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CHEMICAL SENSES IN THE RELEASE OF GASTRIC AND PANCREATIC SECRETIONS

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INTRODUCTION

Within the context of nutrition, the chemical senses—taste (gustation) and smell (olfaction)—function in search, identification, and ingestion of food (70, 108). The complexity of behaviors involved in these functions is appreciable, and the influence of experience leads ultimately to the catalog of information on foods carried within the memory of the organism (6). A less-appreciated function of the chemical senses is their action in triggering digestive processes that anticipate arrival of food in the gut (83, 85, 138). In this context, the chemical senses act as components of a larger group of effects collectively termed cephalic. Cephalic effects result from stimulation of sensory-receptive relay systems in the region of the head and neck. Pavlov (97) used "psychic effects" to denote the cephalic phase. Didactic arguments about the terminology are reviewed by Powley (101). An historical perspective on the study of gastric function and its relationship to eating, emotions, and general health is given in an enjoyable account by Wolf (143).

Stimulation of digestive secretions is classified into cephalic, gastric, and intestinal phases (43, 62, 126). The digestive sequences triggered by the cephalic phase are in the same direction as those triggered by the gastric and intestinal phases. Usually the cephalic-stimulated responses are of smaller magnitude and shorter duration than responses to the gastric and intestinal phases. Nevertheless, it is inappropriate to ignore the cephalic function of the chemical senses, since it could have important consequences for overall digestive efficiency and nutritional well-being.

The digestive effects that result from cephalic reflexes are initiated most reliably by the taste and smell of food. The sight of food and other circumstances associated with eating may also act as stimuli, although these seem to be less potent. Initiation of digestive events by cephalic-phase stimulation depends upon intact vagi (e.g. 3, 12, 64, 74, 97, 103). It is generally assumed that direct neural innervation to the site of secretory activity is responsible for the cephalic-phase effects (12), although for some secretory responses an indirect hormonal relay cannot be ruled out (46, 139; but see 11). With the conscious animal, the cephalic phase can be isolated for experimental study by the technique of sham feeding (30, 97) in which ingested food is diverted to the exterior. This is usually achieved by using an esophageal fistula. With human subjects, sham feeding may be performed simply by having the subject chew and then expectorate the food (63). The latter method, designated "modified sham feeding" (MSF), is experimentally simpler than sham feeding using a fistula, but it omits the action of swallowing. Several experiments (see below) suggest that swallowing may be an important component of the cephalic phase, and caution should be exercised when activation of neural receptors of the pharynx and esophagus is ignored (1).

In each experimental situation, stimuli of the cephalic phase may be varied and controlled to isolate one component from the others, or to combine one or more of these components.

In addition to the stimulus provided by sham feeding, the efferent vagus can be stimulated either directly, by electrical stimulation, or indirectly, by glucose deprivation of the higher vagal centers. The latter can be achieved, for example, by insulin-induced hypoglycemia (50, 56, 65) or by intravenous infusions of 2-deoxy-D-glucose (5, 28, 48). Under normal conditions the efferent vagus is stimulated reflexively either from higher centers of the brain, after the cephalic phase components are activated, or by visceral afferents. Impulses are transmitted from the cortex and subcortical areas to the anterior hypothalamus and then to the medullary vagal centers (14). In the case of gastric secretion, the impulses then proceed via vagal nerves either to oxyntic glands of the fundus, where they stimulate acid and pepsin secretion, or to the neuroendocrine cells of the antrum, where they stimulate the release of gastrin (12).

In this review we focus on the effects of taste and smell on digestive and metabolic reflexes. We emphasize cephalic-stimulated responses leading to gastric, pancreatic exocrine, and endocrine secretions. We indicate the mechanisms operating in these responses and where appropriate suggest future experiments, particularly ones we feel may help clarify the specific role of the chemical senses in nutrition. Other major aspects of the chemical senses have been covered adequately in recent reviews. These include the morphology and ultrastructure of taste (82) and olfactory (40) peripheral structures, the central neuroanatomy of taste (91) and olfactory pathways (121), the biochemical basis of taste and olfaction (15), the neurophysiology of taste cells (110), and the functioning of the chemical senses during aging (113, 114).

CEPHALIC-PHASE EFFECTS ON GASTRIC SECRETION

Control of Secretion

Gastric secretion is regulated by both neural and hormonal mechanisms (12, 62). For the cephalic phase, impulses from the vagal nucleus stimulate secretory cells in the oxyntic glands of the fundus. Gastric distention also causes secretion through local reflex arcs and via vagal afferent and efferent fibers (12, 21, 22, 42, 125). At least in the dog, gastric distention stimulates release of the hormone gastrin from the antrum (21, 22); and in both dog and human, distention potentiates acid secretion (21, 22, 42, 44, 125). Vagal impulses to the antrum stimulate gastrin release, and impulses to the oxyntic gland potentiate the secretory action of gastrin (12). This sequence is not

as clear in humans. Grotzinger et al (44) reported that for humans, fundic distention is an adequate stimulus for acid release but a poor stimulus for gastrin release. Even when stomach contents were neutralized during distention, serum gastrin did not rise significantly (44). In a similar study (125), serum gastrin rose only slightly at the highest distention pressures, but no correlation was found between rate of acid secretion and increases in serum gastrin.

Numerous reports employ cephalic-phase stimuli to study gastric secretion. Here we review studies either reporting recent advances in understanding the mechanism for cephalic-phase stimulation or employing variables relevant to the chemical senses. The general observation that the cephalic phase affects gastric secretion dates to the 18th century (143), but credit is usually given to Pavlov for placing this phenomenon on a sound experimental basis. The common pathway used by the cephalic phase to trigger gastric secretion is the vagus nerve; vagotomy abolishes the reflex (12, 14, 30, 43, 62, 64, 97). The neurotransmitter for vagal release of gastric acid is atropine-sensitive (12, 64, 88), and H_2-receptor antagonists cause a marked decrease (80%) in acid secretion (115). Under normal conditions the gastric secretory response to sham feeding appears after a latent period of 5–7 minutes and continues for as long as 3 hours after the food is eaten (78, 97, 106). Maximal secretion in response to sham feeding is reached by around 30 to 45 minutes (64, 78, 106), and stomach distention potentiates the secretory effect caused by sham feeding and prolongs the maximal rate of secretion (106).

