

CLINICAL REVIEW

Pathophysiological Changes of the Gastrointestinal Tract in Ischemic Stroke

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OBJECTIVE: Dysphagia is common after stroke and represents a marker of poor prognosis. After ischemic stroke, dysphagia represents only one part of the clinical spectrum of changes in the gastrointestinal (GI) tract and includes GI hemorrhage, delayed GI emptying, and colorectal dysfunction. State-of-the-art imaging techniques have started to revolutionize to study the cortical and brainstem control of these GI symptoms. It has become increasingly obvious that GI alterations after stroke are complex and its recovery following stroke is even more so.

METHODS: In this review, an electronic database research was performed in MEDLINE, EMBASE, and the COCHRANE database using the terms stroke, dysphagia, GI motility, or cortical reorganization; an extensive manual searching was additionally conducted.

RESULTS: Cerebral ischemia may lead to an interruption of the axis between central nervous system and GI system. This altered interrelation between the central nervous system and the GI system may cause, among other things, mainly dysphagia, GI dysmotility, and GI hemorrhage. The consecutive clinical symptoms can often be directly attributed to specific cerebral ischemic lesions involving the brain stem as well as certain cortical and subcortical structures. However, in some cases the pathophysiological mechanisms leading to GI symptoms are incompletely understood. Recent improvement of imaging techniques, especially in functional imaging, has lead to new insights of the central control of the GI tract, suggesting that its cortical and medullar organization is multifocal, and bilateral with handness-independent hemispheric dominance.

CONCLUSIONS: Following stroke, patients may have swallowing impairment and other changes of the GI tract that could affect nutritional and hydration status and that lead to aspiration pneumonia. Impaired nutritional status is associated with reduced functional improvement, increased complication rates, and prolonged hospital stays.

(Am J Gastroenterol 2006;101:1655–1665)

INTRODUCTION

After ischemic stroke, various secondary functional alterations can be expected in peripheral organs that are in close interrelation to the affected cerebral vascular territories (1–3). This is especially the case in the different segments of the gastrointestinal (GI) system that is partly controlled by a complex hierarchy of neural substrates in the central and peripheral nervous system. There is considerable clinical and experimental evidence that the incidence of certain GI alterations, such as dysphagia and GI tract dysmotility, are strongly related to the topographical location of the cerebral ischemic damage itself and does not represent a general state of severe illness (4–6). Main vascular territories involved seem to be those of the middle cerebral artery and the posterior inferior cerebellar artery (7, 8) and to a lesser extent the vertebral artery (9). Positron emission tomography (PET) and magnetic resonance imaging (MRI) studies in normal human subjects have also identified multiregional

representation of the GI tract mainly within sensorimotor cortex (inferior precentral gyrus) and the brainstem. Dysphagia represents a common and distressing consequence of stroke in these vascular territories, occurring in up to 50% of patients immediately after the event (9). Post-stroke dysphagia increases the risk of deaths (10) and worsens functional outcome after stroke, with lower recovery (11) and longer hospital stay. However, despite similar dysphagia severity at onset, individual recovery pattern vary widely. The reason for this remains unclear; in particular, it does not appear to be directly related to stroke severity (12). In addition to swallowing, a number of other GI symptoms that are related to changes in the brain after stroke are not well understood.

The severity and extent of neurological deficits in the GI system after ischemic stroke are likely to depend on the amount and location of brain tissue that suffers from an impairment of blood supply below the critical flow threshold (13). While not the sole determinant of damage (duration of reduced flow is also important), experimental work on

ischemic flow thresholds has demonstrated the existence of two critical levels of decreased perfusion: (i) a level below which reversible neuronal failure occurs (cerebral blood flow (CBF) < 20 mL/100 g/mL) and (ii) a lower threshold below which irreversible membrane failure and morphological damage occurs (CBF < 12 mL/100/min) (13). The range of perfusion values between these limits is termed the “ischemic penumbra” and is characterized by the potential for functional recovery without morphological damage (3, 14, 15). Added to this, further improvements in the state-of-the-art imaging modalities in terms of spatial resolution and sensitivity have given new insights into the cortical representation of the GI tract and may help to better understand the complex processes underlying the disorders of the GI system following stroke as prerequisite for the development of new treatment options.

This review thus focuses on recent experimental and clinical findings regarding the interrelationship between ischemic stroke and GI dysfunction and on research needed in the future to better understand pathophysiological mechanisms and thereby enable the development of improved treatment options.

METHODOLOGY

For the purpose of this review, MEDLINE, EMBASE, and COCHRANE databases were searched for trials, case series, or case reports published between the dates of 1966 and August 2003 and 1986 and August 2003, respectively. The search terms used were swallowing, stroke, cerebral ischemia, cerebral infarction, middle cerebral artery, dysphagia, GI motility, cortical reorganization, GI hemorrhage, GI emptying, aging, and treatment or references from relevant articles. The study or report had to be published or translated in English, French, or German. More recent publications were used in preference to older ones, as the purpose of the review is to give an up-to-date review of current experimental or clinical knowledge of pathophysiological changes of the GI tract in ischemic stroke. Older publications were retrieved if they were cited in the selected publications and deemed significant for the purposes of this review.

