

# The Aging Colon: The Role of Enteric Neurodegeneration in Constipation

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**Abstract** Constipation is a common problem in the elderly, and abnormalities in the neural innervation of the colon play a significant role in abnormalities in colonic motility leading to delayed colonic transit. The scope of this review encompasses the latest advances to enhance our understanding of the aging colon with emphasis on enteric neurodegeneration, considered a likely cause for the development of constipation in the aging gut in animal models. Neural innervation of the colon and the effects of aging on intrinsic and extrinsic nerves innervating the colonic smooth muscle is discussed. Evidence supporting the concept that neurologic disorders, such as Parkinson's disease, not only affect the brain but also cause neurodegeneration within the enteric nervous system leading to colonic dysmotility is presented. Further research is needed to investigate the influence of aging on the gastrointestinal tract and to develop novel approaches to therapy directed at protecting the enteric nervous system from neurodegeneration.

**Keywords** Colon · Constipation · Enteric nerves · Extrinsic nerves

## Introduction

Studies have shown that 35–40% of older individuals complain of gastrointestinal (GI) problems, most commonly

constipation [1]. Constipation in the elderly has many potential causes, including but not limited to reduced fluid intake and poor nutrition, an undesirable effect of medication, acute or chronic illness, and as a consequence of a stroke. An underlying neurologic disorder can also be a cause for constipation; for example, constipation is common in patients with Parkinson's disease (PD), and it has been associated with a future risk of developing PD [2]. Many articles have provided outstanding overviews of the pathophysiology of constipation in the elderly [3–5]. This review focuses on neurodegeneration of the enteric nervous system as an underlying cause of constipation, building upon these three recent excellent reviews on the subject of the aging gut [3–5].

## Neural Innervation of the Colon

The colonic musculature and epithelium are densely innervated by intrinsic and extrinsic (sympathetic and parasympathetic) nerves. The intrinsic innervation of the enteric nervous system (ENS) of the colon consists of a vast interconnected network of two plexuses, the myenteric plexus (of Auerbach) and the submucosal plexus (of Meissner), which can function autonomously from central nervous system (CNS) control. The myenteric plexus—located between the longitudinal and circular muscle layers of the colon—controls predominantly smooth muscle function, whereas the submucosal plexus—located between the circular muscle and mucosa—regulates blood flow and mucosal secretion. Normally, the ENS propels gut contents toward the anus via peristalsis, which involves local enteric reflexes leading to an ascending and descending phased release of neurotransmitters that results in coordinated movements of the longitudinal and circular smooth muscle, resulting in ascending contraction and descending relaxa-

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tion of colonic musculature. The observation that a combination of muscarinic and tachykinin antagonists abolish ascending contractions points to the importance of acetylcholine (ACh) and substance P as excitatory neurotransmitters participating in regulating ascending excitation. On the other hand, nitric oxide (NO), vasoactive intestinal polypeptide (VIP), neuropeptide Y (NPY), and adenosine triphosphate (ATP) have been shown to be important inhibitory neurotransmitters regulating descending relaxation. The extrinsic innervation of the ENS consists of parasympathetic pathways that originate in the dorsal motor nucleus of the vagus (DMV) and the sacral parasympathetic nucleus; both synapse with cell bodies of the myenteric plexus within the colon and serve to modulate ENS activity. The DMV modulates the motility of the cecum, ascending colon, and transverse colon, whereas the sacral parasympathetic nucleus modulates the motility of the distal colon and rectum. The extrinsic sympathetic pathway innervation of the colon consists of postganglionic adrenergic neurons, which are innervated by preganglionic neurons and modulate peripheral reflexes that inhibit colonic motility. When food is swallowed, several ENS reflexes are synchronously initiated that autonomously control colonic motility and secretion as well as the preparation of the fecal bolus for expulsion. Local reflexes of the ENS control colonic motility and secretion through intrinsic primary afferent neurons (IPANs). IPANs, which are located in the myenteric and submucosal plexuses, project dendritic processes orally and aborally that synapse with interneurons and motor neurons. When the mucosa is stimulated by stretching or chemical content, serotonin is released by enterochromaffin cells, which activate IPANs via 5-HT<sub>3</sub> receptor-mediated mechanisms. Once activated, IPANs release ACh to initiate peristaltic and secretory reflexes. In the small intestine and colon, the peristaltic reflex causes propulsion of digestive material through the lumen of the GI tract via an ascending smooth muscle contraction induced by ACh and substance P, coupled with a descending relaxation of circular smooth muscle induced by VIP and NO. Normally, contents are propelled along the colon via short local reflexes located within the wall of the colon that stimulate peristalsis. Gastric distension is also capable of stimulating peristaltic contractions in the colon that similarly serves to propel material anally and into the rectum via a long neural reflex arc, commonly referred to as the gastrocolic reflex. This process typically results in evoked sensations of the urge to defecate shortly after meal consumption. Filling, thus distending, the rectum induces release of VIP and NO from intrinsic nerves. The release of VIP and NO causes relaxation of the internal anal sphincter, which is simultaneously balanced by increased tone in the external anal sphincter, a process known as the recto-anal inhibitory reflex. This reflex prevents accidental leakage of