A recent report by Konturek et al (64) details the time course of gastric secretion after cephalic-phase stimulation and the effect of atropine. Normal human subjects showed elevated gastric acid and pepsin output after modified sham feeding (MSF). Gastric acid attained a maximal release in normal subjects at the end of the 30 min sham feeding period, reaching 62% of the peak pentagastrin response. Infusion of atropine (20 μg/kg/hr) resulted in almost complete inhibition of basal acid and pepsinogen secretions, while the serum gastrin concentration remained at the pre-atropine level. MSF in atropinized subjects failed to stimulate release of gastric acid or pepsinogen above the pre-MSF level. However, when MSF was superimposed on pentagastrin-induced gastric secretion, acid output was increased compared with simple pentagastrin stimulation, but pepsinogen output was not augmented. In all cases with healthy human subjects, serum gastrin levels did not change with MSF.

Increases in serum gastrin levels with cephalic phase stimulation in humans are not consistently observed (reviewed in 12; see, for example, 64, 80, 131; but also 32, 34). When pH of the gastric contents was not permitted to fall, a distinct increase in serum gastrin was reported with MSF (34).

When atropine was administered in the study by Feldman et al (34), gastric acid and pancreatic polypeptide levels fell in response to sham feeding, but gastrin levels rose. In contrast, with dogs the cephalic phase usually induces serum gastrin increases. Electrical stimulation of the distal ends of the cut vagus reliably increased serum gastrin levels that were usually, but not always, related to gastric acid output (66). These increases in serum gastrin could be blocked by antrectomy or by perfusion of the antrum with acid (66). An apparent independence (or, at least, not strict dependence) of acid and gastrin was recently found in dogs using β_2-agonists with vagal stimulation induced by insulin or 2-deoxyglucose (39).

Hirschowitz & Gibson (48) reported that central vagal excitation induced by 2-deoxyglucose produces a higher level of serum gastrin (and of gastric acid secretion) after fundic vagotomy compared with the intact fundic innervation. The effects after atropine injection in both groups of animals led the experimenters to conclude that the mechanism for gastrin release is not cholinergic. It was found in dogs that low doses of atropine (1.25 μg/kg and 25 μg/kg) enhanced serum gastrin levels in response to food given orally (52). [Gastrin responses in this study (52) could have been due to gastric as well as cephalic stimulation.] Dockray & Tracy (27) report that using sham feeding in dogs, serum gastrin rose soon (4–7 min) after sham feeding began. If intragastric pH was not permitted to fall, serum gastrin was always higher than under unregulated conditions. When the same meal was delivered through a gastric fistula, serum gastrin did not change until after 10 min. Atropine given at 25 μg/kg did not change the meal-stimulated gastrin response but it did abolish the decline in serum gastrin normally observed after 10–20 min. Vagotomy in these animals abolished the early rise in serum gastrin after feeding, but also caused an increase in basal serum gastrin. These investigators (52) concluded that since "high doses of atropine reduced the gastrin response to [normal] feeding, but had little effect on the gastrin response to sham feeding . . . presence of food in the stomach might initiate a cholinergic stimulatory pathway of gastrin release."

In a previous study (23) atropine blocked gastrin release that was initiated by normal eating in the vagotomized dog. In the report of Hirschowitz & Gibson (48), the fundic vagotomized dogs displayed an increase in serum gastrin compared with intact animals when under stimulation by 2-deoxyglucose. Atropine (100 μg/kg), however, completely abolished this elevation. The conclusions from these studies are that fundic vagotomy removes an inhibitory pathway of gastrin release and that the inhibitory neurons are cholinergic. This conclusion is supported by observations that vagal denervation of the oxyntic mucosa led to a food-stimulated increase in gastrin release in both humans (31) and dogs (147). To further confirm this hypo-

thesis, it was recently reported (127) that excision of the fundic mucosa led to an increased release of both gastrin and acid after meal stimulation, suggesting that an inhibitory mechanism directly related to the fundic mucosa was removed. It appears at present that gastrin secretion is under complex control involving both cholinergic and peptide (neurotransmitter) mediation (29, 79).

Effects of Chemical Senses on Secretion

Although the effects of sham feeding on gastric responses are well known, the effect of taste or smell stimuli themselves on gastric secretion is not clearly understood. For example, does a "very palatable" meal increase gastric secretion to levels higher than a "less palatable" meal? Obviously, "palatability" must be determined on an individual basis, since food preferences are not the same for all individuals of a species (6). One widely cited reference directly addressing the effect of the cephalic phase on gastric secretion, but also cautioning a respect for individuality, is that from Pavlov (97). He noted that "the majority of dogs prefer flesh to bread, and correspondingly less [gastric] juice will be produced by sham-feeding with bread than with flesh. Sometimes, however, we find dogs which will devour bread with greater appetite than flesh. In these cases one obtains more and stronger [gastric] juice in sham-feeding with bread than with flesh."

While sham-feeding is known to be a potent stimulant to gastric secretion in humans [and has been suggested as a test for the completeness of vagotomy (33)], few experimental studies have considered the hedonic quality of the food. Those that did employ palatability as a variable have documented results parallel to Pavlov's. An earlier study of Janowitz et al (54) reports volume, total acid, and pepsin secretion from a stomach tube of a human subject who was maintained in caloric equilibrium by introduction of predigested diet into the stomach. In experiments to test the potency of cephalic stimulation, the subject was given one of three meals, randomly presented over several days between 9:00 A.M. and noon, following 10 hours of fasting. One meal consisted of a cereal gruel, a second the standard hospital diet for the day, and the third a meal composed of the subject's unrestricted choice. Because the subject selected this latter meal on the day previous to its administration, she was aware of the contents of the meal before it was presented. In all cases the self-selected meal led to higher levels of acid secretion than the cereal gruel (Figure 1). Parker et al (95) reported that sham feeding of the healthy human subject led to immediate increases in gastric volume secretion and large increases in potassium output. In general the pattern of changes in acid, volume, potassium, sodium, and chloride were similar for both sham feeding and histamine injection. They noted greater changes from basal levels for evening meals than for breakfast

