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Review article

Contribution of membrane receptor signalling to chronic visceral pain

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ABSTRACT

Irritable bowel syndrome and inflammatory bowel disease are major forms of chronic visceral pain, which affect over 15% of the global population. In order to identify new therapies, it is important to understand the underlying causes of chronic visceral pain. This review provides recent evidence demonstrating that inflammation or infection of the gastrointestinal tract triggers specific changes in the neuronal excitability of sensory pathways responsible for the transmission of nociceptive information from the periphery to the central nervous system. Specific changes in the expression and function of a variety of ion channels and receptors have been documented in inflammatory and chronic visceral pain conditions relevant to irritable bowel syndrome and inflammatory bowel disease. An increase in pro-nociceptive mechanisms enhances peripheral drive from the viscera and provides an underlying basis for enhanced nociceptive signalling during chronic visceral pain states. Recent evidence also highlights increases in anti-nociceptive mechanisms in models of chronic visceral pain, which present novel targets for pharmacological treatment of this condition.

1. Clinical relevance of chronic visceral pain

Pain is an unpleasant sensory and emotional experience that normally serves as an alarm mechanism. This allows the body to protect itself against actual or potential tissue damage, by allowing withdrawal from and avoidance of noxious stimuli. In chronic pain, this alarm signal fails to reset following cessation of the threat or healing of the damaged tissue. Accordingly, chronic pain is a maladaptive, relapsing and remitting condition characterised by nociceptor sensitisation, allodynia (pain response to stimuli that do not normally cause pain) and hyperalgesia (an enhanced pain response) in the absence of overt tissue damage (Brierley and Linden, 2014; Costigan et al., 2009). Chronic visceral pain (CVP) derives from our internal organs and is a common and debilitating symptom for patients with gastrointestinal disorders, such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD).

IBS and IBD are major clinical problems affecting up to 15% of the global population (Chey et al., 2015; Enck et al., 2016; Kaplan, 2015). Consequently, CVP is an important public health issue, which places a large economic burden on health care resources (Camilleri and Williams, 2000; Chey et al., 2015; Sandler et al., 2000). In the early 2000′s, the economic impact of IBS and IBD were estimated in the USA alone to exceed $25 billion and $6 billion per annum respectively. Since then the incidence rates of IBS and IBD, and their associated costs have steadily increased over time (Enck et al., 2016; Kaplan, 2015). Despite such a burden, treatments for IBS and IBD are generally lacking. IBS and IBD patients report reduced quality of life and have additional clinical symptoms, including stool irregularities, as well as somatic, visceral

Abbreviations: 5-HT, 5-hydroxytryptamine; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; CAMKII, Calcium/calmodulin-dependent protein kinase II; CaV, voltage-gated calcium (channel); CGRP, calcitonin gene-related peptide; CB, cannabinoid receptor; CNS, central nervous system; CVP, chronic visceral pain; CVH, chronic visceral hypersensitivity; DRG, dorsal root ganglia; ENS, enteric nervous system; GABA, gamma-aminobutyric acid; GC-C, guanylate cyclase-C; GPCR, G protein-coupled receptor; HR, histamine receptor; Hm, 1aδ-theraphotoxin-Hm1a; IBS, irritable bowel syndrome; IBS-C, constipation-predominant IBS; IBS-D, diarrhoea-predominant IBS; IBD, inflammatory bowel disease; K2P, two-pore domain potassium channel; K_V, voltage-gated potassium (channel); MAPKK, mitogen-activated protein kinase kinase; mGluR, metabotropic glutamate receptor; NaV, voltage-gated sodium (channel); NKR, tachykinin receptor; NKA, neurokinin A; NKB, neurokinin B; NMDA, N-methyl-d-aspartate; PAR, protease-activated receptor; PET, positron emission tomography; PKC, protein kinase C; PLA_2, phospholipase A2; PLCβ, phospholipase C β; SP, substance P; TNBS, trinitrobenzene sulfonic acid; TNF-α, tumour necrosis factor α; TTX, tetrodotoxin; TRP, transient receptor potential (channel); TRP, TRP ankyrin repeat; TRPC, TRP canonical; TRPM, TRP melastatin; TRPML, TRP mucolipin; TRPP, TRP polycystin; TRPV, TRP vanilloid