fecal content, yet allows for the voluntary elimination of fecal matter from the GI tract.

### Effect of Aging on the Innervation of the Colon

#### Enteric Innervation

Colonic transit is known to slow as a function of age. What is unknown is whether constipation and reduced colonic transit are caused by an age-related loss of enteric neurons. Studies of the aging intestine have shown enteric neurodegeneration to be associated with a significant decrease in cell number and density throughout the GI tract. A significant loss of enteric neurons seems to occur in the colon, although controversy exists as to which neuronal populations are lost with age. In animal and human studies, the neurons that appear to be altered with age include those that contain NO, VIP, substance P, and ACh. Based on data from aged rats, evidence suggests that the age-related cell loss in the myenteric plexus is exclusively caused by cholinergic neuronal loss, whereas the nitrergic neurons in the myenteric plexus are spared the effects of aging [6]. However, others have shown that the expression of neuronal nitric oxide synthase (nNOS) is differentially affected in young and aged rats [7]. Preclinical studies in the guinea pig colon have also shown that aging has been associated with a decrease in neurons in the ENS; however, a fall in density rather than the number of myenteric neurons is thought to be the major change with age [8]. Although data from humans to investigate age-related changes in the colon are limited, recent evidence from human sigmoid colon circular muscle suggests that a decrease in nerve fiber density occurs with growth in response to an increase in circular muscle thickness that occurs during early childhood to adolescence; however, this study found no further changes were observed with aging [9]. Moreover, the effect of age on the ENS of the human colon was recently studied in 16 patients (7 females and 9 males) with no underlying colonic disease and aged between 33 and 99 years. Although the number of subjects is rather low and comprised of tissue from males and females, the trends suggest that neurons in the myenteric plexus decline with age [10•]. This study further suggests that cholinergic neurons are most affected by aging, and nNOS neurons appear to be spared [10•]. Taken together, these findings suggest that as we age, NO-induced smooth muscle relaxation remains normal, but cholinergic neurons are reduced in number. The functional consequence of this decrease in cholinergic neurons is likely the cause of the delay in transit because there is less contraction behind the bolus, leading to inefficient peristalsis. To further support diminished contractions as a cause of constipation, Lui et

al. [11] found that in isolated sigmoid colonic circular muscle segments taken from females with constipation, there were cyclooxygenase-dependent alterations in substance P-mediated contractility as well as neurokinin-1 (NK1) receptor expression. Although these findings are interesting, future studies are required in tissue taken from elderly women with constipation to determine whether the same mechanisms occurs with aging.

Less is known of how aging affects the submucosal plexus, which is located between the circular muscle layer and the mucosa. In one study using whole-mount colonic preparations from Fischer-344 rats, cuprolinic blue-stained submucosal plexus neurons showed a significant loss in number as early as 12 months of age. Furthermore, this number progressively decreased linearly with advancing age in both the proximal and distal colon such that by 27 months of age, 24% of the submucosal plexus neurons had been lost compared to 6-month-old adult rats [4, 12]. However, the 2009 study by Bernard et al. [10•] comparing human colonic tissue from young and old subjects (male and female, 33–99 years old) found that myenteric plexus neurons stained positively for neuron-specific antigens HuC/D and choline acetyltransferase (ChAT), but not nNOS, declined with age. In the submucosal plexus from the same patients, however, there was no loss in the number of neurons with advancing age. Taken together, these conflicting data from rodents and humans suggest that future studies are required to delineate the effect of aging on submucosal plexus neurons.