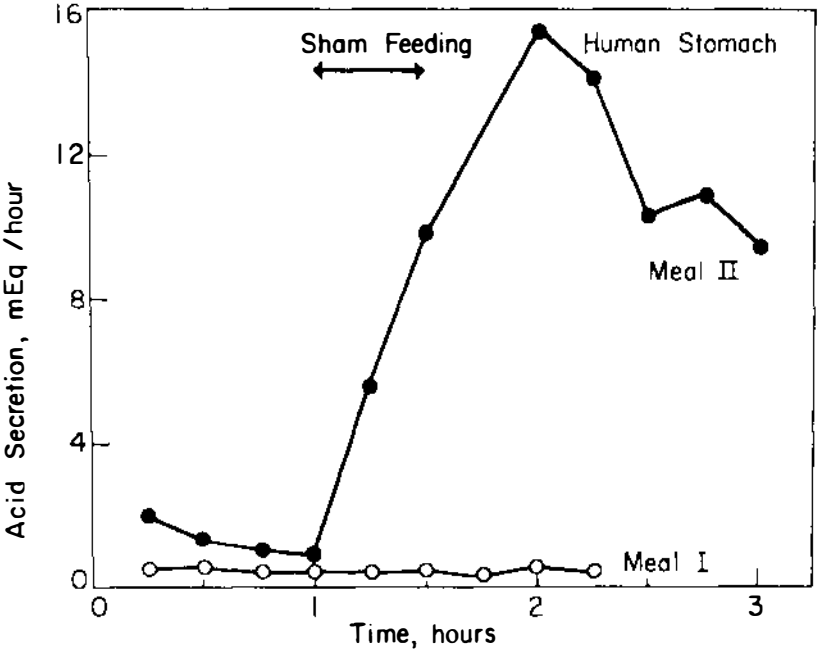

Figure 1 Rate of gastric acid secretion from one human subject vs time for two types of meals. Meal I is a cereal gruel, meal II is composed of the subject's unrestricted choice. Points of meal I are means of 4 experiments, and those of meal II are means of 12 experiments. The figure is reproduced with permission from Davenport (19), page 168 [adapted from Janowitz et al (54)].

meals (both following 12-hr deprivation) and suggested that since the evening meals were composed of the subject's choice, greater gustatory and "anticipatory" cephalic stimuli were responsible.

A recent study (76) using healthy volunteers demonstrated that a solid-liquid meal given orally elicited stronger gastric (acid, pepsin, and volume) responses than a homogenized meal of identical composition delivered intragastrically. The volunteers were unaware of which type meal they would encounter until immediately before the meal was served. Most of the early responses observed in this study to the solid-liquid meal compared with the homogenized meal are probably due to a greater stimulation of the cephalic phase evoked by the former meal's being tasted, smelled, masticated, and swallowed.

A study reporting the relative potency for stimulating gastric secretion between cephalic stimulation and stomach distention has been published by Richardson et al (106). The technique of modified sham feeding (MSF) was employed using an "appetizing" meal consisting of steak, french-fried potatoes, and water. Following a 10 hr fast, all subjects received the same meal;

the MSF lasted 30 min. For control stimulation (no meal) the subject chewed on a plastic tube for 30 min. Under MSF conditions, this meal led to an increase in gastric acid secretion compared to the no-meal condition. Gastric acid output rose significantly within the first sampling period (15 min) using MSF and reached maximal output by 30 min, the end of the MSF period. After this, acid secretion declined (Figure 2A). The amount of acid secreted was approximately 45% of the subject's maximal acid response to histamine.

Distention of the stomach also stimulated gastric acid secretion (106). One of three distention-causing equiosmolar solutions was delivered intragastrically: a NaCl solution, a glucose solution, or a slurry of blended food (steak, bread, butter, water). All three test meals led to acid stimulation, although the food slurry was the most potent stimulator. The onset of acid secretion was delayed after delivery of the food-slurry test meal, not being significantly different from basal levels until 30 min into the test period. If the stomach was first distended by food slurry and then MSF begun, the amount of acid secreted during the first 30 min owing to the MSF was not increased above the nondistended condition. However, acid was secreted for a longer period, lasting beyond the 2-hr collection period. These results point to the importance of cephalically derived increased vagal activity as an initiator of gastric secretion while a meal is being eaten.

In addition to measuring gastric acid secretion, this study (106) also found that serum gastrin was not significantly increased by MSF (Figure 2B). However, distention of the stomach with the food slurry, along with buffering of the stomach contents to pH 5 (to prevent acid-induced inhibition of gastrin release), did give rise to a significant increase in serum gastrin. This increase was not significantly augmented by superimposing MSF onto the intragastric infusion of the food slurry.

One component of the cephalic phase that has received little experimental study is the suspected stimulation of digestive sequences due to smell, to sight of food, or to association with events surrounding food ingestion. Moore & Motoki (80) reported that when subjects were permitted to observe (and presumably smell) the preparation of meals of their choice, gastric acid secretion increased significantly, to 55% of their normal pentagastrin-stimulated response. Blood glucose and gastrin levels were not affected by this procedure. Presumably, however, the subjects in this study could both see and smell the food, so simple anticipation was not the only stimulant. In a previous study (81) with a single subject it was reported that "anticipation" alone was a sufficient stimulus for acid release. A recent study (32) reported that the sight and smell of food and even simply talking about food were sufficient stimuli to initiate gastric secretion. The authors report their results as a combination of all types of stimulation so that effects