SWALLOWING

Swallowing represents a sequential, semiautomatic contraction and relaxation of the 55 muscles of the oro-pharyngeal, laryngeal, and esophageal regions, 5 cranial nerves, and 2 cervical nerve roots. Central control of swallowing is organized on two levels, involving both the brainstem (16) and the cerebral cortex (5, 17, 18). Uni- or bilateral supratentorial ischemic stroke and particularly brainstem stroke often impairs swallowing due to functional or morphological damage of corresponding areas of the motor cortex and/or their connections to the brainstem and/or the cranial nerves modulating deglutition (19). Up to 50% of patients with ischemic

stroke have been estimated to present with signs of dysphagia (19, 20), albeit temporary in most of them. Besides the known ischemic brainstem syndromes with accompanying dysphagia, it is now well established that the cerebral cortex plays an important role in the central regulation of swallowing (21). While the reflexive component depends on swallowing centers in the brainstem, the initiation of swallowing is a voluntary action that involves the integrity of the corresponding motor areas of the cerebral cortex (22). A number of brain regions with increased activation during swallowing were detected by [¹⁵O]H₂O-PET studies: the strongest activation was found to be predominantly in the sensorimotor cortices, the right anterior insula/claustrum, the left cerebellum and the dorsal brainstem (18). Therefore, swallowing recruits multiple cerebral regions, indicating that swallowing involves the recruitment of a neural network with areas outside the primary motor cortex and the medullar brainstem (8, 17).

Cortical Organization and Swallowing

The cortical representation of swallowing is thought to be multifocal, and bilateral, with handedness-independent hemispheric dominance (23, 24). Various areas of the cerebral cortex, such as the sensory motor cortex, cingulate gyrus, and insula have been demonstrated to become activated during volitional swallowing (23). However, within the motor cortex, the representation of swallowing muscles is somatotopic, with oral muscles more lateral and pharyngeal muscles more medial (4, 25). Of interest, it appears that reflexive swallowing also shows bilateral activity concentrated to the primary sensory/motor regions (26). From the present knowledge, patients with combined cortical/brainstem stroke associated with bilateral cranial nerve signs seem to be at greatest risk of dysphagia, but swallowing difficulties also occur in the context of unilateral signs (27). In addition, bilateral supratentorial stroke—that is located in both hemispheres—is associated with a higher incidence and greater severity of dysphagia than unilateral, supratentorial stroke—that is located in only one hemisphere (28).

The majority of cortical lesions that result in dysphagia are believed to impinge of projects from the precentral gyrus or the internal capsule (29, 30). Lesions in these anatomical areas will affect the voluntary actions of pharyngeal and laryngeal support musculature on the contralateral side, with spasticity and peristaltic dyscoordination, which may, in turn, lead to aspiration. Lesions in the lower part of the inferior precentral gyrus or posterior portion of the inferior frontal gyrus in either hemisphere have been reported to cause a delay in the initiation of pharyngeal response, suggesting a problem with feedback (22, 31), and providing further evidence for the role of the cortex in modulating deglutition. A lesion in the insular region can apparently increase the swallowing threshold and delay the pharyngeal phase of swallowing thereby increasing the risk of aspiration (32). The importance of the insula in swallowing is reflected in the fact that this region has multiple close functional connections to several brain regions linked

to swallowing, including the lateral and mesial premotor cortex, the primary and secondary somatosensory cortex, and the frontal parietal, and temporal opercula (33, 34).

In animal studies, there is evidence that both hemispheres play a role in controlling swallowing (35). Despite animal evidence for bilateral central control, pathological studies tend to suggest that, at least in humans, one or the other hemisphere might be dominant (36, 37). This fact may partly explain the difficulties in correlating the extent, the side and the location of the ischemic altered brain tissue with the severity and location of GI dysfunction in clinical studies.

Brainstem Organization and Swallowing

Swallowing problems are particularly common in brainstem stroke, and are likely to include increased risk of subsequent aspiration. Jean (38, 39) and Kessler (40) have provided experimental evidence for two levels of integration within the swallowing center in the medulla oblongata (38–40). One level of integration (dorsal region consisting of the neurons within and around the nucleus of the solitary tract (NTS)) is involved in the initiation of swallowing and the organization of the entire swallowing sequences (see Figs. 1–3), whereas a second level of organization (ventral region corresponding to the reticular formation surrounding the nucleus ambiguus (NA)) appears to serve primarily as a connecting pathway to the various motor pools involved in the swallowing sequence (6). These two regions are represented on both sides of the brainstem and are interconnected extensively so that either side can coordinate the pharyngeal and esophageal phase of swallowing (41, 42). Afferent information from the periphery enters into the afferent receptor portal of the swallowing center to synapse on “premotor neurons” (6). This sensory information can initiate deglutition and the swallowing sequence, alter previously initiated activity in the swallowing center, and therefore modify ongoing motor activity (6). The esophageal premotor neurons also receive input from pharyngeal premotor neurons in the intermediate and interstitial subnuclei of NTS and connect with third-order esophageal neurons in multiple nuclei of the reticular formation, including the parvocellular neurons (43). The reticular formation nuclei contain interneurons that are active as part of the central pattern generator control for swallowing and esophageal peristalsis (16, 44).

