Aging and Neural Control of the GI Tract II. Neural control of the aging gut: can an old dog learn new tricks?

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Hall, Karen E. Aging and Neural Control of the GI Tract. II. Neural control of the aging gut: can an old dog learn new tricks? Am J Physiol Gastrointest Liver Physiol 283: G827–G832, 2002. First published May 29, 2002; 10.1152/ajpgi.00162.2002.—There has been a dramatic increase in funding available for aging research, primarily due to the fact that answers to questions on aging are likely to have a major impact on the well-being and healthy aging of the world’s population for decades to come. The incidence of certain gastrointestinal problems, such as dysphagia and constipation, increases dramatically with age. Changes in gastrointestinal neuromuscular function with aging have been demonstrated in both human and animal models of aging. This article focuses on recent advances in our knowledge of the effects of aging on gastrointestinal function, treatment options, and future opportunities for research.

THE MORE THINGS CHANGE, THE MORE THEY STAY THE SAME

In the past decade, it has become clear that much of the gastrointestinal tract maintains youthful function well into the eighth and ninth decades of life. There is little difference between a 20 yr old and an 80 yr old in the quantity and quality of biliary, pancreatic, and intestinal secretions, in the absorptive capacity of the small intestine, and general nutritional requirements for height and weight (although percentage of body fat increases with age). There are some notable exceptions, however. The areas at greatest risk of developing aging-related dysfunction are the upper gastrointestinal tract, particularly the oropharynx and esophagus, and the distal tract (colon and rectum). In practical terms, swallowing and defecation are the two most likely functions to be affected by aging. This situation is exacerbated by superimposed neurological diseases, such as Parkinson’s disease or dementia, or by side effects of medications. A clinical point worth making is that impairment in sensory and myenteric neuronal function with aging may significantly diminish the acute response to gastrointestinal inflammation and/or perforation. Increased confusion and fatigue may be the only outward manifestation of an acute abdomen.
rather than the traditional signs of peritonitis, such as abdominal guarding or rigidity. The result is often a significant delay in diagnosis of acute abdomen in older patients. It has been estimated that up to two-thirds of initial emergency room diagnoses of abdominal problems in this age group are subsequently found to be incorrect. An increased awareness of these issues could improve diagnosis and treatment of gastrointestinal disease in older patients.

EFFECT OF AGING ON PERIPHERAL NERVE FUNCTION

Due to an explosion of interest and funding of geriatric research, there is a substantial literature concerning the effect of aging on the peripheral nervous system (PNS) (25). Anatomic changes include loss of myelinated and unmyelinated nerve fibers, demyelination, remyelination, and myelin balloon figures. Deterioration of the myelin sheath may be the result of decreased expression of major myelin proteins. Axonal atrophy has been correlated with a reduction in expression and axonal transport of cytoskeletal proteins in peripheral nerves. Generalized functional and electrophysiological changes with age include declining nerve conduction velocity, sensory discrimination, autonomic responses, and endoneurial blood flow. These age-related changes are often not linearly progressive with age and are observed most commonly in advanced senescence.

EFFECTS OF AGING ON GASTROINTESTINAL NEUROMUSCULAR ANATOMY AND FUNCTION

Integration of extrinsic innervation and intrinsic neuromuscular control is required for normal function of the gastrointestinal tract. Vagal innervation is lateralized and afferent terminal phenotype and/or target tissue selection occurs during embryonic development, and both are essentially complete by postnatal day 1 in the rat (18). Myenteric command neurons have been postulated to transmit vagal impulses to enteric microcircuits. However, ex vivo studies of guinea pig stomach with intact vagal innervation suggest that vagal input may be diffusely spread over the gastric plexus, rather than concentrated in a few neurons. Myenteric circuits are activated by extrinsic inputs or other stimulation promote motility via the specialized muscle cells, the interstitial cells of Cajal (ICC) (9). Electrical slow waves generated in the ICCs propagate into the smooth muscle and coordinate peristaltic activity. Smooth muscle contraction amplitude measured in vivo and in vitro is decreased with advanced age; however, relatively little is known about the effect of aging on ICC function. Abnormal intracellular calcium metabolism has been implicated in age-related impairment of gastrointestinal smooth muscle contraction. Both diminished sarcoplasmic release and impaired resequestration of cytoplasmic calcium ([Ca^{2+}]) has been described.