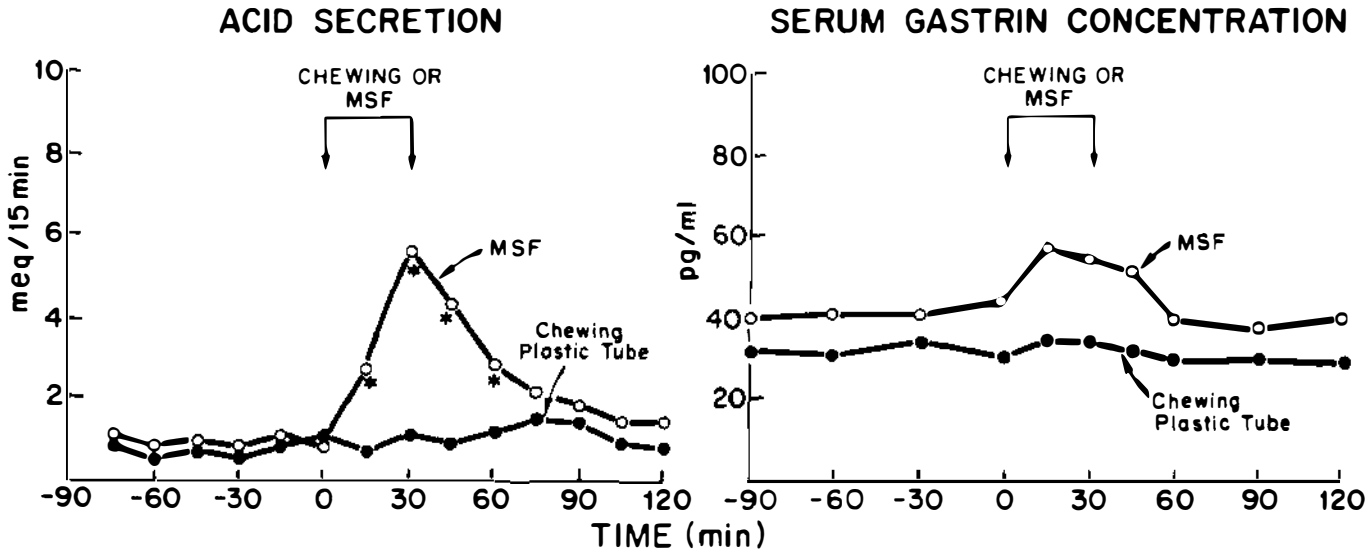

Figure 2 Acid secretion and serum gastrin concentration vs time in human subjects before, during, and after modified sham feeding (MSF) or chewing of a plastic tube. Significantly different ($p < 0.05$) mean values between the two types of stimulation are indicated as *. Time of chewing and MSF is shown by bracketed arrows. Points are mean values from nine human subjects. Figure is from Richardson et al (106), reproduced with permission of the publisher.

of individual stimuli, such as sight alone or smell alone cannot be determined. They report significant increases in both acid output and serum gastrin concentration after the 30 min sham sessions. The acid output was 28% of the peak acid output to pentagastrin. What is particularly notable about this study, for the purposes of the present review, is that the experimenters requested each subject to list his or her favorite (most appetizing) foods. It was these preselected meals that were either smelled, seen or talked about.

In order to achieve maximal responses to food stimuli, most investigators employ what they believe to be appetizing meals. Only a few studies have examined the effects of foods of varying palatability. This raises a question of what the effect of marginally palatable or even unpalatable foods may be, not only on secretion itself, but also on its duration and character. For example, if stomach distention precedes sham feeding as in the Richardson et al study (106), could unpalatable food in the subsequent sham feeding stage of the experiment truncate the secretion that would normally occur due to distention? Would the rate be altered and would sham feeding with unpalatable food fail to increase the amount of time that secretion was evident? Also, what would be the effect of marginally palatable food or the effect of sham feeding with a food that the subject anticipated as being palatable, but that was adulterated to be unpalatable?

CEPHALIC-PHASE EFFECTS ON EXOCRINE PANCREATIC SECRETION

Control of Secretion

Pavlov was the first investigator to report a convincing cephalic-phase stimulation of exocrine pancreatic flow (97). Since then the effect has been demonstrated several times (7, 84, 92, 93, 104, 109), but its precise nature is still difficult to explain. It is possible that pancreatic exocrine output after cephalic stimulation is due to secondary effects of gastric acid entering the duodenum and thus releasing secretin, to primary effects of cephalically released gastrin, or to direct vagal stimulation of pancreatic exocrine secretory cells (3, 61, 84, 103, 104, 126). An account of the probable mechanisms during the cephalic phase is provided by Solomon & Grossman (126). It is interesting to note that Pavlov (97) was convinced that the increased pancreatic output he observed to sham feeding in dogs was not secondary to a gastric acid effect. His reasoning was based on the time course of the effect. "The latent period of the gastric secretion in dogs has a sharply marked lower limit, and is never less than four and a half minutes. The pancreatic juice, on the contrary, begins to flow 2–3 min after the application of the

exciting agency, for example, an acid. In the experiment of teasing the animal by offering it food, the pancreatic flow also generally begins after two to three minutes. This appears to me to point to a direct psychic influence through the secretory nerves of the pancreas . . ." (97).

Some portion of the pancreatic response to cephalic stimulation appears to be due to secondary effects, particularly to hormone release. Especially in dogs, where cephalic stimulation reliably releases gastrin, this argument must be considered, although the physiological relevance of experiments using exogenous gastrin is not yet clear. In the human, large increases in gastrin following cephalic stimulation are not as obvious (see also preceding section), yet a cephalic phase of pancreatic output has been documented. Its magnitude relative to the gastric and intestinal phases has not been directly assessed (126). Other reflexive pathways are well known, often confusing interpretation of cephalic-phase experiments on pancreatic exocrine function; these include gastric vago-vagal reflexes (45, 140) and modifications of hormone release (20, 63, 141).

In dogs, an ingested meal causes a larger volume and protein response than does sham feeding, the latter being responsible for only 10–15% of volume and up to 25% of the normal amount of protein (17). Preshaw et al (104) observed that protein output, volume flow, and bicarbonate output from the pancreas all increased in sham-fed dogs, but acidification of the antral pouch with 0.1 N HCl abolished the stimulation of protein release by the pancreas. They concluded that gastrin was a permissive requirement for protein release under these conditions since antral acidification will effectively block gastrin release. However, their surgical procedure for forming an innervated pouch of the pyloric gland may have resulted in partial damage to vagal fibers innervating the pancreas (104, 126). Because the pancreas has vagal innervation, direct vagal stimulation (i.e. not mediated by gastrin) can affect pancreatic output (20, 47, 57, 123). Anticholinergic drugs inhibit the cephalic phase of pancreatic secretion in humans (109), but the site of action of the drugs cannot be determined under the experimental conditions used. Atropine was reported (141) to reduce pancreatic amylase output in response to vagal (electrical) stimulation in the monkey, but complete abolishment of the enzyme release was not observed.

It is assumed that the intestinal phase is quantitatively very important for the pancreatic exocrine response to a meal (20, 103, 126) and that a vago-vagal enteropancreatic reflex (sensitive to atropine and vagotomy) is important for rapid release of pancreatic enzymes (4). Malegalada et al (76) observed that trypsin output of the pancreas in response to two types of meals, a solid-liquid meal (chewed and swallowed) and a homogenized meal (delivered intragastrically) did not differ initially. After one hour, however, the pancreatic output with the homogenized meal had declined faster than

that for the solid-liquid meal. However, because the homogenized meal also emptied faster from the stomach, the difference in pancreatic response could have been due to transit time and not to differences in cephalic-phase stimulation.