The central pattern generator serially activates the cranial nerve motor neurons, including the NA and dorsal motor nucleus of the vagus (DMV), which then innervate the muscles of deglutition (4). Because the corticobulbar fibers (including NA and DMV) are involved in triggering of the voluntarily initiated part of the swallow reflex, and because they have facilitatory effects on the bulbar swallowing center, a delay in triggering of the swallowing reflex after stroke would be associated with the involvement of the corticobulbar fiber system (4, 41). Less commonly, in more severe corticobulbar disease, the voluntary oro-pharyngeal swallow reflex cannot be initiated at all, although reflex swallowing can be still initiated by the bulbar swallowing center (31, 45). These dis-

turbances of the swallowing reflex can be detected clinically as well as electrophysiologically (46, 47). The second mechanism affected in swallowing disorders may be associated with suprasegmental inhibitory influences on the bulbar center. These influences appear to have been removed through some peculiar pathological involvement of corticobulbar fibers. The abnormal electromyographic patterns recorded from the cricopharyngeal sphincter in stroke patients is similar to those obtained from patients with amyotrophic lateral sclerosis with corticobulbar involvement (47). There is further evidence for the presence of pyramidal inhibition on the swallowing reflex (48). Therefore, it appears that the involvement of corticobulbar pathways not only alters the direct excitatory influences, but also results in dysinhibition of the neuronal network in the hierarchical interaction between the cerebral cortex, the brainstem swallowing centers, and cranial nerves (trigeminal nerve, glossopharyngeus nerve, vagus nerve, and hypoglossus nerve) by affecting inhibitory control (49). Further support for this mechanism comes from observations in (stroke) patients who have increased mandibular and palatopharyngeal reflexes (50). Likewise, it has been suggested that in amyotrophic lateral sclerosis the possible involvement of suprabulbar inhibitor control may be accountable for the increase in brainstem reflexes through a release from inhibitory influences (46, 47, 51, 52).

Following lacunar stroke, the duration of sub-mental muscle contraction is also prolonged (53), indicating that the extrapyramidal influences on the bulbar center are also affected. This assumption is supported by observations in patients with Parkinson’s disease with dysphagia (54) and suggests that the functional organization of swallowing is even more complex than explained above. Similarly, the accumulation of saliva in the mouth and drooling may be related to both, the involvement of the extrapyramidal system as well as the disturbance of the corticobulbar system.

Other Centers

The underlying mechanisms of activation of the cerebellum during swallowing are not fully understood. Although cases of dysphagia related to cerebellar lesions following stroke are reported (55), in most instances widespread lesions extending beyond the cerebellum are involved. Increased activity in the left cerebellar hemisphere during swallowing cannot be explained by tongue movement, indicating that it probably represents a specific pharyngeal/esophageal or swallowing region (8). Given the nature of the contribution of cerebellum to other motor behaviors, the data from healthy humans suggest that the cerebellum may help to control the coordination, sequencing, and timing of swallowing (8).

Among the other areas showing activity during swallowing, the putamen requires particular consideration. Activation of this anatomical region is consistent with the frequent occurrence of dysphagia in patients with basal ganglia lesions (8), such as stroke. At present, it remains unclear to what extent the increased putaminal activity during swallowing reflects tongue movement or other aspects of swallowing. However,

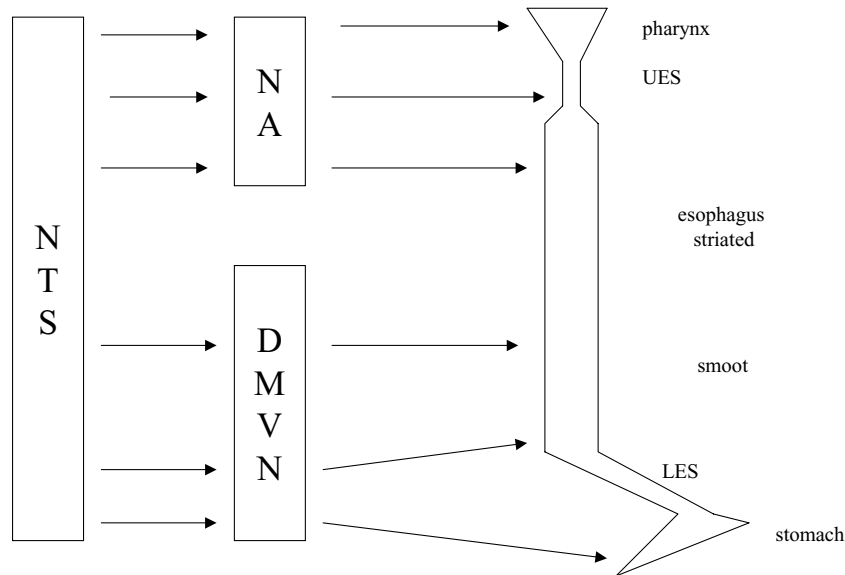


Figure 1. Schematic overview of brainstem control mechanism for swallowing demonstrating the dural levels of integration within the swallowing center in the medulla oblongata. NTS, nucleus tractus solitarius; NA, nucleus ambiguus; DMVN, dorsal motor nucleus of vagus; UES, upper esophageal sphincter; LES, lower esophageal sphincter.

these data implicate that the basal ganglia might play an essential part in the motor control of oromotor behaviors.

