Beyond the Motor Elements of Swallow

In this issue of GASTROENTEROLOGY, Issa reports on his investigations into the elicitation of oropharyngeal swallow in dogs by the infusion of varied gustatory stimuli onto the anterior and posterior surfaces of the tongue. Among the gustatory stimuli tested (water, saline, glucose, NaCO3, and acetic acid), acetic acid was associated with the shortest latency between the onset of infusion and elicitation of a swallow. For all solutions, infusion onto the posterior tongue was more effective than onto the anterior tongue. Furthermore, sleep prevented any of the infused stimuli from triggering a swallow. Instead, when infusions were performed during sleep, animals showed either no response at all (especially with infusion onto the anterior tongue) or arousal followed by swallowing and sometimes coughing. Again, acetic acid was the most potent stimulus. Assuming that these findings generalize to humans, they have relevance both to the response to gastropharyngeal reflux and the treatment of oropharyngeal dysphagia.

Human studies have shown sleep to increase the lower esophageal sphincter (LES) pressure, decrease the upper esophageal sphincter (UES) pressure, vastly reduce the rate of spontaneous swallows, inhibit salivation, and prevent the occurrence of transient LES relaxations. One could argue that this combination of effects effectively eliminates the oral cavity as a source of secretion or ingested to the gut and prevents the retrograde escape of gastric contents, thereby protecting the airway from all potential fluid intrusions. Thus, during sleep, the oral cavity serves only as a respiratory conduit. However, in certain circumstances, the LES proves to be an imperfect barrier to nocturnal reflux as evidenced by the propensity of patients with reflux esophagitis and patients with reflux laryngitis to sustain periods of esophageal acidification. One could argue that this combination of effects effectively eliminates the oral cavity as a source of secretion or ling to the gut and prevents the retrograde escape of gastric contents, thereby protecting the airway from all potential fluid intrusions. Thus, during sleep, the oral cavity serves only as a respiratory conduit. However, in certain circumstances, the LES proves to be an imperfect barrier to nocturnal reflux as evidenced by the propensity of patients with reflux esophagitis and patients with reflux laryngitis to sustain periods of esophageal acidification at night. When these events occur, the defensive responses aimed at the elimination of the refluxate and restoration of intraesophageal pH to a normal value are attenuated. Unfortunately, along with making acid intrusions less likely, sleep also suppresses salivation, UES pressure, and swallowing, which might otherwise constitute an effective defensive response to these acid incursions. Only when the stimulus becomes overwhelming, as with threatened aspiration or asphyxiation, is a response elicited, and in this circumstance the response is preceded by arousal. However, the periods of arousal are often too brief to complete the process of acid clearance. Findings from the present study by Issa suggest that the brevity of these arousals may stem from the fact that the object of arousal may focus more on the prevention of aspiration rather than preventing mucosal acidification. Thus, by increasing the threshold of defensive responses to reflux, the mucosa becomes more vulnerable should reflux occur. On the positive side, it is interesting to note the increased efficacy of the acid stimuli compared with others in causing arousal and swallowing in the Issa study. Although the defenses of the mucosa may be reduced, they are at least “tuned” to respond to the most likely invader.

Another aspect of the Issa study relevant to clinical medicine is the differential ability of acetic acid to elicit a swallow response during wakefulness. Our modern understanding of the swallow response dates back to studies by Doty and Bosma, although some investigations into the elicitation of swallows by electrical stimulation were performed in the laboratory of the classical neurophysiologist Sir Charles Sherrington. These early studies of deglutition focused on the patterned motor sequence, involving scores of oropharyngeal muscles, as the most complex reflexive response of the human body and the medullary swallowing center, the neuronal pattern generator responsible for orchestrating this complex response. Defining the complexity of the sensory parameters required to elicit the swallow response was circumvented by using electrical stimulation of the superior laryngeal nerve to trigger the pharyngeal swallow response. Under such circumstances, Doty was able to trigger as many as 1620 swallows in 67 minutes. However, under normal circumstances, it is much more difficult to define the sensory parameters that will predictably trigger a pharyngeal swallow.

The sensory cues required for eliciting the pharyngeal swallow are unclear but, experimentally, tactile stimulation of the anterior faucial pillars has been suggested to be effective. On the other hand, swallowing can also be initiated solely by volitional effort without any exogenous mechanical stimulus. However, it becomes progressively more difficult to sequentially initiate swallows without adding food or fluid to the mouth; it is virtually impossible to swallow 4 times in 10 seconds or 12 times in 30 seconds when the mouth is free of saliva. In con-
trast, there is minimal limitation of the rate at which swallows can be initiated with food or liquid within the oral cavity. Thus, the limitation of initiating the swallow response is of orchestrating the afferent signal rather than fatigue of the central circuitry or peripheral musculature involved in enacting the swallow. Deep anesthesia to the entire oral cavity with cocaine makes it impossible to initiate a swallow. Therefore, the required afferent signal for initiation of the swallow response is comprised of a mixture of both peripheral sensory input from oropharyngeal afferents and superimposed control from higher nervous system centers. Neither element of the afferent signal is capable of initiating the swallow without some contribution from the complementary element as evidenced by the inability to swallow during sleep, in which the higher centers are disconnected, or with deep anesthesia to the oral cavity, in which case peripheral afferents are deactivated. However, the relative contributions of the two afferent elements actually responsible for initiating a particular swallow varies with circumstance. During eating, the sensory environment is permissive and the timing of swallowing largely voluntary. At the other extreme, in pathological circumstances in which one or the other neural substrate of the afferent signal has been damaged, patients may experience a relative inability to initiate a swallow. Swallow apraxia in not an uncommon accompaniment of central nervous system injury after a cerebrovascular accident or head injury.