In order to eliminate the possibility that the pancreatic response to sham feeding was due to gastric acid stimulation of secretin or cholecystokinin, Novis et al (92) used achlorhydric human subjects. They were sham fed (using MSF) a breakfast of their choice, the preparation of which they were permitted to observe (and smell). Sham feeding maintained volume flow and bicarbonate concentration at or slightly above basal levels, while the activities of lipase, trypsin, and chymotrypsin were generally increased. Amylase activity increased in only 2 of the 5 subjects during the sham period. These investigators suggest that the increase in pancreatic protein output was due primarily to vagal stimulation. It was previously reported (67) that pentagastrin could maintain basal pancreatic flow and increase enzyme concentration only slightly. Novis et al (92) concluded that the suggestion of Preshaw et al (104) that gastrin mediates the cephalic phase of pancreatic release in dogs could not explain their results with human subjects. Although a cephalic phase of pancreatic enzyme release exists, the results of Novis et al (92) suggest that it is quantitatively of minor importance.

Effects of the Chemical Senses

Sarles et al (109) report a cephalic phase of pancreatic secretion in humans. Their experimental paradigm varied the type of meal presented to their subjects. When allowing their subjects to see and smell a typical breakfast, they observed an increase in lipase activity, volume output and bicarbonate concentration compared with the condition of having the subjects see and smell a less typical breakfast (steak). When subjects were permitted to chew (but not swallow) the less typical breakfast, lipase volume and bicarbonate increased beyond levels present when subjects simply saw and smelled it. Sarles et al (109) also report that time of day had an effect on their results, early morning being a period of decreased secretory activity. Also, in one anorectic patient no obvious stimulation due to any of the test conditions was observed. These researchers concluded that even though pancreatic release by the cephalic phase is quantitatively small, its effects last long after (1 hr) sham feeding ceases, so that it could play a significant role in augmenting further release during normal eating.

Previous studies (92, 104, 109) employed food as a stimulus for sham feeding-excitation of the cephalic phase. The experiment of Sarles et al (109) suggested that palatability of the food may influence the amount of exocrine pancreatic secretion to cephalic stimulation. Experiments with conscious dogs have shown that both pancreatic flow and protein output can be affected by the palatability of the diet during a sham feeding regimen (7).

In this experiment (7) a basal diet was adulterated with either acceptable or aversive taste stimuli, and the animals generally showed a greater pancreatic response to the acceptable than the aversive diet.

A subsequent study (83, 84) explored the relationship between specific taste stimuli and pancreatic exocrine secretion. Dogs were prepared with gastric and duodenal fistulas for continuous drainage of gastric and intestinal contents. The duodenal fistula permitted direct cannulation of the main pancreatic duct. Taste stimulation was achieved by application with cotton swabs soaked in aqueous taste solutions to the dogs tongue for 6 minutes. Sucrose at a concentration to produce positive acceptance, and quinine sulfate or citric acid at concentrations that produced aversive responses were selected as stimuli. Dog saliva was employed as a control stimulus. During the experiment, the gastric and duodenal fistulas were kept open.

At first, oral stimulation with these substances produced a large increase in both the pancreatic volume and protein output during the 45-min collection (Figure 3). However, after one or two trials with each stimulus with each dog, an increased output no longer occurred. It is probable that the

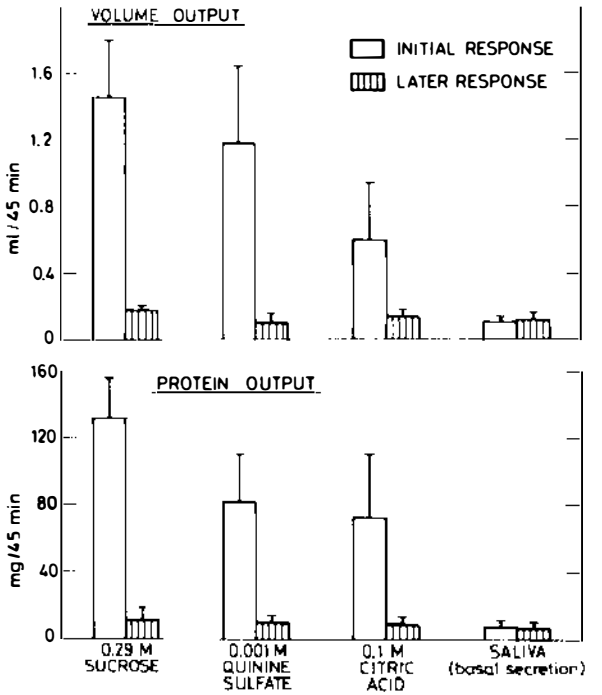

Figure 3 Total pancreatic volume and protein output during 45 min following oral stimulation of 4 dogs with three different taste stimuli using a swab technique. Values are mean ± S.E.M. of 4 experiments for each stimulus during either the initial or later sessions. Figure is adapted from Naim & Kare (83).

dogs associated the initial taste stimulations with anticipated feedings; however, after repeated trials, when food was not forthcoming, they no longer responded. The phenomenon of reduced response (extinction) following repeated trials has not been reported with sham feeding, but the orogastric reflexes, in addition to being excited by taste stimuli, are subject to inhibition by the hypothalamic area (67).

Since swallowing is usually involved with sham feeding in dogs, the same dogs were next given orally 100 ml of taste-stimulus solution mixed with 25 g of cellulose (Figure 4) (84). A pancreatic secretory response, which occurred within 40 min following the 6-min period of sham feeding with the cellulose mix, was restored primarily for a sucrose-cellulose mixture. Oral administration of the less palatable citric acid–cellulose or quinine-cellulose mixtures resulted in low pancreatic output, similar to that for the

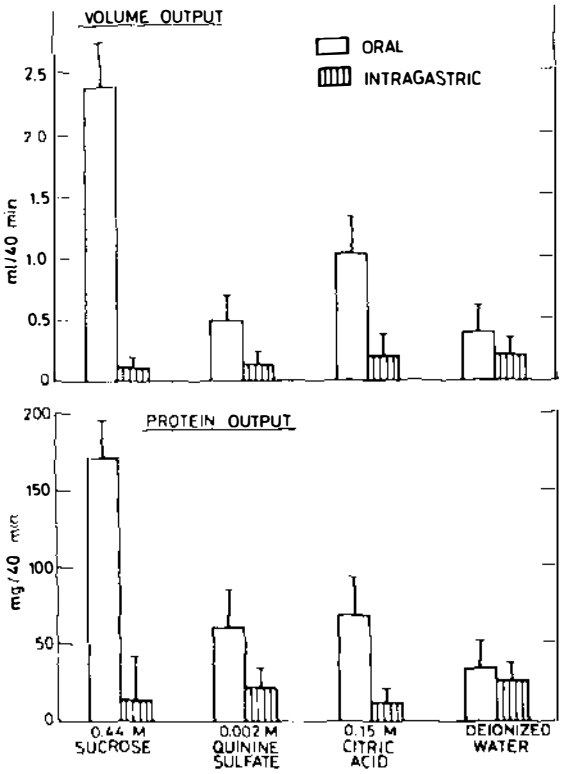

Figure 4 Total pancreatic volume and protein output during 40 min following oral or intragastric administration of taste-cellulose mixtures to 4 dogs. Values are means ± S.E.M. of 6–8 experiments on each dog. Figure is adapted from Naim et al (84).