Lower and Upper Esophageal Sphincter

Ischemic brain tissue damage in the medullar brainstem (including the NA) is associated with decreased tone of the lower esophageal sphincter (LES) and increased tone of the upper esophageal sphincter (UES) (6). These neurons are normally tonically active and are inhibited first and then activated forcefully as part of the programmed swallow sequence (56, 57). They are likely to receive input from the primary motor cortex together with the motor neurons to the pharynx and striated muscle esophagus, and they can be activated by a direct paucisynaptic pathway from the cortex and via stimulation of the vagus or other cranial nerves (40, 48, 58). Furthermore, the UES tone decreases during sleep (when cortical drive is reduced) in the relative absence of swallowing (56), suggesting that swallowing neurons of lower level brain circuitry such as the dorsal medullary regions are involved. Therefore, other inputs to these neurons can apparently operate independently of the swallowing central pattern generator (59) and distribute the swallowing excitation to the various motoneuron pools involved in swallowing. The absence of the normal swallow-induced relaxation and contraction of the UES, along with the absence of contraction in the adjacent pharyngeal and esophageal striated muscle, is consistent with ischemic damage primarily to the second (ventral) level of organization in the medullar brainstem that acts as a connecting pathway to the NA neurons serving these regions during the sequence of swallowing (60).

Motor neurons to the smooth muscles of the esophagus, including the LES, are located in two subregions of the DMV. This nucleus lies in the central gray matter of the medulla and is lateral to hypoglossus nerve and

dorsal to the NA (61). Experimental evidence from LES studies suggests that the rostral region contains neurons that mediate excitation and that the caudal region neurons mediate inhibition of the esophagus (62). The documentation of coordinated activity of the smooth muscle esophagus and LES in patients with stroke indicates that the motor nucleus for this region (DMV), its connections to the brainstem circuitry that controls the entire ordered sequence of swallowing (NTS and neighboring reticular formation), and this circuitry itself are largely intact and functional (6, 55, 63).

Detailed information regarding the effect of ischemic stroke on esophageal peristaltic function is rather limited. The one or two available studies on this topic reports a higher number of non-peristaltic esophageal contractions in four of nine hemiplegic patients with or without dysphagia demonstrating a possible functional relevance in unilateral supratentorial stroke (64). Manometry, performed at variable intervals from the onset of stroke (4–47 days) (64), demonstrates that abnormal elevation of UES pressure remains. The other study revealed significant peristaltic dysfunction during the early phase of stroke in a selected subgroup of patients without clinical evidence of oro-pharyngeal dysfunction (65).

Clinical Implications

Since the risk for aspiration pneumonia is linked to dysphagia (66), an accurate evaluation of swallowing ability is a prerequisite for the care of patients after ischemic stroke. This is more important as outcome for persons who survive acute ischemic stroke depend largely on whether subsequent further stroke or pneumonia develops (67). For this reason straightforward techniques that can accurately evaluate swallowing ability are needed. Various techniques have been developed, although most screening tests for dysphagia evaluate

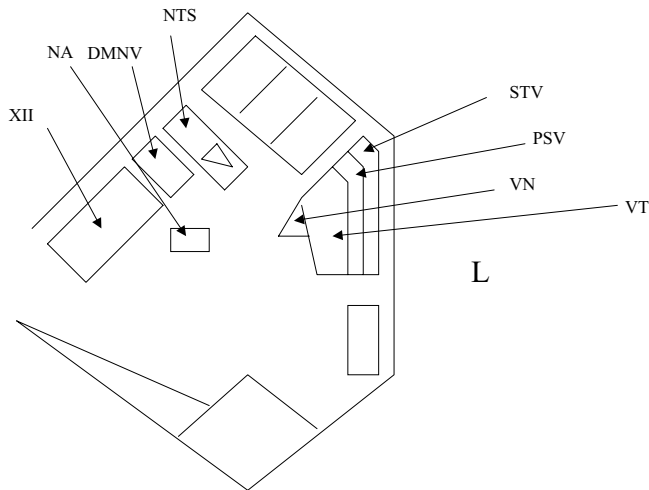


Figure 2. Schematic cross-section of the left human medulla oblongata projecting to the motor divisions of the V, VII, XII cranial nerve nuclei. Dorsal medullary inputs to the motor division of the V, VII, and XII cranial nerves arise primarily from the dorsal medullary reticular column immediately ventral to the nucleus of the solitary tract. Projections from the dorsal medullary reticular column are distributed preferentially to the ventral subdivisions of motor division of the V cranial nerve, to the dorsal and intermediate subdivisions of the VII cranial nerve, and to both the dorsal and the ventral subdivisions of the XII cranial nerve. A subpopulation of large multipolar neurons in the dorsal medullary reticular column gives rises to a primarily crossed input to the dorsal subdivisions of the motor division of the V cranial nerve. In contrast, dorsal medullary inputs to the nucleus ambiguus arise from the nucleus tractus solitarius, are primarily uncrossed, and are organized such that the ventrolateral, intermediate, and intestinal subdivisions of the nucleus tractus solitarius project to the region of the loose and semicompact formations, whereas the central subdivisions of the nucleus tractus solitarius. NTS, nucleus tractus solitarius; NA, nucleus ambiguus; DMNV, dorsal motor nucleus of vagus; VN, trigeminal nucleus; VT, trigeminal tract; NA, nucleus ambiguus; STV, spinal tract of the trigeminal nucleus; L, left; R, right.