Significant effects of aging on gastric and colonic motility in rats include slow gastric emptying of liquids and decreased fecal pellet transit and production (24). There may be variable effects of aging in different animal models, because studies of aged cats (11 yr) do not demonstrate significant changes in gastric emptying compared with cats aged 3 yr (15). Another explanation for discrepant results may lie in the age ranges studied. There is an emerging consensus in aging research that aging-related changes are far more pronounced in extreme old age (corresponding to the "oldest-old" humans aged 85 or older). Corresponding animal ages in rats and cats would be 28 mo and 15 yr, respectively. Nitric oxide and neuronal calcium regulation play an important role in local control of motility by the myenteric plexus. Histochemical studies of distribution and colocalization of NADPH-diaphorase (a marker for nitric oxide) and the calcium-binding protein calretinin in human small intestine myenteric neurons demonstrate age-related changes in these molecules (1). Colocalization of both molecules was only observed in fetal neurons. In adult specimens, expression decreased to 50% of fetal levels, and reorganization of the neuronal subtypes was observed with calretinin-positive neurons surrounded by NADPH-positive neurons. In specimens from patients over age 65, the expression of both molecules increased two- to threefold over age 60.

EFFECT OF AGING ON NEUROMUSCULAR CONTROL OF SWALLOWING

Dysphagia, or difficulty swallowing, is a very common problem with aging. The problem is usually multifactorial (22). Poor dentition and decreased saliva production make chewing and preparation of the bolus difficult. Slow transfer of the food bolus to the posterior oropharynx, delayed closure of the larynx, delayed relaxation of the upper esophageal sphincter (UES) with food reflux into the larynx, and impaired transit of food through the esophagus have been described. Mylohyoid muscle contraction is an important initial step in swallowing. The timing is critical, because delay in laryngeal elevation may result in aspiration of the food bolus. Increased asynchronous contractions of the mylohyoid muscle and slowing of the contractile response during swallowing occur in healthy older patients. This is associated with an increase in the duration of the apneic period of epiglottal occlusion of the larynx. The net result is a significant increase in the risk of laryngeal pooling of liquids that may predispose to aspiration. Additional risks for inappropriate bolus transit include age-related thinning of the muscles that open the UES. This results in increased resistance to movement of the bolus past the UES (10), and food may be propelled into the larynx instead of the pharynx. When superimposed neuromuscular disease is also present in older patients, dysphagia is almost inevitable. Parkinson’s disease, amyotrophic lateral sclerosis, bulbar and pseudobulbar palsies, strokes, and dementia are all significant causes of severe dysphagia.

Although primary neurodegenerative disease is often irreversible, significant benefit can be obtained by training patients to perform maneuvers, such as a chin
tuck during swallowing, to protect the airway. UES musculature can be strengthened by repetitive head-raising (23). Thickening foods or using special utensils improves bolus transfer. Inserting a feeding tube directly into the stomach speeds up the process of eating, which may improve caloric intake. Feeding tubes are often inserted for ease of nursing; however, several studies confirm that they also significantly increase the risk of aspiration and subsequent pneumonia. European studies of supervised hand feeding indicate that this time-consuming technique does decrease the risk of aspiration and improves caloric intake. However, the intensive staff requirements for hand feeding make it an unappealing option in most long-term care settings. The dramatic increase in the number of individuals with dementia has brought the issue of feeding tubes into the public eye. Several recent studies and position statements have clarified the utility and risks of feeding tubes in dementia. Demented patients live an average of one year longer if fed via a tube, most likely due to improved caloric intake. This appears to be at the expense of quality of life, as feeding tubes were associated with an increased number of adverse outcomes including infection, aspiration, and invasive medical intervention.

Achalasia is an important cause of dysphagia in advanced age. There is a female preponderance, with progressive dysphagia of both solids and liquids. Barium studies of the esophagus and upper stomach demonstrate a smooth narrowing of the lower esophageal sphincter (LES) to a “bird’s beak,” caused by uninhibited contraction of the LES. Because of the high incidence of malignancy in this age group, endoscopy should always be performed as part of the investigation. Although pharmacological treatment with smooth muscle relaxants such as nitroglycerin, calcium channel antagonists, anticholinergic agents, and sildenafil have been used, they are less effective than pneumatic balloon dilation. Other treatments used in an attempt to avoid the risk of perforation and acid reflux caused by balloon dilation include injection of the LES with botulinum toxin injection and laparoscopic myotomy.