The present study by Issa increases our knowledge of the oropharyngeal sensory signal acting to stimulate swallowing. As alluded to earlier, previous work has shown that afferent sensory fibers from the larynx capable of initiating swallowing travel centrally via the internal branch of the superior laryngeal nerve. However, although superior laryngeal nerve stimulation provides the best experimental model of swallowing, afferents from the pharyngeal plexus traveling centrally via the glosso-pharyngeal nerve are also capable of initiating swallowing and may have a dominant role in the initiation or modification of the pharyngeal swallow response in vivo. Issa’s findings suggest that acetic acid is a particularly potent stimulus for all oropharyngeal afferent fibers. Perfusion of the tongue with the acid solution elicited swallowing with the shortest latency in all experimental circumstances; perfusion on the anterior tongue, perfusion on the posterior tongue, or during sleep. These findings lend experimental evidence to support the use of swallow therapy aimed at enhancing sensory awareness as a compensatory strategy in patients with swallow apraxia.

In the hypotheses developed above, the medullary swallowing center is activated by interplay between the volitional and oropharyngeal somatosensory cues. These two components merge in the nucleus of the solitary tract. Clinically, swallow apraxia most commonly results from damage to the neuronal substrate of the volitional centers. With a relative decrement in one source of afferent input, a logical compensatory strategy is to augment the other afferent source in an attempt to decrease the level of volitional input required to achieve the threshold for triggering the central pattern generator. Thus, the clinical quest has been to find the most effective way to augment the sensory component. To date, swallow therapists have largely approached this issue empirically. Specifically, increasing downward pressure of the spoon against the tongue, thermal stimulation, or presenting a sour bolus (50% lemon juice and 50% barium) have been used as compensatory strategies aimed at altering sensory input. Preliminary data from Logemann suggest that the sour bolus is particularly effective in some patients with swallow apraxia, which is consistent with the findings in the present study by Issa and provides some hope for the treatment of this disabling condition.

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References

Cellular Antisocial Behavior Leads to Gastrointestinal Malignancies

See article on page 701.

The epitome of cellular antisocial behavior is the invasion and destruction of other organs of the body by cancer leading to the death of the host, often with the violence and functional disorder reminiscent of an all-out war. The rhetoric in World War II characterizing Hitler and the Nazi legions as the cancer of Europe may prove to be more applicable to biology than its mere use as a striking propaganda metaphor. Just as we wonder what there was about the childhood of the Hitlers of society that led to their antisocial behavior, researchers are asking what allows a cell to become deviant and elude those controls that enable it to participate in the constructive behavior of cell-cell interrelationships required to form, maintain, and continually renew a specific organ, such as the intestine.

Recent work has shown that the deviant cells that cause colon cancer are those with mutations in genes referred to as proto-oncogenes, "tumor-suppressor" and growth factor genes, as schematized by Vogelstein and Kinzler. When the accumulation of these mutations becomes permissive of eluding tissue restrictions on growth and allows the cell to avoid destruction by the police of the immune system, cancer results. Many, if not most, cancers stay localized within their tissue of origin and have limited invasive capacity. In time, a few undergo a change that makes them more aggressive, perhaps another gene mutation or a nongenetic alteration in the cell's responses to adjacent tissues and peptide signals. Whatever the mechanism, the change enables more aggressive invasion of adjacent tissue and distant metastasis; the deviant cells exhibit a "social disease."

Many of the genes implicated in malignant transformation are responsive to external signals or serve as communicators with other cells. Thus, although it may be confusing that there appears to be a seemingly unending increase in the number of peptide growth factors, cytokines, and signal transduction molecules being discovered, the discoveries are indicative of the complicated cell socialization process being delineated. This should be expected for a social system in which cells must continually communicate with each other to form a well-functioning organ. Furthermore, to integrate the functions of one organ with the needs of the whole animal, cells also have to receive and respond to signals from other tissues, many far from the target cell. These extensive communication networks appear necessary for the cell to participate in morphogenesis and to fulfill its designated functions. For example, the mesenchymally derived myofibroblast seems to be essential for normal development, morphogenesis, differentiation, and function of intestinal cells. The thin basement membrane that separates the myofibroblast from the enterocyte functions as a scaffolding for organ structure and as a bed of growth and differentiation factors through which the two communicate. The altered relationship of the myofibroblast to the malignant behavior of colon cancer cells is the subject of the report by Pujuguet et al. in the present issue of GASTROENTEROLOGY.

The findings of Pujuguet et al. were that less-differentiated adenocarcinomas of the colon (1) contained less basement membrane, particularly a marked reduction in collagen IV content, (2) were associated with a shift of basement membrane from within the tumor to areas of neovascularization at the tumor periphery, and (3) were related to more aggressive malignant behavior as they increased their separation from the intestinal myofibroblast with which they normally are intimately associated. These observations were made on two rat colon cancer cell lines transplanted in the thoracic wall of rats.