the ability to swallow water. However, some tests fail to identify mild dysphagia or subclinical aspiration. To overcome the problems of conventional methods, Smithard *et al.* (68) evaluated a bedside test to assess swallowing ability. This test consists of two stages, can be performed easily at the bedside, and measured swallowing ability at multiple time points.

CLINICAL IMPACT IN THE LIGHT OF CORTICAL REORGANIZATION

It is recognized that as many of patients with dysphagia after unilateral hemispheric stroke, show degrees of spontaneous recovery within the first few weeks after the onset stroke (11, 69). Conversely, the recovery process from dysphagia in lateral medullary infarction is rather slow, although steady (70). The mechanisms for this recovery remain obscure. In a detailed study using TMS, both dysphagic and non-dysphagic patients were serially mapped over several months after ischemic stroke while swallowing recovered (5). These findings

demonstrated that the area of pharyngeal representation in the undamaged hemisphere increased markedly in patients who recovered, while there was no change in patients who had persistent dysphagia or in patients who were nondysphagic (5). No changes were seen in the damaged hemisphere in any of the subgroups (5). These observations imply that, over a period of weeks, the recovery of swallowing after stroke depends on compensatory reorganization in functionally undamaged brain areas. The situation appears not to differ substantially from that for the limb muscles, where some TMS studies have indicated that limb recovery after hemiparesis is likely to result from an increased recovery potential in the functionally undamaged areas of the affected hemisphere, including the penumbra (71). This reorganization of swallowing areas and the improvement of dysphagia often occur independent of the recovery of any associated hemiparesis (72) and is not interrelated with functional changes within the brainstem.

Techniques for treating dysphagia have been described involving either direct or indirect strategies. The latter includes stimulation of oral and pharyngeal structures. However, different swallowing therapies, involving diet modification or facilitatory swallowing techniques have been tried albeit with inconclusive evidence (73). Facilitatory techniques rely on the use of oro-pharyngeal sensory stimulation. In addition, it has recently been suggested that thermo-chemical modification of fluid consistency alters swallowing behavior after stroke (74).

GI HEMORRHAGE

The pathogenesis of upper GI tract hemorrhage after stroke is not entirely understood. After acute ischemic brain damage, so-called stress ulcers may develop from what is believed to be vagal hyperactivity resulting in increased gastric acid secretion or from mucosal ischemia (75). This is in line with the findings that upper GI tract hemorrhage after stroke is more common in undernourished patients (76), which are reported with a frequency of 8–34% after stroke (77). The increased incidence of upper GI tract hemorrhage in this subpopulation (in the absence of pharmacological factors, *e.g.*, acetylsalicylic acid (ASA)) might have several causes: pre-existing GI disease (*e.g.*, peptic ulceration) that predisposes to undernutrition and hemorrhage, impaired healing of potential hemorrhagic lesions, and adverse effects of enteral tubes inserted to support nutrition (76). However, erosive or hemorrhagic gastritis with upper GI tract hemorrhage occurs also after stroke (78). Wijdicks *et al.* (78) documented a potential trigger other than stress for upper GI tract hemorrhage in the majority of patients with stroke. This finding suggests that stress from acute ischemic brain damage may in fact be quite infrequent or perhaps may act as an additive risk factor in patients with other predispositions for upper GI tract hemorrhage. It seems that delayed gastric emptying (gastroparesis) and malnutrition may play a major role in upper GI tract hemorrhage in stroke (76, 78). However, in a retrospective analysis of 16,672 patients with stroke, history

