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HIGH AMPLITUDE PROPAGATED CONTRACTIONS

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Abstract

While most colonic motor activity is segmental and non-propulsive, colonic high amplitude propagated contractions (HAPC) can transfer colonic contents over long distances and often precede defecation. HAPC occur spontaneously, in response to pharmacological agents or colonic distention. In this issue of Neurogastroenterology and Motility, Rodriguez and colleagues report that anal relaxation during spontaneous and bisacodyl-induced HAPC exceeds anal relaxation during rectal distention in constipated children undergoing colonic manometry. Moreover, and consistent with a neural mechanism, anal relaxation often precedes arrival of HAPC in the left colon. This editorial comprehensively reviews the characteristics, physiology and pharmacology of HAPC, their assessment by manometry, and relevance to constipation and diarrhea.

Keywords

constipation; colonic inertia; slow transit; children; bisacodyl; diarrhea; HAPC

> "Suddenly during the examination, the segmentation in the transverse colon disappeared so rapidly that the eye could hardly follow the movement. We had the impression that the haustral segmentation disappeared at the same instant along the whole of this part of the intestine."
>
> Holznecht (1)

Introduction

Shortly after the first report by Hertz (2), Holznecht observed mass movements only twice in over 1000 studies in humans (1), which is a striking testament to the preponderance of non-propagating or segmental motility in the colon (3). Because mass movements occur infrequently and are so brief, their manometric counterparts (i.e., high-amplitude propagated contractions [HAPC]) were characterized only with the advent of 24-hour manometry in the late 1980s (4). The relationship between HAPC and mass movements was verified by simultaneously assessing pan colonic isotope movement and pressure changes in 2000 (5). Over 100 years after the report by Holznecht, Rodriguez and colleagues now use the same approach (i.e., meticulous observation) to refine our understanding of the temporal relationship between HAPC and internal anal sphincter relaxation (IASR) in children with chronic constipation (6). These intriguing observations provide an opportunity to summarize our current understanding of HAPC in health and disease.

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Characteristics of HAPC

The salient features of HAPC are summarized in Table 1. While most attention has focused on HAPC, perhaps because they are easier to recognize by manometry, low amplitude propagated contractions can also propel colonic contents. Indeed, in one study of 6 healthy adults, low and high amplitude propagated contractions were equally effective at transporting isotope in the proximal colon (7). The threshold for distinguishing between low and HAPC is partly influenced by methodology and varies from 50 to 116 mmHg (7–12). However, regardless of amplitude, propagated contractions increase upon awakening and are much more common during the day, particularly after meals (5, 12–14).

Most HAPC begin in the cecum or ascending colon and travel for variable distances, typically longer than those that originate more distally (15). However, pressure waves which arise proximally generally do not propagate beyond the midcolon and fewer than 5% reach the rectum (15). The propagation velocity averages 1–2 cm/second in the right colon but increases as the waves migrate caudally, frequently to the point of synchronicity, which arrests the progress of content moving ahead of the contractile front (15). HAPCs may be followed by defecation.

Physiology and Pharmacology of HAPC

In addition to occurring spontaneously, HAPC can be induced by pharmacological agents, which are perhaps more potent stimuli than colonic distention in adults (16) and children (17). Similar to lower esophageal sphincter relaxation at the onset of esophageal peristalsis, anal relaxation precedes the arrival of HAPC in the rectosigmoid colon (6, 18–20). While the lower esophageal sphincter relaxes due to a “flood” of inhibition originating from the dorsal motor nucleus of the vagus, activation of intra-colonic descending inhibitory pathways probably explains early anal relaxation (i.e., before HAPC arrive at the rectosigmoid colon) (21, 22). Inhibition of nitrergic neurotransmission by recombinant human hemoglobin, which inactivates NO, increased the amplitude, duration and velocity of esophageal peristaltic contractions and also inhibited LES relaxation in humans (23). Likewise, a low dose of the nitric oxide inhibitor N(G)-monomethyl-L-arginine (L-NMMA) increased the frequency of colonic HAPC (24); anal pressure was not recorded in this study. In addition to nitrergic nerves, tonic extrinsic sympathetic input also inhibits colonic motility and HAPC, partly in responsible to afferent feedback originating in the colon (i.e., colo-colonic reflexes) and involving prevertebral ganglia (25). Consistent with this mechanism, the adrenergic α_2 antagonist yohimbine induced colonic HAPC in healthy subjects (20, 26). Thus, the central nervous system initiates primary esophageal peristalsis but suppresses HAPC. Indeed, HAPC were more frequent in a canine model of colonic extrinsic denervation (27) and in patients with autonomic neuropathy and diarrhea (28). However, the specific colonic neurophysiological mechanisms or substrate responsible for generating HAPC are incompletely understood.