EFFECT OF AGING ON COLONIC FUNCTION

Constipation, defined as infrequent, hard, and/or painful defecation, is very common in Western countries. This is likely due, in part, to a decrease in fiber intake, but an additional major contribution is the slowing of colonic motility caused by aging-related impairment in enteric neuromuscular function. Decreased neuronal number and increased fibrosis (6) may explain slow colonic transit and increased tendency to mucosal herniation (diverticulosis) observed in older patients. Both human and animal studies confirm that intraluminal colonic pressure increases with age, possibly as a result of a shift in the character of contractions from peristaltic to nonperistaltic. Interestingly, fiber supplementation decreases intraluminal pressure. Animal studies suggest that fiber may also decrease the incidence of nonperistaltic contractions. Smooth muscle calcium release from intracellular storage pools is diminished and reuptake is impaired, leading to prolonged, lower-amplitude colonic contractions in animal models of aging. Similar findings are observed in normal colonic tissue obtained from aged individuals undergoing surgery for colon cancer.

These physiological changes also predispose older individuals to experience significant complications from other superimposed conditions that impair cholinergic transmission or result in metabolic abnormalities that impact motility. Insidious onset of constipation due to thyroid disease, hypercalcemia, hypoglycemia, and other metabolic conditions should be considered. Medications are a particularly common cause of new-onset constipation in older patients. Culprits include drugs with anticholinergic side effects, such as neuroleptics, antihistamines, anti-Parkinsonian medications, and tricyclic antidepressants (Table 1). Drugs that impair calcium signaling, such as calcium channel antagonists used to treat hypertension, can also result in significant constipation. Aged patients are very sensitive to the inhibitory effects of opiates on motility, and this problem should be anticipated when opiates need to be prescribed. Diminished activity due to arthritis and impaired mobility also makes a significant contribution in many patients. Most bedridden patients are constipated and need aggressive monitoring and management to avoid developing impaction.

Given the increased risks of colon cancer in older patients, recommendations for investigation and treatment are primarily based on the duration of symptoms, the age of the patient, and whether surveillance endoscopy has been performed. In the face of age-associated impairment in neuromuscular control of colonic motility, many older patients may require a cleansing enema to remove hard stool and a stimulant laxative, such as milk of magnesia or stronger products, to maintain regular movements.

A common problem in older patients, particularly women, is a pattern of diarrhea, or diarrhea alternating with constipation, suggestive of irritable bowel syndrome (2). As in younger patients, no serious underlying condition can be documented to explain the symptoms, and treatment consists of symptomatic control. At least 60% of patients with this problem present for the first time in later life. Symptomatic treatment with antidiarrheal medications and soluble fiber are

Table 1. Examples of medications that cause constipation (the “antis”)

<table>
<thead>
<tr>
<th>Anticonvulsants:</th>
<th>phenytoin, carbamazepine, phenobarbital</th>
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</thead>
<tbody>
<tr>
<td>Antidepressants:</td>
<td>amitriptyline, nortriptyline, venlafaxine</td>
</tr>
<tr>
<td>Antihistamines:</td>
<td>diphenhydramine (Dramamine), chlorpheniramine</td>
</tr>
<tr>
<td>Antihypertensives:</td>
<td>acebutolol, prazosin, amiodipine</td>
</tr>
<tr>
<td>Antilipemics:</td>
<td>cholestyramine, colestipol</td>
</tr>
<tr>
<td>Antipsychotics:</td>
<td>haloperidol, risperidone</td>
</tr>
<tr>
<td>Antacids:</td>
<td>aluminum-containing (i.e., Amphojel), sucralfate</td>
</tr>
<tr>
<td>Antispasmodics:</td>
<td>codeine, morphine, hydrocodone</td>
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Animal studies demonstrate a significant decrease in the human colon and anal sphincter (6). Internal anal sphincter thickness increases, possibly as a compensatory response to an age-related thinning of the external anal sphincter (14, 19). Women are at particular risk for age-associated anal sphincter dysfunction due to a combination of several factors. These include pelvic floor laxity, decreased rectal pressure (likely due to weakening of muscular con traction), and increased latency of pudendal nerve firing. Interestingly, some of these problems have been attributed to multiparity and/or menopause. In a study of women aged 20–83 yr, Ryhammer et al. (20) reported that the effect of aging on anal function was more important than parity in uncomplicated deliveries. Gradual impairment with aging was observed in both pre- and postmenopausal women, suggesting that aging has a gradual and progressive effect on anal function in normal aging.