(control) water-cellulose mixture. Although the gastric and intestinal fistulas remained open, intragastric administrations of the same taste-stimulus cellulose mixtures were performed in order to separate any pregastric factors that affect pancreatic secretion from those due to postingestive stimulation, e.g. the vago-vagal reflex (45, 140). These intragastric experiments resulted in low pancreatic output during the 40 min after administration. It was concluded that chewing and swallowing actions were necessary to trigger the feedback mechanisms that could restore the pancreatic response.

Schwartz et al (119) also found that in humans the cephalic phase of pancreatic polypeptide secretion from the endocrine pancreas was larger and less variable when the food was not only tasted and chewed, but also swallowed. Naim et al (84) concluded that taste stimulation alone is not sufficient to affect pancreatic exocrine secretion, but when coupled with swallowing, palatable taste stimuli exert a greater effect than do unpalatable stimuli on the cephalic phase of pancreatic exocrine secretion. Using a design similar to that of Naim et al (84), Ohara et al (93) reported that the effect of taste stimulation on pancreatic exocrine secretion of Beagle dogs depended upon the carrier used. Statistically significant increases in pancreatic response to orally delivered sucrose-cellulose mixtures compared with water-cellulose stimulation were not found in these dogs. However, the mean for sucrose stimulation was about 18-fold higher than that for water. It is apparent that the individual responses varied markedly among these dogs, not allowing a statistically significant difference in the group data.

Taken collectively, the experimental results of cephalic-phase effects on pancreatic exocrine secretions suggest that the response is quite fragile. When food was presented to human subjects to determine if sight and smell alone are sufficient stimuli for exocrine pancreatic release, little (109) if any (122) secretion was observed. Apparently, the full complement of the cephalic-phase cascade is required for the secretory response, and even then the response is small, although prolonged (76, 84, 109). Since pancreatic polypeptide is also released by the cephalic phase (see below) and has been implicated as an inhibitor of exocrine pancreatic secretion (137), the low secretory response of the exocrine pancreas to cephalic stimulation could be partly due to this inhibition.

CEPHALIC-PHASE EFFECTS ON ENDOCRINE PANCREATIC SECRETION

Insulin and Glucagon

During the past 15 years, many studies have demonstrated that stimulation by specific tastes, by food intake, or by the smell (and sight) of food can lead to a rapid increase in plasma insulin. This is assumed to be a preabsorptive elevation (8–11, 13, 36, 38, 51, 58, 74, 75, 94, 98, 100, 107, 124, 129, 132,

133, 142). Although the studies cited are not exhaustive, they serve as a guide to hypotheses formulated both to document the cephalic-phase response of insulin and to explore the physiologic mechanisms for the preabsorptive insulin release and its nutritional significance. Although the mechanisms are not clearly understood, the phenomenon is clearly demonstrable. Fischer et al (36) and Hommel et al (51) demonstrated that in the conscious dog immunoreactive plasma insulin increases after oral glucose stimulation. Stimulation of the oral cavity with fluids or food seems to be the critical factor, since saccharin solutions (8, 11, 74, 132) and even water (51) are sufficient to initiate this response, suggesting that the rise is a true cephalic effect and not dependent upon the presence of ingested glucose. In addition, drenching the oral cavity of the conscious dog with a topical anesthetic resulted in failure to observe the early rise in plasma insulin with oral glucose as the stimulant (35). As with other cephalic phase–mediated reflexes, the early rise in insulin resulting from oral stimulation can be blocked by atropine (99) or by vagotomy (74, 102, 144).

The effects of vagotomy indicate that direct vagal stimulation should lead to insulin release. It is known, for example, from morphological studies that pancreatic beta-cells receive cholinergic innervation (89), and the implications of neural innervation to the endocrine pancreas have been discussed (105, 145). Experiments performed by Frohman et al (37) and Daniel & Henderson (18) demonstrate that immunoreactive insulin is released following direct vagal stimulation. When the cut right vagal trunk was stimulated electrically (18) a 50% increase in plasma insulin was observed in blood taken from the inferior vena cava. Vagal stimulation did not alter blood glucose levels at any time during the experimental period. After a stimulation period of 10 min, plasma insulin levels remained elevated for about 100 min. These experiments support the hypothesis that the rise in peripheral plasma insulin observed to cephalic phase stimulation is vagally mediated.

Nicolaidis (85) reported hyperglycemia after either oral sucrose or oral saccharin stimulation in anesthetizied, food-deprived rats. He has hypothesized (86) that during food deprivation, anticipatory processes that result in release of endogenous glucose prevail, resulting in early hyperglycemia. Conversely, during *ad libitum* feeding, glucose storage processes predominate, and the early hyperglycemia is not consistently observed. This hypothesis is congruent with the observation that the release of insulin during the first minute of feeding is much smaller in food-deprived rats than in rats fed *ad libitum* (132).

The hyperglycemic hormone glucagon is also released by the cephalic phase, although this phenomenon is not as completely documented as is the cephalic phase–stimulated release of insulin (24, 25, 90). The report of

Nilsson & Uvnäs-Wallensten (90) provides evidence that the sight, smell, and taste of a meal are all effective stimuli for glucagon release in the dog and that the glucagon rise can be abolished by atropine (0.2 mg/kg) injections. The sight and smell of the food (minced boiled beef liver in water) were not as effective stimuli for glucagon release as was sham feeding. That the two apparently opposing hormones, insulin and glucagon, should both be released by the cephalic phase is interesting, yet not too surprising when viewed from the point of regulation and maintenance of the internal milieu. The possible reciprocal modulation by the CNS of release of glucagon and insulin has received some attention and is discussed in a recent review (87).

