Scandinavian Journal of Pain xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Scandinavian Journal of Pain

journal homepage: www.ScandinavianJournalPain.com

Topical review

Psychoneuroimmunological approach to gastrointestinal related pain

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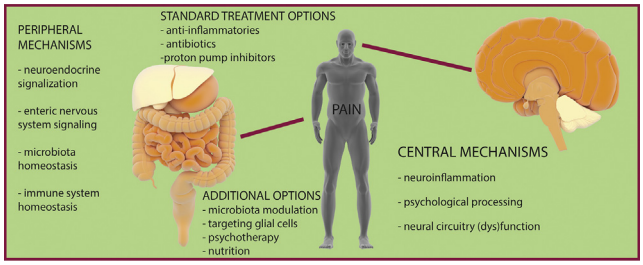
HIGHLIGHTS

- Psychoneuroimmunology brings theoretical and clinical tools to treat GI related pain.
- The gut represents an intersection of immune and nervous system.
- Neurohormonal signalling is a crucial intermediary mechanism in chronic pain.
- Microbiota and glial modulation should be considered as adjunct treatment options.
- Adding specific nutrients represents a useful lifestyle modification to reduce pain.

GRAPHICAL ABSTRACT



ARTICLE INFO

Article history:
Received 19 July 2017
Received in revised form 11 October 2017
Accepted 12 October 2017
Available online xxx

Keywords:
Psychoneuroimmunology
Microbiota
Inflammatory bowel disease
Functional gastrointestinal disorders
Pain

ABSTRACT

Background and purpose (aims): Psychoneuroimmunology is both a theoretical and practical field of medicine in which human biology and psychology are considered an interconnected unity. Through such a framework it is possible to elucidate complex syndromes in gastrointestinal related pain, particularly chronic non-malignant. The aim is to provide insight into pathophysiological mechanisms and suggest treatment modalities according to a comprehensive paradigm. The article also presents novel findings that may guide clinicians to recognize new targets or scientists to find new research topics.
Methods: A literature search of 'PubMed' and 'Google Scholar' databases was performed. Search terms included: 'Visceral pain', 'Psychoneuroimmunology', 'Psychoneuroimmunology and pain', 'Pain in GI system', 'GI related pain', 'Pain and microbiota', 'Enteric nervous system', 'Enteric nervous system and inflammation', 'CNS and pain', 'Inflammation and pain in GI tract', 'Neurogastroenterology', 'Neuroendocrinology', 'Immune system in GI pain'. After searching and reading sources deemed recent and relevant, a narrative review was written with a tendency to discriminate the peripheral, intermediate, and central pathophysiological mechanisms or treatment targets.

Abbreviations: ACC, anterior cingulate cortex; ATP, adenosine triphosphate; CB, cannabinoid receptor; CD, Chron's disease; CGRP, calcitonin-gene related peptide; CNS, central nervous system; CRF, corticotropin releasing factor; ECC, enterochromaffin cell; ENS, enteric nervous system; FGID, functional gastrointestinal disorder; GI, gastrointestinal; GLP-2, glucagon-like peptide-2; HPA, hypothalamus–pituitary–adrenals; IBD, inflammatory bowel disease; IBS, irritable bowel syndrome; IDO, indolamine dioxygenase; LDN, low-dose naltrexone; MT, melatonin receptor; NAD, nicotinamide dinucleotide; NMDA, N-methyl-D-aspartate; NO, nitric oxide; NPY, neuropeptide Y; PAG, periaqueductal grey; PFC, prefrontal cortex; RNS, reactive nitrogen species; ROS, reactive oxygen species; TNF, tumor necrosis factor; TRPV, transient receptor potential cation channel subfamily V; UC, ulcerative colitis; VIP, vasoactive intestinal peptide.

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https://doi.org/10.1016/j.sjpain.2017.10.010

Please cite this article in press as: Toljan K, Vrooman B. Psychoneuroimmunological approach to gastrointestinal related pain. Scand J Pain (2017), https://doi.org/10.1016/j.sjpain.2017.10.010

Results: Recent evidence point out the importance of considering the brain–gut axis as the main connector of the central and peripheral phenomena encountered in patients suffering from chronic non-malignant gastrointestinal related pain. This axis is also a prime clinical target with multiple components to be addressed in order for therapy to be more effective. Patients suffering from inflammatory bowel disease or functional gastrointestinal disorders represent groups that could benefit most from the proposed approach.

Conclusions (based on our findings): Rather than proceeding with established allopathic single-target central or peripheral treatments, by non-invasively modulating the brain–gut axis components such as the psychological and neuroendocrinological status, microbiota, enteric nervous system, or immune cells (e.g. glial or mast cells), a favourable clinical outcome in various chronic gastrointestinal related pain syndromes may be achieved. Clinical tools are readily available in forms of psychotherapy, prebiotics, probiotics, nutritional advice, and off-label drugs. An example of the latter is low-dose naltrexone, a compound which opens the perspective of targeting glial cells to reduce neuroinflammation and ultimately pain.

Implications (our opinion on what our findings mean): Current findings from basic science provide sound mechanistic evidence and once entering clinical practice should yield more effective outcomes for patients. In addition to well-established pharmacotherapy comprised notably of anti-inflammatories, antibiotics, and proton-pump inhibitors, valid treatment strategies may contain other options. These disease modulating add-ons include probiotics, prebiotics, food supplements with anti-inflammatory properties, various forms of psychotherapy, and low-dose naltrexone as a glial modulator that attenuates neuroinflammation. Clearly, a broader and still under exploited set of evidence-based tools is available for clinical use.

Contents

1. Introduction

1.1. Psychoneuroimmunology as a framework in pain management

Since the last quarter of the past century, the field of psychoneuroimmunology has been growing both as a theoretical and a practical medical approach [1–3]. This combines the findings of the physiological interconnectedness between the immunological, neurological, and endocrine aspects of the organism as well as the psychological one [1–4]. Medical terms that describe behaviour such as 'sickness behaviour' [5,6] and syndromes such as 'chronic fatigue syndrome' [7] rarely find the appropriate theoretical and practical medical way of addressing. Common concepts divide the

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