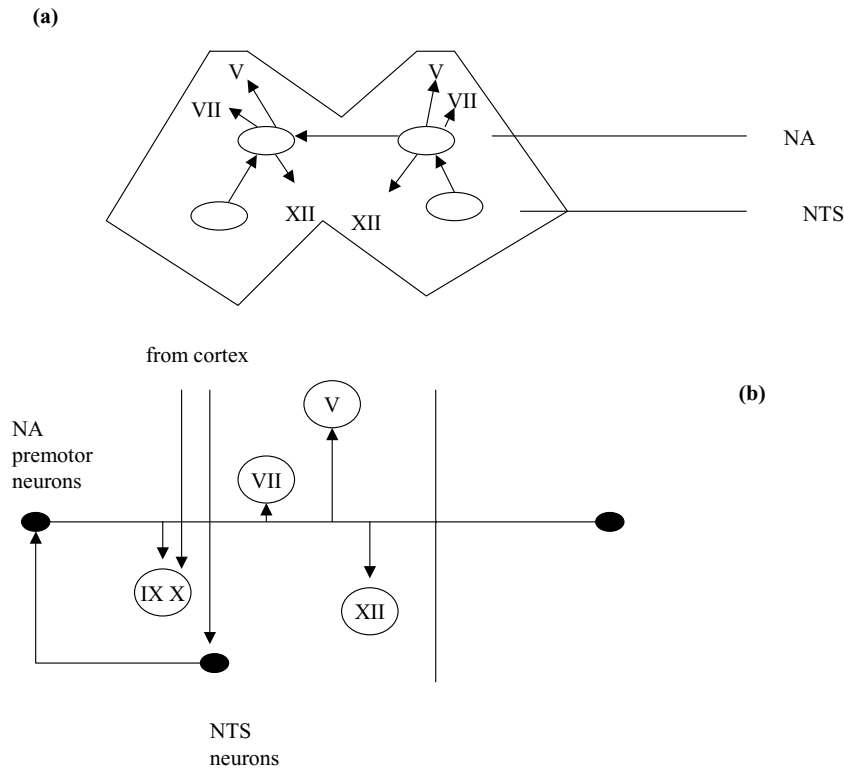


Figure 3. Schematic cross section of the medulla oblongata, pointing out swallowing-associated connectivity. *Top*, area affected by brainstem area with swallowing difficulties after ischemic stroke and the involvement of nucleus tractus solitarius and the nucleus ambiguus. *Bottom*, schematic representation of premotor neurons and their ipsilateral connections to V, VII, IX, X, and XII cranial motor neuron pools and the contralateral swallowing center. NTS, nucleus tractus solitarius; NA, nucleus ambiguus.

of non-steroidal anti-inflammatory drugs (without cytoprotection), aspirin, corticosteroid therapy, and *Helicobacter pylori* infection were found to be contributing to upper GI tract hemorrhage (78).

Clinical Implications

Upper GI tract hemorrhage has been reported to be low and usually does not contribute to increased morbidity and mortality in patients with stroke (78–80). In a prospective study, upper GI tract hemorrhage was noted in 0.1% of patients with stroke (79). In another study, patients with severe stroke, especially those with Glasgow Coma Scale score below 10 demonstrated a higher frequency of GI hemorrhage (80).

ASA is a very useful medication for the prevention of cerebrovascular thrombotic event in patients with or those at risk for cerebrovascular disease. ASA, however, carries an increased risk for GI injury (e.g., ulceration) and its complication (e.g., hemorrhage), which may be caused by its antiplatelet and gastric mucosal effects. Secondary prevention refers the use of ASA to prevent cerebrovascular events in patients with established cerebrovascular disease. The risk for GI hemorrhage with ASA is at least additive to the risk associated with stroke alone (81). Patients being treated with ASA after stroke should be assessed for factors that increase the risk for GI hemorrhage. Studies have confirmed that cotherapy with a proton pump inhibitor

(PPI) or misoprostol decreases the risk for GI injury and complications under these conditions (81). Three of the currently available PPIs are manufactured as capsules containing enteric-coated granules that may be mixed with soft foods or fruit juices before oral administration to those with swallowing difficulties. In addition, omeprazole and lansoprazole may be administered via gastrostomy or nasogastric feeding tubes as suspensions in sodium bicarbonate. Novel dosage formulations of lansoprazole that may be appropriate for patients with dysphagia include the commercially manufactured lansoprazole strawberry-flavored enteric-coated granules for suspension and lansoprazole orally disintegrating tablets.

GASTRIC EMPTYING

The receptive relaxation reflex is an important mechanism that increases gastric volume and reduces intragastric pressure to ensure that swallowed food is efficiently transported from esophagus to stomach (82, 83). A number of investigators have shown that this potent proximal gastric relaxation is triggered by the activation of low-threshold vagal afferent mechanosensors in the esophagus (83). The reflex requires intact vago-vagal connections between the esophagus, brainstem, and stomach (82). Several anatomical tracing studies have demonstrated that vagal afferent projections from the

esophagus terminate in and near the central division of the NTS. Previous studies have shown that neurons in the NTS are intensively activated by low-level esophageal distension (82). The relationship between the NTS and the vagal motor neurons that control the stomach has only recently been addressed. Physiologically guided nanoinjections of retrograde and anterograde tracer onto NTS neurons that respond to esophageal distension demonstrate that these neurons project heavily throughout the full anterior-posterior extent of the DMV and present the primary source of pre-ganglionic autonomic control over the stomach (82). Vagal reflex control over gastric tone and motility is affected by modulating the activity of two antagonistic vagal efferent projections. Vagal efferent-mediated increases in gastric tonic and motility occur after the activation of cholinergic neurons in the gastric enteric plexus by loosely aggregated pre-ganglionic neurons in the DMV (82). Conversely, rapid gastroinhibition can result from the inhibition of these DMV neurons. Indeed, it is well-known that intestinal, gastric, and esophageal distension causes an abrupt cessation in the tonic firing of DMV neurons coinciding with the rapid onset of a reduction in gastric and esophageal distension-sensitive afferent fibers and can also produce a potent GI inhibition through the activation of a vagal, noradrenergic, non-cholinergic pathway to the fundus (83). Little is known about the mechanisms by which NTS neurons produce changes in DMV neurons that result in the receptive relaxation reflex. The NTS area contains a number of different neuronal phenotypes. Two neurochemical phenotypes that are especially prominent are noradrenergic and nitrergic (84). The core of the NTS contains an especially dense concentration of nitric oxidative synthase neurons, whereas tyrosine hydroxylase-immunoreactive neurons are found throughout the NTS. Of particular interest is the subset of tyrosine hydroxylase-immunoreactive neurons found encircling the NTS-nitric oxidase synthase neurons. Previous immunohistochemical studies have shown that virtually all of these tyrosine hydroxylase-containing neurons near the NTS tract also express dopamine β -hydroxylase and are therefore, norepinephrine-producing neurons (85).

