropharyngeal-induced insulin secretion can be inhibited by vagotomy [1,13]. Taste solutions given intragastrically [2] or given after superficial anesthesia of the oral mucosa [10] do not alter blood insulin levels, indicating that the preabsorptive secretion of insulin is dependent on oropharyngeal stimulation. It has also been demonstrated that the sight, smell and taste of food can elicit pancreatic glucagon release [45]. This response is inhibited by atropine and thus, is probably mediated by cholinergic neural pathways. A cephalic phase of pancreatic polypeptide release that is vagally mediated has also been demonstrated [46, 47]. Deglutition appears to augment the release of pancreatic polypeptide [48].

The palatability of taste stimuli is important in the oropharyngeal stimulation of pancreatic endocrine secretion. For example, when rats are fed diets containing saccharin, the magnitude of the preabsorptive insulin response observed is greater than when the animals are fed an unflavored diet [49], whereas the addition of quinine resulted in insulin levels lower than those of either the saccharin or unflavored diets. Berthoud et al. [44] reported similar results when rats ingested a small amount (1 mL) of saccharin and quinine solutions, demonstrating that a direct neural link between oropharyngeal sensory input and the pancreas is involved.

**CEPHALIC-METABOLIC REFLEXES**

The effects that chemosensory and other cephalic stimuli have on the systemic physiology of an organism have received relatively little attention since Pavlov's research. Numerous investigations performed on human subjects and other animals have demonstrated that cephalic stimulation activates both the sympathetic and parasympathetic nervous systems [50–53]. As a result, many of the anticipatory metabolic reflexes that have been documented may be secondary to the direct effects of cephalic phase vagal and sympathetic nervous system activation. However, this does not detract from the possible physiological significance of these events. For example, the increase in respiratory quotient in response to eating [2] and the hyperglycemic responses to oropharyngeal stimulation with sweet-tasting substances in hungry rats [2] are two metabolic reflexes that are probably a secondary result of the activation of the parasympathetic and sympathetic nervous systems. Recent neuroanatomical studies are beginning to provide new insight into the neural pathways between chemosensory and autonomic systems. This area is beyond the scope of this paper and the reader is referred to Norgren [54].

Postprandial thermogenesis, which is the normal increase in heat production that occurs after food is ingested, also is probably a secondary cephalic response. In recent studies by LeBlanc, Cabanac and Samson [53] in which human subjects were allowed to consume food orally, heat production increased threefold within 15 min after eating. However, when the food was given by gastric gavage to circumvent sensory inputs, the early increase in postprandial thermogenesis was four times smaller. Although this technique cannot directly assess the contribution of cephalic stimulation, other studies with dogs have shown that sham feeding produces an increase in heat production that is quantitatively similar to the one that occurs in the first 40 min after the oral ingestion of food [55]. Interestingly enough, the smell and even the sight of food were also sufficient to initiate a cephalic phase of heat production that was similar in magnitude to that produced by sham feeding [55]. The initial increase in heat production observed in these studies during ingestion is too rapid to be the result of the absorption of the ingested nutrients and cannot be accounted for by the processes of ingestion. Because early thermogenesis is paralleled by increases in both norepinephrine and insulin, it has been hypothesized that the cephalic phase of thermogenesis may be related to the levels of catecholamines [53, 55]. In support of this idea, when human subjects ingested foods that were unpalatable or when the oropharyngeal cavity was bypassed by gastric gavage, sympathetic activation as measured by both catecholamine levels and postprandial thermogenesis was suppressed [52, 53].

Recent studies have demonstrated that the cardiovascular system also responds to feeding in essentially two phases [56–58]. During anticipation and the initial ingestion of food, there is a transient increase in cardiac output, aortic blood pressure and heart rate accompanied by either an increase or no change in mesenteric vascular resistance [57, 58]. Within 5–30 min after feeding, cardiac output, heart rate and blood pressure return to normal while blood flow through the superior mesenteric artery begins to rise and continues to do so for 30–90 min. These responses can be attenuated by
administration of sympathetic blocking agents (56). Thus, as in the case of early postprandial thermogenesis, the secretion of catecholamines may play an important role in the cardiovascular changes that occur during this ingestion phase.

CEPHALIC-INTESTINAL ABSORPTION REFLEX

Studies have not been conducted to investigate the possibility that changes in the intestinal function are reflexively stimulated by taste and smell and activation of cephalic receptors. It seems possible that an increase in the capacity of the intestine to transport nutrients may serve in a feed-forward action to prepare the intestine for the efficient absorption and transport of incoming nutrients.