#### Extrinsic Innervation

Although loss of enteric neurons with age has been documented, much less is known about the age-related changes in extrinsic innervation of the colon. Rodents appear to experience a dramatic age-related degeneration of sympathetic motor neurons innervating the myenteric plexus with advancing age, which could explain age-related decline in colonic transit [13]. Furthermore, the same study demonstrated a significant level of cholinergic vagal afferent age-related degenerative changes. Data are lacking about the potential effects of aging on the extrinsic innervation of the human colon, which represents an important area for future research.

#### Role of Interstitial Cells of Cajal in the Control of Colonic Motility in the Elderly

The interstitial cells of Cajal (ICC) are important cells in the GI tract that regulate motility by acting as the intestinal pacemaker. Specifically, the ICC generate spontaneous electrical slow waves and propagate the electrical signal

to the smooth muscle, leading to smooth muscle contraction via a wave of depolarization that initiates calcium entry by means of voltage-dependent calcium channels. ICC are also involved in mediating neural input from enteric motor neurons, and ICC-deficient mice display reduced responses to ACh and NO. Finally, ICC can also respond to stretch of the GI muscle, and thus affect the frequency of pacemaker activity. Saunders et al. [14] published an excellent review of ICC. Although we have considerable knowledge of ICC physiology, the effect of aging on ICC has received virtually no attention. However, indirect animal and human data suggest age-related changes in ICC number. ICC number was examined by immunohistochemistry in the murine small intestine and colon [15, 16]. These studies found an age-dependent proliferation of ICC around the myenteric plexus in both the small intestine and colon from postnatal day 0 to day 56. However, future studies are needed to examine whether the number and density of ICC are changed in colons from older mice. Recent data are lacking regarding the effect of aging on ICC number and morphology in human tissue. However, evidence exists that ICC—especially those in a dense network surrounding the myenteric plexus and along the submucosal surface of the circular muscle layer—are reduced in number in the rectosigmoid of patients with colonic aperistalsis associated with Hirschsprung's disease, slow transit constipation, and megacolon [17–19]. Taken together, these limited data argue for a need for research to determine whether a decline in ICC number is a potential cause for constipation in the elderly.

#### Effect of Neurologic Disorders, Including PD, on the ENS

Although PD is a progressive neurodegenerative disorder of dopamine-containing neurons in the substantia nigra (SN), evidence suggests that neuronal structures outside the SN are affected by the neurodegenerative process of PD [20, 21]. A prominent manifestation of PD is GI dysfunction, including but not limited to severe constipation. Reports from studies using colonic biopsies from patients with PD have shown that ENS pathologies occur in the GI tract of patients with PD (e.g., the presence of Lewy bodies in the myenteric and submucosal plexus) that are commonly observed in the early stages of the disease, possibly preceding the onset of neuronal damage in the brain [22, 23, 24]. In rodent models of PD induced by prototypical parkinsonian neurotoxin MPTP (1-methyl 4-phenyl 1,2,3,6-tetrahydropyridine), rotenone, or unilateral 6-hydroxydopamine lesions of the nigrostriatal dopaminergic neurons, the loss of enteric dopaminergic neurons is associated with abnormal colonic contractility leading to a