Intraluminal stimuli such as glycerol, bisacodyl, oleic acid, and bile acids can elicit HAPC in humans (16, 29–31). The laxative effects of bisacodyl in rats have been attributed to fluid and electrolyte secretion partly mediated by PGE2 and nitric oxide (32, 33). However, those studies used much higher doses, (e.g., 20 or 50 mg/kg) (32, 33) than the typical doses (i.e., 5–10 mg daily) necessary to accelerate proximal colonic emptying or improve symptoms in humans (34, 35). Rectal delivery of bisacodyl and even chenodeoxycholic acid in physiological concentrations (31) induced propagating contractions which can originate in the left colon. This strongly suggests a neural mechanism of action because the active metabolite of bisacodyl works locally and systemic absorption is minimal (36). Perhaps bisacodyl induces HAPC by a sequence of events similar to that responsible for initiating

colonic migrating motor complexes in mice (37), i.e. 5-HT release from enterochromaffin cells, activation of mucosal endings of myenteric and submucosal AH/Type II neurons by 5-HT, propagation of excitation along the colon through interneuronal pathways which converge onto other AH neurons, and excitation of myenteric interstitial cells of Cajal which concurrently activate neighboring longitudinal and circular muscle. When excitatory motor neurons are active, contractions can summate, giving rise to powerful, lumen-occlusive contractions that may last longer than slow waves and that may propagate substantial distances along the colon.

Neostigmine, which is a cholinesterase inhibitor that increases the availability of acetylcholine in the myenteric plexus and at the neuromuscular junction, induces HAPC in dogs and humans (27, 38). Perhaps this effect explains why neostigmine relieves colonic distention in acute colonic pseudoobstruction (39). In contrast, bethanechol, which is an agonist at muscarinic M2 and M3 but not M1 receptors, increased non-propagated colonic phasic pressure activity but did not induce HAPC in healthy subjects (38). Also, the relatively selective muscarinic M1 receptor antagonist pirenzipine but not relatively selective M2 (AF-DX116) or M3 (darifenacin) antagonists inhibited HAPC in dogs (27). Taken together, these observations suggest that stimulation of muscarinic M1 receptors is necessary for coordinated colonic propulsion.

HAPC are triggered by awakening, suggesting that clock genes, which are central and peripheral (i.e., in the colonic epithelium and myenteric plexus), may be involved. Indeed, clock genes may directly or indirectly control the transcription of a subset of colonic genes (e.g., neuronal nitric oxide synthase (nNOS), vasoactive intestinal peptide) that regulate colonic motility (40). Hence, it is conceivable, but unknown, if rhythmic changes in nNOS expression, for e.g. reduced expression upon awakening, contribute to diurnal variations in colonic motor activity and HAPC.

Assessment of HAPC by Colonic Manometry

In clinical practice, manometry is more useful and widely used to investigate colonic motor function in children than in adults with refractory constipation (41). In contrast to adults, there is only one published report with prolonged colonic manometry in children (42). Initial studies with prolonged colonic manometry were performed after colonic cleansing and patients were stationary during the test (4, 8). Since then, several prolonged colonic manometry studies have been performed without colonic cleansing in ambulatory subjects (7, 11–15, 43–46); per nasal intubation provides better access to the right colon than per anal intubation. Colonic cleansing with polyethylene glycol-based solutions does not affect diurnal variation in colonic motor activity or the contractile response to eating but does increase the frequency of HAPC in humans (47, 48). Manometric catheter design and post processing techniques are also important. Colonic manometry with solid-state sensors identified more HAPC than similarly-spaced (10 cm apart) water-perfused sensors (i.e., 107 versus 91) in children with chronic constipation (49). Also, more closely spaced sensors (e.g., 7.5 cm instead of 10 cm) can identify sequences which are propagated for a shorter distance (e.g., those that are propagated for 15 cm) (44). Finally, specialized software algorithms may facilitate the identification of temporo-spatial relationships between sequential propagating sequences. For example, the tail end of the preceding and the front end of the following antegrade propagating sequence often overlap (46). Conceptually, this overlap is akin to passing a baton between 2 runners in a relay. While most single propagating sequences do not span the length the colon, collectively a series of linked propagating sequences may do so. Perhaps this linkage is important for transporting contents over long distances in the colon.