Preliminary studies conducted in our laboratory have supported the hypothesis that oropharyngeal stimulation with a sweet taste results in an increase in the absorption of glucose from the small intestine of conscious, unrestrained rats. By infusing a glucose solution (containing [14C-U]glucose) directly into the intestine and estimating the uptake of glucose (by sampling hepatic portal blood and determining the rate of appearance of glucose) before and after oral stimulation, it was demonstrated that both 0.3 M sucrose and water, when given orally (100 μL), result in an increase in the appearance of glucose in the hepatic portal blood. From these studies, the area under the curve of time versus nm glucose/mL blood was estimated (59) during the first 10 min immediately following presentation of the oral stimuli (Table 1). From these data, the mean S:W was 2.90 ± 0.27 (n = 4) indicating that the increase in glucose in the hepatic portal blood that resulted from the intraoral delivery of sucrose was three times greater than that following the intraoral delivery of water, which indicated some specificity of the induced response. Studies are currently in progress to confirm these preliminary findings.

As with many cephalic-metabolic responses, a change in intestinal transport of nutrients may not be a primary response, but may be secondary to other reflexes elicited along the gut and/or in response to vagal and sympathetic activation produced by oropharyngeal sensory and mechanical input. The vagus has been shown to mediate many of the cephalic phase responses as described previously and may be involved in mediating cephalic-induced changes in intestinal function. However, although the vagus has a demonstrable effect on the motor and secretory functions of the gastrointestinal tract, direct control of intestinal absorption has been difficult to demonstrate (50, 59–61). On the other hand, sympathetic stimulation appears to increase the absorption of fluid and electrolytes (50, 62, 63).

As discussed above, the sympathetic nervous system is believed to play a significant role in the cardiovascular changes that occur in the anticipation and ingestion of food (56–58). Alterations in blood flow to the absorptive site concomitantly with changes in gut motility can also influence the net absorption of nutrients such as amino acids and electrolytes (64, 65). Winne (65), reviewing numerous studies, observed a positive correlation between blood flow and the absorption of passively and actively transported substances. Increased blood flow can increase absorption by increasing O2 delivery to the mucosa, altering tissue colloid osmotic pressure or increasing the removal of an absorbed nutrient, thus increasing the concentration gradient between the lumen and the blood (65). Correlations between motility, blood flow and absorption were observed by Pytkowski and Michalowski (66): The absorption of amino acids from the jejunum was directly proportional to blood flow and inversely proportional to gut motility.

Changes in intestinal absorption may also occur secondarily to the release of gastrointestinal hormones whose secretion is stimulated by the anticipation and presence of food in the oropharyngeal cavity (61, 64, 67). Sarr, Kelly and Phillips (61) observed a postprandial increase in the absorption of glucose, water, sodium and chloride from an isolated, extrinsic denervated canine jejunal segment. Because the effect occurred in the absence of extrinsic innervation, they suggested that the hormones secreted in response to a meal may, in part, affect intestinal function. These hormones may directly affect enterocyte functions, or alter intestinal blood flow or motility (61, 65, 67–69). For example, glucagon has been shown to increase intestinal blood flow (70). Other peptides, such as substance P and vasoactive intestinal peptide, may act locally to alter enterocyte function, possibly through cAMP, as shown in the rat (71). Vasoactive intestinal peptide receptors are present on the basolateral membranes of enterocytes of rat jejunum (71).

**TABLE 1**

<table>
<thead>
<tr>
<th>Rat</th>
<th>Water</th>
<th>Sucrose</th>
<th>(nM glucose • min)</th>
<th>mL blood</th>
<th>S:W</th>
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<tr>
<td>1</td>
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<td>392</td>
<td>3.60</td>
<td></td>
<td></td>
</tr>
<tr>
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<td>186</td>
<td>558</td>
<td>3.00</td>
<td></td>
<td></td>
</tr>
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<td>53</td>
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<td>2.60</td>
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<tr>
<td>4</td>
<td>145</td>
<td>347</td>
<td>2.39</td>
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</tbody>
</table>

1 Sucrose-to-water ratio of areas resulting from oral stimulation.

**CONCLUSIONS**

The chemical senses may influence the nutritional status of an organism by affecting digestion and met-
abolic processes at several levels. This review focused on (a) well-known gastrointestinal secretory responses to oropharyngeal stimulation, (b) metabolic processes that are stimulated by parasympathetic (especially vagal) and sympathetic activation that are induced by oropharyngeal sensory and mechanical inputs and (c) changes in intestinal absorption that could result from oropharyngeal stimulation. These cephalic-induced responses probably function to "prime" the gut physiologically for the meal and thus, play an influential role in the nutritional status of an organism.

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LITERATURE CITED