**EFFECT OF AGE ON ANAL SPHINCTER FUNCTION**

Significant effects of aging have been described for both extrinsic and intrinsic innervation of the distal gastrointestinal tract with advanced age (17). Calcitonin gene-related peptide (CGRP) increases and maintains acetylcholine receptor expression and acetylcholinesterase production at the rat neuromuscular junction. Age-related slowing of CGRP transport in sciatic neurons occurs in rat models (4) and likely contributes to the sarcopenia and slow contraction of skeletal muscle observed with aging. A similar decrease in CGRP delivery to the small bowel and colon (presumably from sensory neurons) has also been documented in mesenteric arteries of aged rats (12). There is other evidence that aging results in decreased trophic or protective responses mediated by sensory nerves. The hyperemic response of intestinal mucosa to capsaicin and hydrochloric acid is significantly blunted in aged rats, compared with youthful animals (21). Diminished sensory input, rather than changes in arteriolar caliber, appears to underlie this phenomenon. Impaired or diminished sensory innervation may be relatively less important in the small bowel. Despite significant changes at the myenteric molecular level, small bowel motility and secretion is relatively unaffected by aging in both human and animal models.

**TROPHIC ACTIONS OF EXTRINSIC INNERVATION DIMINISHED IN AGING**

Sensory innervation of target tissues, such as skeletal muscle, smooth muscle, and skin, has been identified as an important factor in maintaining structural integrity and function. Extrinsic innervation of the gut appears to exert a trophic effect on myenteric survival. Animal studies demonstrate a significant decrease in both extrinsic and intrinsic innervation of the distal gastrointestinal tract with advanced age (17). Calcitonin gene-related peptide (CGRP) increases and maintains acetylcholine receptor expression and acetylcholinesterase production at the rat neuromuscular junction. Age-related slowing of CGRP transport in sciatic neurons occurs in rat models (4) and likely contributes to the sarcopenia and slow contraction of skeletal muscle observed with aging. A similar decrease in CGRP delivery to the small bowel and colon (presumably from sensory neurons) has also been documented in mesenteric arteries of aged rats (12). There is other evidence that aging results in decreased trophic or protective responses mediated by sensory nerves. The hyperemic response of intestinal mucosa to capsaicin and hydrochloric acid is significantly blunted in aged rats, compared with youthful animals (21). Diminished sensory input, rather than changes in arteriolar caliber, appears to underlie this phenomenon. Impaired or diminished sensory innervation may be relatively less important in the small bowel. Despite significant changes at the myenteric molecular level, small bowel motility and secretion is relatively unaffected by aging in both human and animal models.

**NEURONAL INJURY AND REGENERATION**

Aged subjects demonstrate impairment in nerve regeneration after injury (25). Wallerian degeneration is delayed in aged animals, as is the interaction between Schwann cells and regenerative axons. This results in slow axonal regeneration and decreased axon density. Terminal and collateral sprouting of regenerated fibers is limited and/or delayed, which impacts target reinnervation and restitution of function (11). In studies of vagal nerve axotomy, similar degenerative changes of vagal nerve endings in the gut wall were observed. Recovery and reinnervation of the lumen was delayed in aged animals, with significantly fewer new terminals present by 4 mo (20 vs. 38%). An important stimulus to reinnervation is secretion of neurotrophic factors by the target tissue. The quantity of trophic factors secreted by Schwann cells and target organs are diminished in older subjects, an observation that has fueled interest in the potential role of neurotrophin delivery as a treatment for aging-related neurodegeneration.