One question of current interest is whether the release of insulin to sweet taste is innate. Deutsch (26) found that the hypoglycemic effect induced by saccharin injection into rats was reversible by exposing the animals to long-term oral access to saccharin. Based on the results of various studies (9, 36, 85, 129) the preabsorptive insulin release to sweet taste should be innate. Yet the response can be conditioned, being associated with the time of eating [and sensitive to atropine (146)]; it is not observed in response to saccharin in the newborn rat pup, but is observed by the time of weaning (8). More recently, Berridge et al (9) demonstrated that the preabsorptive release of insulin evoked by glucose could be abolished by pairing the taste with LiCl in a conditioned aversion paradigm. This result suggests that experience can alter not only consummatory behavior but neuroendocrine function as well.

The observations of a preabsorptive rise in insulin after cephalic-phase stimulation raises the question of whether the magnitude of the rise is modulated by the "palatability" or "hedonic quality" of the stimulus. Berridge et al (9) showed that even though the stimulus solutions NaCl, saccharin, and glucose were presented to naive rats at preferred levels, only glucose resulted in a preabsorptive insulin response. Solutions shown to be aversive resulted in no preabsorptive release of insulin. [Preference was determined by a catalog of mimetic responses to the stimuli flowed into the oral cavity of the rat (41).]

Other experiments have measured preabsorptive insulin responses to complex foods. Strubbe & Steffens (132) observed an increase in plasma insulin within 1 min after the unanesthetized rat begins consuming a carbohydrate-free, high-fat meal (43% fat: type not specified). Food deprivation was not necessary to observe this effect. When the animals were changed from the carbohydrate-rich food to a "dummy food" (56% paraffin oil, 8% vaseline, 36% cellulose), insulin levels nevertheless rose, although blood glucose did not rise. For the groups of rats fed *ad libitum,* comparison of their data (132) for the carbohydrate-rich and fat-rich diets with the diets composed of dummy foods indicates that the former diets provoked a larger

rise in insulin levels. The preabsorptive insulin rise to food can be observed when the blood glucose level does not change. Indeed, only with the food-deprived rat, or when a carbohydrate meal is offered to the rat at any time, is blood glucose significantly elevated (128, 132). Louis-Sylvestre & Le-Magnen (75) reported that quinine-adulterated food led to a decrease in the preabsorptive insulin response compared with nonadulterated food, while food adulterated with 0.2% sodium saccharin resulted in higher levels of preabsorptive insulin release. Based on the amount of food consumed, these researchers report that the saccharin-adulterated diet was preferred to the normal diet, which in turn was preferred to the quinine-adulterated diet.

Could these early neuroendocrine reflexes have physiologic or nutritional significance? As noted in the above sections on digestive secretions, the postabsorptive effects are usually larger in magnitude and duration than their counterpart preabsorptive effects. According to Nicolaidis (86) the sensory-endocrine reflexes take on an optimizing role in the metabolism of nutrients. Oral ingestion of saccharin, for example, improved the anabolic utilization of nutrients administered intravenously (86). A more direct role for the preabsorptive rise in insulin could be in its promotive effect to initiate eating. Prolonged insulin administration can lead to increased food intake (49) and to changes in preference for taste solutions (53, 107). Louis-Sylvestre & LeMagnen (75) discuss the preabsorptive insulin release as an "on transient response." They suggest that the initial insulin release can decrease glucose availability and thereby actually enhance hunger arousal. Palatability modulates this effect by modulating the quantity of preabsorptive insulin released. They further suggest (75) that even though an animal may be satiated on a given food, sampling a different food could initiate a new sequence of insulin release, which in turn would initiate further ingestion. This hypothesis could be a physiologic basis for the observations of LeMagnen (69) on the effect of food variety on intake. The general hypotheses for explaining these observations have been recently discussed (107, 108).

Rodin (107) found that individual human subjects whose eating was most responsive to cues associated with food (such as taste or caloric density) showed the largest insulin release in response to sight and smell of grilling steaks. In previous studies (124, 133) insulin levels were higher after food presentation (sight and smell) in obese subjects than in the non-obese. These investigators suggested that the insulin response might act as an index of appetite. They also pointed out that the response was quite variable and tended to extinguish on the second trial. Fragility of response to certain types of cephalic stimulation for both pancreatic exocrine and endocrine responses has been noted before (84, 119). In a recent experiment (10) rats

that displayed the highest degree of cephalic-phase response for preabsorptive insulin release also ate more than those animals showing a lower response. This result is congruent with the observation that ventromedial hypothalamic hyperphagic rats have an exaggerated cephalic phase–stimulated insulin response (102, 128) and that the hyperphagia can be mitigated by vagotomy (102). Recent work has, however, demonstrated that the mitigating effects of vagotomy are modulated by parameters such as completeness of vagotomy, sequence in which vagotomy and the hypothalamic lesions are made, and the type of diets offered to the animals following the lesions (111, 112). These experiments collectively suggest that response to cephalic-phase stimulation could be an indicator of potential dietary obesity.

Pancreatic Polypeptide

In addition to the well-documented release of insulin from the endocrine pancreas by the cephalic phase, the peptide hormone pancreatic polypeptide is also released by cephalic stimuli (2, 116, 118, 119, 134, 135). Pancreatic polypeptide is a 36 amino acid polypeptide bearing little similarity to other polypeptide hormones (16, 59). It is localized to specific endocrine cells of the pancreas (68). Specific functions for pancreatic polypeptide have not been defined, although it has been implicated in a number of gastrointestinal processes (71). For example, it may act as a local regulator of pancreatic exocrine secretion (72). A recent report by Taylor et al (137) demonstrated that pancreatic polypeptide, exogenously administered at levels normally observed after feeding, inhibited exocrine pancreatic output of bicarbonate and protein stimulated by secretin and caerulein. Pancreatic polypeptide may also play a role in satiety (77). The peptide appears to have little regulatory effect on gastric acid secretion, at least as this phenomenon was experimentally investigated using pharmacological initiators of acid secretion (96).

The mechanism of pancreatic polypeptide release by cephalic-phase stimulation involves vagal mediation and is to a large degree cholinergic (2, 116, 118, 134, 135). Using insulin-induced hypoglycemia in normal and duodenal ulcer patients, Schwartz et al (116) demonstrated a reliable increase in serum pancreatic polypeptide following the insulin injection. Atropine injections of 0.03 mg/kg given before insulin reduced the pancreatic polypeptide response. After truncal vagotomy in the ulcer patients, no increase in pancreatic polypeptide was observed to insulin-induced hypoglycemia. Also, basal levels of pancreatic polypeptide in these patients after vagotomy were at levels not significantly different from those in control healthy subjects.

