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SYMPATHETIC (ADRENERGIC) INNERVATION MODULATES BUT DOES NOT GENERATE BASAL TONE IN THE INTERNAL ANAL SPHINCTER SMOOTH MUSCLE

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The smooth muscle of the internal anal sphincter (IAS) performs 2 important functions: It maintains tone in the basal state and relaxes in response to the rectoanal inhibitory reflex (RAIR; *Neurogastroenterol Motil* 2005;17:50–59; *Handbook of physiology, alimentary canal*. Vol. IV. 1968;2121–2139; *N Engl J Med* 2007;356:1648–1655; *Gastroenterology* 2004;126:S14–S22; *Aliment Pharmacol Ther* 2001;15:887–898; *Gastroenterology* 2007;133:1069–1074). The basal tone in the IAS is important for rectoanal continence and relaxation functions for the successful completion of the RAIR. An impairment in these events leads to serious consequences, such as rectoanal incontinence, certain forms of constipation, and other related gastrointestinal motility disorders.

The IAS is innervated by the extrinsic (sympathetic and parasympathetic nerves), and the intrinsic or enteric nervous system (ENS; *Aliment Pharmacol Ther* 2001;15: 887–898; The enteric nervous system. 2007;1–288). The sympathetic nerves reaching the IAS are postganglionic, whereas the parasympathetic nerves are preganglionic. The parasympathetics may connect with the postganglionic adrenergic, cholinergic, and noncholinergic nonadrenergic (NANC), and sympathetics may connect with the cholinergic and NANC neurons within the IAS. These connections constitute a part of the ENS. Some of the neurotransmitters for the postganglionic sympathetic fibers terminating in the IAS are noradrenaline (NA) and neuropeptide Y (*Am J Physiol Gastrointest Liver Physiol* 1990;258:G59–G64; *Regul Pept* 1991; III:29–35). NA by the activation of α -adrenoceptors (especially α_1 [α_1 -AR]) causes increase in the sphincteric tone and inhibition in the adjoining nonsphincteric smooth muscles (Goodman & Gilman's the pharmacological basis of therapeutics, 10th ed. 2001;115–153; *Aliment Pharmacol Ther* 2001; 15:887–898; *Neurogastroenterol Motil* 2005;17:50–59; *J Clin Invest* 1990;86:424–429). The parasympathetic postganglionic fibers are either excitatory (neurotransmitters [eg, acetylcholine/substance P]), or inhibitory (via nitric oxide [NO], vasoactive intestinal polypeptide, adenosine triphosphate (ATP), or related substances; *Am J Physiol Gastrointest Liver Physiol* 1992;262:G107–G112; *J Clin Invest* 1988;81:1146–1153; *Neurogastroenterol Motil* 2005;17:50–59; *J Auton Nerv Syst* 1999;19:29–37).

The role of α_1 -AR in the basal tone may be examined by evaluating the effect of electrical field stimulation (EFS) after the blockade of cholinergic and NANC effects, α_1 -AR agonists

and antagonists, and neurotoxins in the isolated IAS smooth muscle strips. Such studies in humans and different species (Aliment Pharmacol Ther 2001;15:887–898; Br J Surg 2008;92:1263–1269; Br J Surg 2007;94:894–902; Neurogastroenterol Motil 2005;17:50–59; Gastroenterology 1983;84:409–417; Gastroenterology 1992;102:679–683; Gut 1993;34:689–693) have led to the conclusion that, although α_1 -AR activation exerts important excitatory modulation, it may not contribute significantly to the basal tone in the IAS.

Recent studies by Cobine et al (Neurogastroenterol Motil 2007;19:937–945) examined the role of α_1 -AR in the IAS using different animal species (monkeys, mice, and rabbits). The authors examined the effects of EFS, NA, and adrenergic inhibitors in the IAS tone in the isolated smooth muscle strips. In the presence of the nitric oxide synthase (NOS) inhibitor N(ω)-nitro-L-arginine (L-NA) and anticholinergic atropine EFS and NA caused contraction in the monkey IAS but relaxation in the murine and rabbit IAS. The contractile responses in the monkey IAS were converted into relaxation in the presence of α_1 -AR antagonist phentolamine and adrenergic depletor guanethidine. The NA-induced relaxation in monkey IAS was abolished by the β -AR antagonist propranolol. The authors concluded that in contrast to the murine and rabbit, the monkey IAS is functionally innervated by the excitatory sympathetic nerves that contribute significantly to the IAS tone. Accordingly, for the adrenergic effects in the IAS, the monkey may be a more appropriate animal model as compared with mice and rabbits.

Comment

Cobine et al have used a brilliant approach to determine the contribution of adrenergic nerves by carrying out studies in the presence of NOS inhibitor L-NA and anticholinergic atropine to alleviate any interference of the nitrergic inhibitory neurotransmission and muscarinic excitatory transmission, respectively. Their findings in different species are consistent with the bulk of the literature, although with some important differences.

The IAS smooth muscles isolated from different species examined demonstrate the development of spontaneous tone. In such experimental settings, the smooth muscle tissues are devoid of any circulating neurohumoral substances as is the case during the in vivo settings. Such information by itself may not be interpreted as the tone being myogenic because in addition to the smooth muscle cells (SMC) the smooth muscle has a number of inputs from adrenergic, cholinergic and NANC neurons among others and their signal transduction machineries, in various proportions (Handbook of methods in gastrointestinal pharmacology 1996;189–224). Because of such variability, it is conceivable that EFS causes variable effects in different species.