Only few reports deal with the specific topic of altered gastric or upper GI tract emptying in stroke. Data from Crome *et al.* demonstrate a delayed drug resorption of orally administered drugs after stroke and point out that gastric emptying appears to be delayed (14). Further important consequences of this GI effect of stroke include intolerance to enteral nutrition and increased incidence of gastric colonization of *H. pylori* as a consequence of this delayed gastric emptying (86). Taking these findings together, the oral route administration of drugs may be unreliable in patients with stroke as a consequence of this delayed gastric emptying (14). It may also reduce the therapeutic benefit of drugs whose activity depends on a short time to maximum plasma concentrations (87). As a consequence of this altered gastric emptying, some believe naso-post-pyloric tube to be tolerated better than nasogastric tubes. Until further studies in stroke patients are performed to define the prevalence and factors that influence delay in

gastric emptying, careful consideration should be given to methods of food delivery in these patients.

SMALL AND LARGE BOWEL DYSFUNCTION

The small intestine is richly supplied with sensory fibers (88). Vagal and spinal afferent nerves to the central nervous system carry information from activated sensory receptors. The extrinsic supply is divided into efferent and afferent categories with information carried in parasympathetic and sympathetic nerve tracts, provided by the vagus and the splanchnic nerves. Most efferent parasympathetic and sympathetic fibers terminate in the myenteric plexus and form connections in enteric ganglia, although some sympathetic axons terminate directly on sphincteric smooth muscles. Efferent vagal supply is maximal to the upper gut, including the proximal colon. The cell bodies of these efferent nerves reside predominantly in DMV in the brainstem. The vagal nerves contain three groups of efferent fibers:

- Pre-ganglionic parasympathetic cholinergic nerves, which supply excitatory neurons in the enteric plexi.
- Pre-ganglionic cholinergic nerves, which supply inhibitory neurons in the myenteric plexus.
- Sympathetics from the cervical ganglia.

Stimulation of efferent vagal cholinergic neurons principally activates nicotinic receptors within enteric ganglia, exciting motor activity. In humans, the enteric nervous system contains up to 100 million neurons, compared with only 2,000 efferent fibers in the vagus, suggesting that the intrinsic nerves may direct most reflexes and control activities and that the extrinsic innervations may serve only as modulatory function. Typically, frequent long and short non-propagated bursts of phasic pressure activity occur in the jejunum with reduced frequency and amplitude of contractions in both the fasting and fed phases (89). This phenomenon of long and short burst has been attributed to sympathetic denervation, and the composite intestinal motility pattern in the fasting phase is considered to represent dysfunction of both sympathetic and parasympathetic supply.

In most patients with ischemic stroke, colorectal dysfunction is caused by a combination of lesions of the central or peripheral nervous system, immobility, or altered dietary habits. Even so the exact mechanism of constipation in patients with stroke needs to be studied, it has been suggested that disruption of the neuronal modulation of colonic motility may play an important role (90). Colonic transit time is prolonged, especially in the right colon (69). Prokinetic drugs, previously reported as a promising mode of treatment in functional fecal retention, have recently been demonstrated to have poor effect on the delay of colonic transit associated with brain damage, in whom severe damage to central structures may be responsible for dysregulation of the progression of normal contents through the large bowel (90). The mechanism of the intestinal pseudo-obstruction in stroke is unclear, whether

they result from defective enteric neurons, smooth muscles, or both, will require further research.

PHYSIOLOGICAL AGING AND GI TRACT

Careful attention must be given to aging phenomena since many comorbid conditions that can alter physiological functioning of the GI tract after brain disease are also observed in older patients (3, 15, 91, 92). Age-related changes in GI functioning can be categorized in terms of those associated with comorbid conditions of aging or those associated with the aging process itself (93, 94). Identifying GI changes that occur exclusively as a function of aging, independent of comorbid conditions, has proven to be a difficult task. The common occurrence of comorbid conditions renders that available population to a fairly small group, and the invasive character of most studies evaluating GI changes also creates limitations in recruiting volunteers to participate in such studies (93). Moreover, the issues of different methodologies and techniques used to assess GI motility yielding numerous studies with conflicting results are not surprising. It seems reasonable to summarize that there are major sphincteric changes in aging related to decrease in the UES and sphincteric protective reflexes, alteration in LES functioning, and anal canal pressures. In addition, sensory functioning and visceral perception remains an important, but often overlooked component of GI functioning that appears to be significantly diminished with age. From these points of views, GI changes associated with age are relatively subtle. They seem to predispose aged individuals to further significant impairment in swallowing or defecation when stroke and/or medication effects are superimposed. As the older adult population increases, and as the control of disease is improved, much work needs to be done to fully understand the effects of aging on GI functioning.