Schwartz et al (116) also report that electrical stimulation of the vagal nerves of anesthetized pigs produces an increase in circulating levels of pancreatic polypeptide. This effect is inhibited 74% after atropine (0.5 mg/kg) injections. Adrenergic alpha and beta blockers (combined phenoxybenzamine and propranolol) had no effect on the increase in circulating levels of pancreatic polypeptide after electrical stimulation. In an isolated perfused pig pancreas (55, 116) acetylcholine infusions increased pancreatic polypeptide concentrations in the perfusate in a graded manner. This effect could be reduced by atropine. These studies provide evidence for vagal control of pancreatic polypeptide release from the pancreas due to cephalic stimulation. They further suggest that since the release of polypeptide by insulin-induced hypoglycemia lasts beyond 180 min, the vagal mechanism may also contribute to the secondary phase of pancreatic polypeptide release.

Release of pancreatic polypeptide while eating a normal meal occurs in two phases: a rapid primary phase (5–30 min) which can be abolished by truncal vagotomy (118) and a longer and larger secondary phase (30 min–6 hr). This larger secondary release is the result of both gastric and intestinal phases (136). The gastric phase is mediated by vago-vagal stimulation via distention (60, 117, 134). The intestinal phase of release of pancreatic polypeptide may be mediated, at least partially, by cholecystokinin since injections of this hormone lead to increases in circulating levels of pancreatic polypeptide in humans (73). Lonovics et al (73) discuss previous studies that failed to demonstrate a CCK effect on pancreatic polypeptide release (e.g. 134) and conclude that those experiments may have employed a hormone solution that was partially or wholly inactivated during the purification process. Taylor et al (135) observed an increase in serum levels of pancreatic polypeptide in dogs given a standard ground beef liver meal. The increase was significantly different from basal (premeal) levels by the first time point of sampling at 30 min. At this point 80% of the maximal amount was already released. Both atropine (25 μg/kg and 100 μg/kg) and truncal vagotomy reduced this response, with the reduction by truncal vagotomy lasting the entire 4 hr period.

A report by Schwartz et al (119) describes cephalic phase–initiated pancreatic polypeptide release in humans with sham feeding. In two groups, healthy subjects and duodenal ulcer patients, a significant increase in pancreatic polypeptide was observed to MSF. Four of the 26 ulcer patients and 2 of the 8 healthy subjects did not show this response to MSF. Pretreating the subjects with atropine (2.5 mg) or benzilonium (1 mg or 2 mg) led to a decrease in resting levels of pancreatic polypeptide (120) and no response to sham feeding. In the duodenal ulcer patient group, 17 individuals had

a selective parietal cell area denervation and thus secreted no gastric acid. Pancreatic polypeptide release to MSF was found in 13 of these 17 patients, suggesting that pancreatic polypeptide release is not dependent on gastric acid response.

If instead of modified sham feeding, the subjects were permitted to chew and swallow the food, release of pancreatic polypeptide was enhanced (Figure 5) (119). In this experiment food did not reach the stomach, but was carried through a tube temporarily inserted into the distal part of the esophagus. The pancreatic polypeptide response was not only larger with swallowing but was also less variable. That the swallowing reflex leads to more robust release of pancreatic polypeptide is interesting in light of the observations of Naim et al (84) on cephalic-phase stimulation of the exocrine pancreas. They found that including chewing and swallowing in the stimulatory sequence restored the pancreatic response. While swallowing would appear to influence the cephalic phase of pancreatic exocrine and pancreatic polypeptide release, it apparently adds little to the cephalic phase of gastric acid release (130). No study has yet appeared, as far as we are

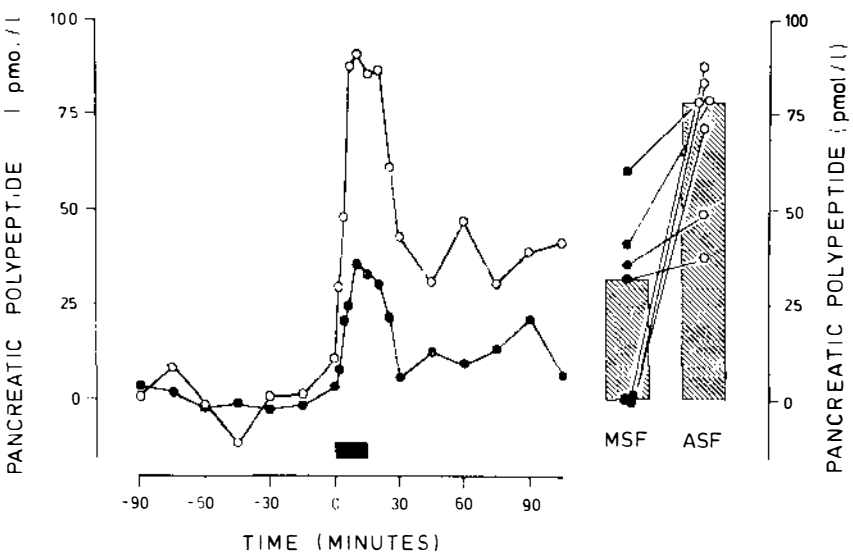

Figure 5 Plasma concentrations of pancreatic polypeptide vs time in 7 human subjects for either normal sham feeding (chewing and swallowing) or modified sham feeding. Normal sham feeding is indicated as (o——o) and "ASF," and modified sham feeding is indicated as (●——●) and "MSF." Sham feeding time is indicated by the length of the horizontal bar beginning at zero minutes. The height of the columns on the right represent the mean of the integrated response over the first 30 min. Individual subject points are indicated for each type of sham feeding. Figure is from Schwartz et al (119), reproduced here with permission of the publishers, Universitetsforlaget.

aware, attempting to determine if the magnitude of the pancreatic polypeptide release is dependent upon the hedonic quality of the food stimulus, or if pancreatic polypeptide can be released by other cephalic-phase stimulants such as odor.

CONCLUSIONS

As components of the cephalic phase, the chemical senses affect digestive and metabolic processes at several levels. Those we reviewed here include gastric acid secretion, exocrine pancreatic secretion and endocrine secretion of gastrin, glucagon, insulin, and pancreatic polypeptide hormone. The primary mediator of cephalic-phase stimuli is the vagus nerve. The responses initiated by the chemical senses have nutritional relevance since they initiate secretions that prepare the organism for digestion and metabolism. The magnitude and duration of these secretions are directly affected by the hedonic status of the stimuli.

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