Studies further show contraction of the monkey IAS, and relaxation in the murine and rabbit IAS in response to EFS in the presence of NOS inhibitor L-NA, and atropine. A majority of the literature, however, in different species including humans, mice, and rabbits shows variable responses to EFS under similar experimental conditions, either almost complete obliteration of the relaxation, or a brief after contraction (Gastroenterology 1992;102:679–683; Am J Physiol Gastrointest Liver Physiol 1993;265:G792–G798; J Pediatr Surg

1994;29: 294–300; Am J Physiol Gastrointest Liver Physiol 2005; 289:G291–G299; Gastroenterology 1997;112:1575–1585; J Pharmacol Exp Ther 1996;277:1376–1382; Aliment Pharmacol Ther 2001;15:887–898; Neurogastroenterol Motil 2005;17:50–59).

The observed differences in the monkey IAS in response to EFS may reflect variability in the degree and nature of NANC inhibitory (NO, VIP, ATP) and excitatory neurotransmissions (NA, acetylcholine, neuropeptide Y, and substance P; Am J Physiol Gastrointest Liver Physiol 1990;258:G59–G64; Regul Pept 1991; III:29–35; Neurosci Lett 1987;74:304–308). The other possible differences may lie in the relative distribution of sympathetic nerves and their terminations, and contribution of α_1 -AR and α_2 -AR after sympathetic nerve stimulation. The latter provide inhibitory input to a number of myenteric neurotransmissions. In addition, whether appropriate stimulus parameters required to activate different structures in the ENS in different species, play a role for the final observed response, remains to be determined.

The authors show important differences in the responses to NA in monkeys compared with mice and rabbits. The inhibitory effects of NA seem to involve activation of α_1 -AR, α_2 -AR, and β -AR in different proportions. The studies clearly point out that with regard to the adrenergic effects in the IAS, monkey and other species (but not mice and rabbits) may be similar to humans. The studies by no means minimize the importance of mice and rabbits for the other functional studies in the IAS. In this respect, mice (especially because of the availability of a number of specific knockouts) will continue to provide important information on the IAS regulation.

In agreement with the literature, the authors also found that in all the species investigated, neither the α_1 -AR antagonist phentolamine nor the adrenergic depletor guanethidine had any significant effect on the basal tone in the IAS. In most of the IAS preparations from different species including humans (Gastroenterology 1983;84:409–417; Aliment Pharmacol Ther 2001;15:887–898; Neurogastroenterol Motil 2005;17:50–59) blockade of different neurohumoral influences, and the neurotoxin tetrodotoxin (which impairs all neural inputs) produced no significant effect on the basal tone. These significant findings suggest that sympathetic innervation via adrenergic activation may provide excitatory modulation, but does not generate the basal tone in the IAS, suggesting the tone to be mostly myogenic in origin.

Understanding of the mechanism(s) responsible for the basal tone in the IAS are vital for the advances in the pathophysiology and therapy of debilitating rectoanal motility disorders, as pointed out. Adrenergic regulation of the IAS tone would have provided important rationale for some of these motility disorders with the use of α_1 -AR agonists (in the case of hypotensive IAS as in certain forms of rectoanal incontinence) and with α_1 -AR antagonist (for the hypertensive IAS as in hemorrhoids and recurrent anal fissures). However, these approaches have not been uniformly successful in treating such conditions (Aliment Pharmacol Ther 2001;15:887–898; Br J Surg 2000;87:38–42; Int J Colorect Dis 2007;22:1319–1324; Colorectal Dis 2001;3:165–168). In addition, stimulation and denervation of the sympathetic nerves supplying the IAS have produced inconsistent results (Gastroenterology 1983;84:409–417; Br J Surg 1987;74: 668–670; Int J Colorect Dis

1991;3:90–95). All data put together suggest that the basal tone in the IAS is largely because of the distinct properties of the SMC of the IAS. Such myogenic phenomenon responsible for the IAS tone is inherent to the SMC (Am J Physiol Gastrointest Liver Physiol 2005;289:G1164–G1175; Am J Physiol Gastrointest Liver Physiol 2007;292:G1747–G1756) to the extent that one can bioengineer the tonic IAS in reverse from the isolated cells (Am J Physiol Gastrointest Liver Physiol 2005;289:G188–G196).

Although no single animal model (including monkeys) can substitute for human studies, basic studies in the IAS using different animal models have added significantly to our present knowledge of the pathophysiology of human anorectal motility disorders. In addition, differences in the effects of EFS and NA in mice and rabbits (vs monkeys) may not suggest the absence of adrenergic innervation and α_1 -AR in these species. The most valid conclusion from the present studies is that mice and rabbits may not be appropriate animal models to investigate the adrenergic effects in the IAS. Detailed studies to tease out different components of sympathetic pathway (mapping out adrenergic innervation, sympathetic stimulation, and α_1 -AR distribution patterns) in mice and rabbits IAS may provide plausible explanation for the observed differences in these animal species. Finally, regardless of the species, critical survey of the literature suggests that although sympathetic motor innervation (via adrenergic activation) provides excitatory modulation, it may not be major contributor for the basal tone in the IAS.