marked inhibition of propulsive motility and daily fecal pellet output [21, 25–27]. Although the loss of dopaminergic neurons in the ENS may be a contributing factor to constipation in PD, the presynaptic protein  $\alpha$ -synuclein has also been implicated in changes in the ENS in the aging gut [28, 29]. Specifically, studies in rodent models have shown that  $\alpha$ -synuclein is expressed in a subpopulation of myenteric neurons and in vagal terminals. The  $\alpha$ -synuclein is coexpressed with nitric oxide synthase (NOS) or with markers of cholinergic neurons, and  $\alpha$ -synuclein immunopositive aggregates have been observed within the myenteric plexus of aging rats [28, 29]. Additionally, evidence exists of abnormal colonic motility in mice overexpressing human wild-type  $\alpha$ -synuclein [30]. Specifically, the number of fecal pellets remaining in the colon 2 h postprandially was increased, and the time to expel an intracolonic bead was more variable compared to wild-type mice [30]. Although the mechanisms by which  $\alpha$ -synuclein leads to impaired colonic motility remain to be established, the fact that the accumulation of  $\alpha$ -synuclein is a major component of Lewy bodies suggests that this murine model may be useful to study constipation associated with PD. In fact, more recent studies in transgenic mice expressing mutant  $\alpha$ -synuclein (either A53T or A30P) showed marked abnormalities in ENS function and synuclein aggregates in ENS ganglia by 3 months of age. These results support that transgenic mice expressing mutant  $\alpha$ -synuclein may serve as a model to investigate the efficacy of potential new therapies targeting  $\alpha$ -synuclein for the treatment of PD by reversing ENS dysfunction and constipation [24]. For detailed reviews of the literature related to the ENS in PD, see the excellent articles by Cersosimo and Benarroch [31] in 2008 and Lebouvier et al. [23] in 2009. That enteric cholinergic neurons are markedly affected in aged animals points to the possibility of enteric neurodegeneration mirroring certain aspects of Alzheimer's disease observed in the CNS. However, currently no animal or clinical data can substantiate a possible link between the overt neurodegeneration associated with Alzheimer's disease and enteric neuronal degeneration.

### Neurogenesis and Neuroprotection

An obvious question is how do we protect enteric neurons from neurodegeneration? Although the ENS has been shown to retain stem cells, the first demonstration of enteric neurogenesis came from Gershon et al. (cited in Lui et al. [32]), who found that 5HT<sub>4</sub> receptor agonists promote enteric neural development and even neuronal cell survival. In addition, age-dependent slowing of colonic transit was more pronounced in 5HT<sub>4</sub><sup>-/-</sup> mice, suggesting that 5-HT may have a neural protective role in the mouse colon [32]. Another intriguing study published in

2009 found that in vitro intestinal epithelial cells affect the neurochemical phenotype. In this study, the percentage of VIP-immunoreactive neurons, but not NOS-immunoreactive neurons, were significantly increased following co-culture with intestinal epithelial cells [33]. Furthermore, it was also found that intestinal epithelial cells impact the survival of enteric neurons, suggesting a novel mechanism for therapy to treat ENS neurodegeneration. Other work has suggested a role for enteric glial cells in neuroprotection, because lesions of enteric glial cells are associated with neuronal dysfunction in animal models, and enteric glial cells have been shown to protect neurons from oxidative stress via a reduction in glutathione [33].

### Evidence from Novel Animal Models Supports the Effect of Aging on Colonic Neuronal Function

#### Rodents

As described previously, rodent models have been used extensively to examine the effect of aging on the GI tract, with strong supportive data showing that myenteric neurons are most affected by aging confirming observations in humans. However, significant strain differences have been observed in rodents, and the effect of aging on the nitrergic innervation of the esophagus differs depending on the rat strain [34]. Preliminary studies in mice have shown changes in GI smooth muscle contractility in Klotho mice, which develop an aging phenotype after 3 weeks [35]. These results suggest that the changes in GI smooth muscle contractility may be the result of impaired inhibitory neurotransmission and loss of the ICC network, but no evidence has been reported of enteric neuronal loss or overt smooth muscle dystrophy. A potential weakness in this study is that normally aged mice were not compared to the Klotho mice.

#### Nonhuman Primates

Although rodents have served as an important animal model to study the effects of aging on colonic function, our recent goal has been to establish methodologies and techniques in a non-human primate model to investigate muscular and mucosal changes within the small and large intestine that occur with aging in the baboon. Specifically, we have found that there are marked regional differences in contractility and epithelial secretion induced by electrical field stimulation, muscarinic agonism, or inhibition of nitric oxide synthase in tissues taken from aged baboons. Our data suggest that baboons may serve as a useful animal model to examine the effect of aging on the neural control of the intestinal musculature and mucosa [36].

## Conclusions

Aging has profound effects on the GI tract. In this review, we outline the evidence that enteric neurodegeneration may be the likely culprit for producing constipation in the elderly. Furthermore, abnormalities in the ENS may precede the onset of neurologic disorders such as PD, and thus may be used as potential biomarkers to predict the future onset of disease. A pivotal question is how do we protect enteric neurons from neurodegeneration? This question must be answered before we can develop novel therapeutic approaches to treat constipation in the elderly.

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