HAPC in Chronic Constipation and Diarrhea

Prolonged manometry studies demonstrate that adults (10, 11, 14, 45, 50) but not children (42) with slow transit constipation have fewer spontaneous (i.e., fasting or postprandial) HAPC than healthy subjects. These studies cumulatively included less than 100 adults with slow transit constipation. Since there were no patients with normal transit constipation, it is unclear if the association with fewer HAPC is specific for slow transit constipation. However, short-duration (not prolonged) colonic manometry identified fewer postprandial HAPC in slow but not normal transit constipation (51). Also, since some healthy subjects do not have any HAPC over a 24 hour period (5, 48), it is unclear if the absence of HAPC during a 24 hour period in constipated patients is abnormal. Finally, it is unclear if the paucity of HAPC explains slow colonic transit or merely represents a marker for an enteric neuropathologic disturbance. While constipated children did not have fewer HAPC they did have fewer total (low and high amplitude) propagated sequences relative to normal values in healthy adults (42).

The absence of HAPC in response to bisacodyl is considered indicative of colonic neuromuscular dysfunction and together with other criteria (i.e., reduced overall colonic phasic pressure activity, lack of a colonic contractile response to a meal, and absence of HAPC) defines colonic inertia (52). In patients who do not have generalized dysmotility or pelvic floor dysfunction, colonic inertia is an indication for surgical therapy (e.g., subtotal colectomy) in children (53) and adults with medically-refractory chronic constipation. As so defined, colonic inertia is a relatively conservative indication for surgery. Indeed, it has been suggested that the “bisacodyl stimulation test may be so powerful that it may trigger propagated contractions even in children in whom colonic distention (possibly a more physiological stimulus) does not” (17). For example, bisacodyl-induced HAPC in 9 of 16 children with chronic constipation in whom balloon distention did not induce HAPC (17). Likewise, in the largest series of colonic manometry in adult constipated patients, 60% of patients with no fasting HAPC or postprandial colonic contractile response responded to bisacodyl (50); by definition, these patients did not have colonic inertia. Perhaps there is scope to refine the paradigm and utility of colonic motor assessments. Might patients who have bisacodyl-induced HAPC but not spontaneous or distention-induced HAPC also benefit from surgical therapy?

In addition to fewer HAPC, the spatiotemporal organization of propagating sequences (14, 54) may also be disturbed in chronic constipation. Specifically, constipated patients did not have the normally observed increase in frequency and amplitude of propagating sequences prior to defecation. Since defecatory disorders can reflexly inhibit colonic motor activity and delay colonic transit (51), further studies are required to ascertain whether these colonic motor disturbances cause or are consequent to pelvic floor dysfunction.

While most attention has focused on infrequent HAPC in constipation, some patients with diarrhea-predominant irritable bowel syndrome (IBS) have more HAPC. Collectively, the data, which are nicely reviewed in (55), suggest that HAPC may explain diarrhea and abdominal pain in some patients with diarrhea.

Conclusions

HAPC are critical for propagating colonic contents and often precede defecation. The paper by Rodriguez et al highlights the synchronization between HAPC and relaxation of the internal anal sphincter. Future studies should clarify the colonic neurophysiological mechanisms and pharmacology of HAPC. While most human studies in health and disease thus far have been limited to counting spontaneous and bisacodyl-induced HAPC, the

availability of newer techniques will facilitate a more refined characterization of low amplitude propagated sequences and identification of spatiotemporal relationships between propagated sequences. These approaches in turn will enhance our understanding of the contribution of HAPC to disease and the development of pharmacological compounds to modulate HAPC.

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Table 1

Key Characteristics of HAPC

- Defined by high amplitude (variable threshold among studies) and presence of propagation; amplitude is higher in the prepped than unprepped colon
- Occur spontaneously, in response to pharmacological agents or colonic distention
- Increase upon awakening, are much more common during the day, and increase after meals
- A majority originate in the proximal colon; most do not propagate beyond the midcolon and fewer than 5% reach the rectum
- Can transfer colonic contents over long distances, can be associated with internal anal sphincter relaxation, and can precede defecation
- HAPC are reduced in slow transit constipation and increased in diarrhea predominant IBS and may explain disturbances of colonic transit in these conditions
- Useful for quantifying colonic motor function in chronic constipation