IMPLICATIONS ON TREATMENT AND PROGNOSIS

Stroke is the most common disease underlying aspiration pneumonia. The mortality rate from aspiration pneumonia is particularly high during the acute phase of stroke. In elderly patients in the chronic phase of stroke, the risk for death from aspiration pneumonia remains high. Aspiration with the possible consequence of aspiration pneumonia is the most important acute complication of dysphagia affecting up to one-third of dysphagic patients. For this reason, swallowing difficulties substantially influence outcome, especially in elderly persons, after stroke (67) and represent a marker of poor prognosis, increasing the risk of chest infiltration, malnutrition, persistent disability, prolonged hospital stay, institutionalization on discharge, or mortality (95).

Swallow recovers in many patients within 2–4 wk following stroke onset (95). Thus, a proper diagnostic assessment and early start to rehabilitative efforts (including tube feeding) is usually recommended. Such a process requires the use of a valid screening tool. The use of gag reflex function alone

cannot be supported but may have a place as a component of or in association with a validated tool (96). The presence of clinical dysphagia indicates an increased risk of lower respiratory tract infection, but the absence of dysphagia does not rule it out. Aspiration seen on videofluoroscopic swallowing studies (VSS) probably also confers increased risk, although this is not a universal finding. Further exploration of the relationship between aspiration and pneumonia is therefore needed. VSS is regarded as the gold standard dysphagia diagnostic tool, but it is limited by its physical requirements and is sometimes hampered by the non-standard manner in which it is carried out and its uncertain relationship to meal-time eating. There is plenty of room for further development and alternative diagnostic procedures.

While screening is the essential first step, the importance of management is highlighted by development of low respiratory tract infection in dysphagic aspirating patients maintained with no oral intake. The tube feeding may be an effective way of supplying nutrition in these patients but its safety in terms of preventing aspiration is somewhat controversial. As with nasogastric tubes, gastrostomy tube does not offer protection from colonized oral secretions and are known to increase gastro-esophageal reflux. Thus, with the exception of a study by Norton *et al.* (97) others have found similar aspiration rates with gastrostomy and nasogastric tubes.

Therapeutics Aspects to the Future

It is best established that sensory input is crucial to the initiation and modulation of normal swallowing, this perhaps being best demonstrated by clinical studies with surface anesthesia of the oropharynx which produces dysphagia in healthy human subjects (98). These observations therefore indicate that sensory afferent input plays a role in the modulation of swallowing rather than being an absolute prerequisite. Of clinical relevance to these observations, it has been recently shown that sensory stimulation of the pharynx in patients with dysphagia following stroke can lead to an increase in the excitability of the swallowing motor cortex in the unaffected hemisphere, which importantly is associated with a functional improvement in swallowing performance (99).

A recent study demonstrated that repetitive transcranial magnetic stimulation (rTMS) over swallowing motor cortex induces a long-term effect on the excitability of the corticobulbar projections to the pharynx that is both frequency and muscle specific (100). This effect is similar to that produced by pharyngeal electrical stimulation (99, 101). One implication, therefore, subject to appropriate safety studies, is that rTMS may be an alternative method of cortical enhancement in dysphagic stroke patients when a sensory system has been damaged. The neural mechanisms of long-term effect of rTMS on human cortex are still unclear.

CONCLUSION

Swallowing and GI motility depend upon a coordinated interplay of voluntary and involuntary neuromuscular activity.

Ischemic stroke may disrupt neural modulation of oropharyngeal and/or GI motility by interrupting or altering the flow of information from the cortex to the lower regulating centers. Currently, attempts to relate the site and the size of focal cerebral lesions to the various GI dysfunctions are being performed employing new PET and MRI technologies. These imaging modalities may help to define more precisely the functionally important brain regions which are involved in the control of GI functions in animal models of focal ischemia as well as in patients with ischemic stroke. Besides the exact physiological mechanisms of swallowing, exact cortical and medullar localization of the different areas involved and the question of lateralization of this reflex remains yet a matter of debate, as there exist no detailed studies. Altered incidence or pathophysiology of GI hemorrhage or GI emptying after stroke compared to other diseases have to be investigated with special reference to changes in pharmacodynamics and pharmacokinetics. In future, brain and molecular imaging technology may help in defining new therapeutic strategies, which aim to achieve early functional improvements with neurorehabilitation and neuronal reorganization after cerebral ischemia.

ACKNOWLEDGMENT

The authors thank Dr. Shaheen Hamdy (MRC Clinician Scientist/Honorary Consultant Physician/Lecturer in GI Science, Department of GI Sciences, Hope Hospital, Salford, UK) for his extraordinary helpful advice in preparing this manuscript and his generous support.

Role of the funding source: None of the funding sources were involved in the writing of this review or the decision to submit it for publication.

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Received February 24, 2005; accepted October 31, 2005.

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