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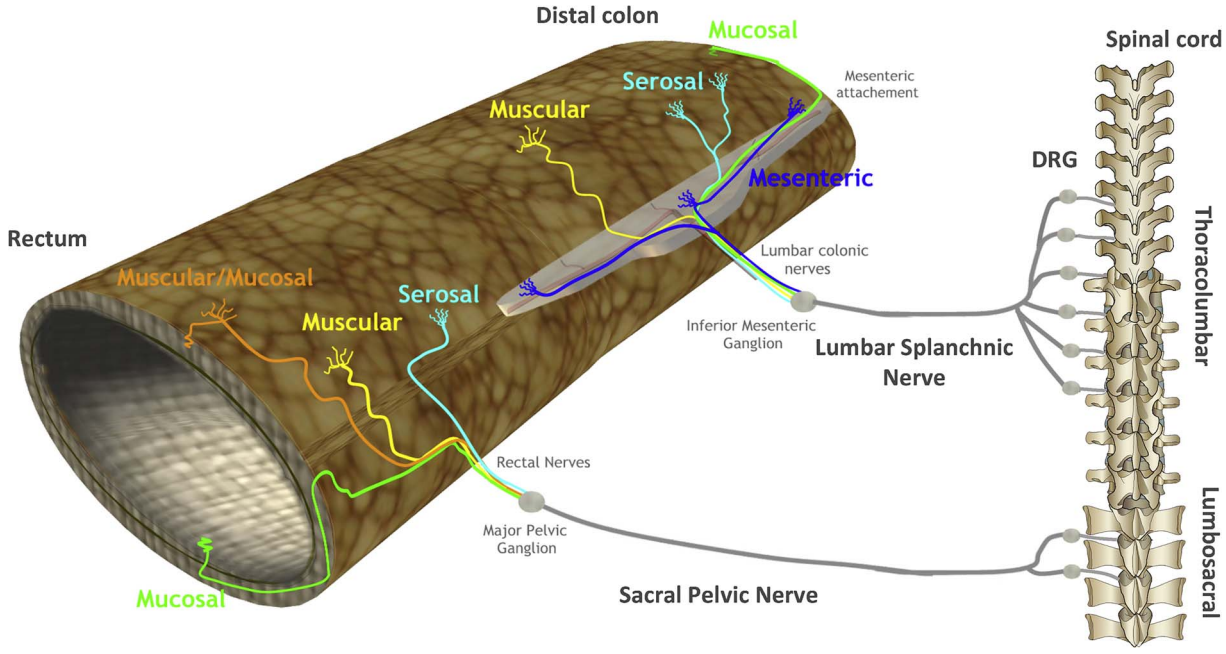

Fig. 1. Extrinsic sensory afferent innervation of the colorectum.
The colon and rectum receive dual spinal innervation via the lumbar splanchnic nerve and the sacral pelvic nerves. The cell bodies of splanchnic and pelvic afferents are located within the thoracolumbar (T10-L1) and lumbosacral (L6-S1) dorsal root ganglia (DRG), respectively. Central axons terminate within the respective thoracolumbar and lumbosacral dorsal horn of the spinal cord, where they synapse onto second order neurons. The peripheral projections of these afferents innervate the mucosa and muscle, and wrap around blood vessels within the submucosa and on the mesenteric attachment. This gives rise to distinct classes of afferents; muscular, mucosal and serosal (splanchnic and pelvic pathway) and mesenteric (splanchnic only) and muscular/mucosal (pelvic only). These afferents allow the full range of mechanical and chemical stimuli occurring within the colorectum to be detected. Mucosal afferents detect low-threshold distortion of the intestinal mucosa and respond to endogenous mediators, whereas muscular afferents respond to low-threshold distension and contraction and have wide dynamic ranges of response, including into the noxious range, and respond to endogenous mediators. Muscular/mucosal afferents display the combined properties of muscular and mucosal afferents. Mesenteric and serosal (also known as vascular afferents) have high thresholds to mechanical stimuli and respond to a wide array of endogenous mediators, particularly, inflammatory and immune mediators.

and psychiatric co-morbidities, including referred pain and higher levels of anxiety and depression than healthy people (Camilleri, 2001; Camilleri and Williams, 2000; Chey et al., 2015; Enck et al., 2016; Grundy and Brierley, 2017).