**CAN THE OLD DOG LEARN NEW TRICKS?**

Neurotrophin-mediated regeneration and growth. Promising advances have been made in the field of neuronal regeneration in adult life. The assumption that adult neurons cannot divide has been refuted by studies demonstrating new neuron development in the central nervous system (CNS). There is strong evidence that increased delivery of neurotrophic factors such as NGF, brain-derived NGF (BDNF), neurotrophin-3, glial-derived NGF, and IGF-I to injured neurons is beneficial to both CNS and PNS neurons. Improved axonal regeneration and neurite outgrowth have been demonstrated in a large number of different models of neuronal injury and neurodegeneration. The ability to respond to neurotrophin treatment may be specific to certain neuronal subtypes, however, because trophic effects on sensory and sympathetic innervation were not observed in the iris of aged rats treated with NGF (5). It is also likely that these trophic substances vary significantly in their efficacy. Overexpression of IGF-I by use of a adenoviral vector does not appear to improve remyelination in some models of CNS injury in aging (13), whereas delivery of NGF or BDNF using similar techniques is highly efficacious. Cell adhesion factors may also play an important role in aged neuronal responses, because transfection of integrin into aged neurons has also been shown to improve regeneration in CNS injury models (3). Overall, these studies suggest that neurotrophin pathways may be a useful target for intervention in treating age-associated neuronal degeneration in both the CNS and PNS.

**Neuronal transplant.** The consensus of results from studies of neuronal transplantation in the PNS and CNS indicate that transplanting tissue from young animals into old animals results in substantially greater neuronal survival and growth than the converse (old tissue into young animals) or old tissue into old animals. Treatment with neurotrophins can improve survival of sensory neurons from old animals in uncomplicated deliveries. Gradual impairment with aging was observed in both pre- and postmenopausal women, suggesting that aging has a gradual and progressive effect on anal function in normal aging.
transplantation studies, as well as in vitro (7); however, the results usually fall short of those achieved using young or fetal tissue. There are significant changes in the level of neurotrophin receptor expression on sensory and sympathetic neurons with age, with many but not all studies indicating a decrease in the high-affinity tyrosine receptor kinase A NGF receptor. It is unclear what the relative importance of p75 receptor stimulation is in aged models, because both increased and decreased neuronal expression of the p75 receptor have been documented. At present, it is not clear whether similar benefits of neurotrophin delivery can occur in the gastrointestinal tract, because studies of gastrointestinal neuronal injury, such as reinnervation after selective vagotomy, have been performed primarily in young animals (16).

**Stem cells.** Embryonic stem cells have a pluripotent ability to differentiate into a variety of cell lineages in vitro. An exciting recent development that may have tremendous implications for restoration of normal gastrointestinal neuromuscular coordination is the report of a functional gut-like unit formed in vitro from embryonic stem cells (26). Several differentiated features of gastrointestinal tissue were observed, including specialization of inner epithelial cells and development of cells immunoreactive for e-Kit (a marker of ICCs). The outer smooth muscle layer exhibited organized electrical slow waves and peristalsis. Cells that were positive for PG9.5 and resembled enteric neurons were located in clusters suggestive of myenteric ganglia. Thus, this model appears to generate the major neuromuscular cell subtypes necessary for integrated gastrointestinal function.

**NEW TARGETS: UNRAVELING THE METABOLIC PATHWAYS**

Several mechanisms have been implicated in the development of neural injury, including abnormal calcium metabolism, impaired mitochondrial function, and oxidant damage (8). Future studies will need to address the apparent paradox of the same signal transduction pathway being both pro- and antiapoptotic in different study designs or animal models. Our present understanding of the mechanisms underlying control of apoptotic neuronal death is based primarily on studies utilizing immortalized cell lines. These cell lines can demonstrate significant differences compared with primary neurons in both the activity and specificity of metabolic pathways implicated in neuronal injury and death. Whether it is possible to extrapolate studies in cell lines to aging is also controversial. The use of short-term culture of aged neurons may allow study of molecular pathways involved in aging, but significant issues concerning the effect of culture on metabolism still remain. Gastrointestinal neuronal survival and function appear to be relatively protected until the last 20% of lifespan, at which time a rapid deterioration occurs, particularly in the upper and distal tract. This appears to predispose aged individuals to further significant impairment in swallowing or defecation when disease or medication effects are superimposed.

**REFERENCES**


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