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Topical review

Mechanisms of visceral pain in health and functional gastrointestinal disorders

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HIGHLIGHTS

- Functional gastrointestinal disorders (FGIDs) are a heterogeneous group of disorders.
- Aetiology remains an enigma but visceral hypersensitivity causes pain in FGIDs.
- Peripheral and central mechanisms cause visceral hypersensitivity and pain.
- Inflammatory mediators activate and sensitize normal and silent nociceptors peripherally.
- Changes in CNS pain modulating mechanisms cause central hyperalgesia.
- Gastrointestinal microbiota is an ecosystem modulating motility and visceral perception.
- Connective tissue abnormalities affect gut mobility and sensations.
- Gastrointestinal neuromuscular disorders disturb gut motility and cause transient dilatations.

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ABSTRACT

Background and aims: Chronic visceral pain is common both in patients with identifiable organic disease and also in those without any structural, biochemical or immunological abnormality such as in the functional gastrointestinal disorders (FGIDs). We aim to provide a contemporaneous summary of pathways involved in visceral nociception and how a variety of mechanisms may influence an individual's experience of visceral pain.

Methods: In this narrative review, we have brought together evidence through a detailed search of Medline in addition to using our experience and exposure to recent research developments from ourselves and other research groups.

Results: FGIDs are a heterogeneous group of disorders whose aetiology largely remains an enigma. The germane hypothesis for the genesis and maintenance of chronic visceral pain in FGIDs is the concept of visceral hypersensitivity. A number of peripheral and central mechanisms have been proposed to account for this epiphenomenon. In the periphery, inflammatory mediators activate and sensitize nociceptive afferent nerves by reducing their transduction thresholds and by inducing the expression and recruitment of hitherto silent nociceptors culminating in an increase in pain sensitivity at the site of injury known as primary hyperalgesia. Centrally, secondary hyperalgesia, defined as an increase in pain sensitivity in anatomically distinct sites, occurs at the level of the spinal dorsal horn. Moreover, the stress responsive physiological systems, genetic and psychological factors may modulate the experience of visceral pain. We also address some novel aetiological concepts in FGIDs, namely the gastrointestinal microbiota, connective tissue abnormalities and the gastrointestinal neuromuscular disorders. Firstly, the gastrointestinal microbiota is a diverse and dynamic ecosystem, that safeguards the host from external pathogens, aids in the metabolism of polysaccharides and lipids, modulates intestinal motility, in addition to modulating visceral perception. Secondly, connective tissue disorders, which traditionally have been considered to be confined largely to the musculoskeletal system, have an increasing evidence base demonstrating the presence of visceral manifestations. Since the sensorimotor apparatus of the GI tract is embedded within connective tissue it should not be surprising that such disorder may result in visceral pain and abnormal gut motility. Thirdly, gastrointestinal neuromuscular diseases refer to a

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heterogeneous group of disorders in which symptoms arise from impaired GI motor activity often manifesting as abnormal transit with or without radiological evidence of transient or persistent dilation of the viscera. Although a number of these are readily recognizable, such as achalasia or Hirschsprung's disease, the cause in a number of patients is not. An international working group has recently addressed this "gap", providing a comprehensive morphologically based diagnostic criteria.

Conclusions/implications: Although marked advances have been made in understanding the mechanisms that contribute to the development and maintenance of visceral pain, many interventions have failed to produce tangible improvement in patient outcomes. In the last part of this review we highlight an emerging approach that has allowed the definition and delineation of temporally stable visceral pain clusters, which may improve participant homogeneity in future studies, potentially facilitate stratification of treatment in FGID and lead to improvements in diagnostic criteria and outcomes.

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1. Background

Visceral pain is a highly variable experience in both health and disease. Chronic visceral pain is common, occurring in patients with organic disease and also in those without any identifiable structural, biochemical or immunological abnormality such as in the functional gastrointestinal disorders (FGIDs). FGIDs are a heterogeneous group of disorders in which a complete understanding of the pathophysiology remains elusive. A central defining feature of the FGID is chronic visceral pain, which is a major factor in motivating patients to seek healthcare and causes a significant reduction in quality of life [1]. Within the European Union, approximately 100 million people are affected by chronic somatic and visceral pain, with 28 million suffering from regular severe pain [2]. This prevalence is associated with a marked societal burden, with 60% sufferers having consulted their doctors between two and nine times in the preceding six months, and approximately 1/5th of patients unable to work [3]. The effective management of visceral pain in FGID is problematic despite substantial progress in basic gastrointestinal (GI) research aimed at identifying the responsible mechanisms [4]. However, the successful translation of this research into improvements in patient outcomes has been limited arguably because a significant proportion of our understanding of visceral nociception has been extrapolated from somatic pain studies [5].

2. Aims

For the purposes of this review we aim to provide the reader with a state of the art update of mechanisms of visceral pain in health but also to provide clinical context through special reference to FGID.

3. Methods

In this narrative review, we have brought together many diverse strands of research through searching the PubMed interface of Medline in addition to using our experience and exposure to recent research developments from colleagues and collaborators across the world. In order to contextualize visceral pain we commence this review with a summary of the sensory pathways from the GI tract to the brain via the spinal dorsal horn that facilitate visceral nociception. In addition, we examine the burden of chronic unexplained visceral pain, and explain how such pain may develop through either peripheral or central sensitization. We also discuss how an individual's experience of visceral pain may be modulated by psychology, genetic factors and the physiological stress responsive systems as well as describing some novel aetiological concepts. Finally we shall introduce, what we believe to be, an exciting and emerging theory in visceral nociceptive research – the definition and delineation of human pain clusters.