In IBD, which is a chronic, relapsing inflammatory disorder of the gastrointestinal tract, a disturbed mucosal epithelial barrier, combined with the release of inflammatory mediators, sensitises peripheral nerve endings within the gut wall, resulting in disturbed visceral sensory perception and abdominal pain (Brierley and Linden, 2014). In contrast, CVP in IBS occurs in the absence of overt colon pathology (Enck et al., 2016). Whilst the aetiology of IBS is multi-factorial and additional risk factors may be required for development (Chey et al., 2015; Spiller and Garsed, 2009), there is a strong correlation between a prior exposure of the patient to gut infection and symptom occurrence. This includes a preceding bout of gastroenteritis induced by pathogens such as *Escherichia coli*, *Salmonella*, *Campylobacter* and *Giardia lamblia* (Spiller and Garsed, 2009). Notably, the duration and severity of the initial illness is one of the strongest associated risk factors for the development of IBS symptoms (Marshall et al., 2010). Such bouts of acute gastroenteritis can trigger IBS symptoms in patients that persist for at least 8 years after the initial infection (Marshall et al., 2010). Biopsy and blood samples from IBS patients, in addition to mechanistic preclinical studies, are now shedding light on the potential reasons why persistent symptoms occur in the absence of overt pathology to the intestinal mucosa (Bashashati et al., 2018; Brierley and Linden, 2014; Hughes et al., 2013b). These studies suggest that infection or inflammation of the intestine releases mediators that sensitise afferents leading to inflammation-induced visceral hypersensitivity. In post-inflammatory states this hypersensitivity persists, resulting in chronic visceral hypersensitivity (CVH), or the long-term enhanced perception of stimuli originating from our internal organs (Brierley and Linden, 2014; Grundy and Brierley, 2017). It is this CVH of sensory pathways innervating the colon that leads to the development and maintenance of chronic abdominal pain in patients with IBS in the absence of overt intestinal pathology (Azpiroz et al., 2007; Lembo et al., 1994; Ritchie, 1973).

In this article, we'll first briefly outline how sensory information at the level of the colorectum is encoded and conveyed to the central nervous system (CNS). For an in-depth discussion on the neuroanatomy, we refer the readers to some of the excellent reviews on this topic (Brookes et al., 2013; Sengupta, 2009; Vermeulen et al., 2014). In the remaining sections, we will discuss how different membrane receptors and ion channels contribute to colorectal hypersensitivity in animal models relevant to IBS and IBD and finish by discussing anti-nociceptive mechanisms, which may provide additional novel candidates for therapeutic targeting.

2. Neuroanatomy of the gastrointestinal tract

2.1. Intrinsic innervation

The enteric nervous system (ENS) contains over 10^8 neurons and acts autonomously to generate basic motor and secretory patterns independent of the CNS. Accordingly, it is often referred to as the 'little brain' in the gut. Arranged into web-like plexuses (the myenteric/Auerbach's plexus and the submucosal/Meissner's plexus) its main roles are to regulate gastrointestinal motility and control secretion, absorption and blood supply (Furness et al., 2013; Lomax et al., 2005). The involvement of the ENS in pain signalling is unclear, but most likely lies in the release of neurotransmitters, such as substance P (SP), calcitonin gene-related peptide (CGRP) and serotonin that in turn can activate and sensitise adjacent sensory nerves to cause aberrant intestinal contractility. In support of such a mechanism, mediators released from mucosal biopsies from IBS patients, but not healthy controls can