

Topical review

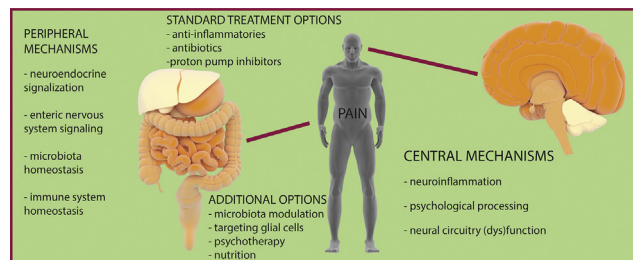
Psychoneuroimmunological approach to gastrointestinal related pain

Karlo Toljan^{a,*}, Bruce Vrooman^b^a Department of Pathophysiology, University of Zagreb School of Medicine, Kispaticeva 12, Zagreb 10 000, Croatia^b Department of Anesthesiology, Dartmouth-Hitchcock Medical Center, 1 Medical Center Dr, Lebanon, NH 03766, USA

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 6 November 2017

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.

* Corresponding author.

E-mail address: karlo.toljan@gmail.com (K. Toljan).<https://doi.org/10.1016/j.sjpain.2017.10.010>

1877-8860/© 2017 Scandinavian Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.

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.

© 2017 Scandinavian Association for the Study of Pain. Published by Elsevier B.V. All rights reserved.

Contents

1.	Introduction	432
1.1.	Psychoneuroimmunology as a framework in pain management	432
1.2.	Methods	433
1.3.	Presenting a comprehensive model for managing gastrointestinal related pain	433
1.4.	Neuroanatomy of pain processing linked to gastrointestinal (GI) tract	433
2.	Pathophysiological mechanisms	433
2.1.	Peripheral pathophysiological mechanisms	434
2.1.1.	Enteric nervous system (ENS) as the third autonomic nervous component	434
2.1.2.	GI tract dysmotility is influenced by kynurenic pathway	434
2.1.3.	Integrity of gut epithelium is affected by inflammation	435
2.1.4.	Serotonin is the ultimate product of an inflammatory cascade in gut epithelium	436
2.1.5.	Microbiota is a salient component in health and disease	436
2.2.	Intermediary pathophysiological mechanisms	436
2.2.1.	Peripheral immune system alterations affect the central nervous system	436
2.2.2.	Chronic pain results from a heterogenic immune cell activation profile	437
2.2.3.	Hormonal dysregulation as a consequence of chronic aberrations	437
2.3.	Central pathophysiological mechanisms	437
2.3.1.	Neuroplastic modifications lead to functional changes of central nervous system	437
3.	Therapeutic approaches	438
3.1.	Treatment focusing on the periphery	438
3.1.1.	Reducing inflammation is possible with medications and lifestyle modifications	438
3.1.2.	Pain associated symptoms are ameliorated by concurrently addressing multiple targets	438
3.2.	Treatment focusing on central components	438
3.2.1.	Reducing central neuroinflammation can be achieved by various modalities	439
3.2.2.	Psychotherapy relies on hierarchical organization of CNS	439
4.	Conclusions	439
4.1.	Strength and limitations of the article	439
4.2.	Future perspectives	439
4.2.1.	Glial cells as novel targets for treating pain	439
4.2.2.	Clinical psychoneuroimmunology supports modulation of pathophysiology	440
	Ethical issues	440
	Conflicts of interest	440
	Acknowledgments	440
	References	440

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

body in subsystems which are then independently considered by various specialists. Fortunately, with the new methods of scientific investigations and an ever growing pool of evidence, this physiologically justified approach gets its application and recognition in a broader medical community [8–10]. From the beginnings in the 1970s by the founder, Robert Ader [1,11], this field now yields more than 50 publications yearly in PubMed database. Psychoneuroimmunology is suited not only when considering chronic diseases [12–14] in which the psychological component is definitely noticed as a factor, but acute states of stress, injury, or disease as well [15–18]. The interplay of cytokines, cellular mechanisms, neural pathways, and hormonal messengers can affect the behaviour if a bottom-up approach is taken, but also the other way around in a top-down approach [3,4,7,17]. The underlying neurobiology of eliciting greater motivation and a favourable response to treatment, including placebo [19], is a valuable tool for a clinician specialized in treating pain and pain related disorders.

Pain is a subjective phenomenon, especially chronic pain which can seem elusive to standard medical classification of the triad aetiology-pathogenesis-clinical presentation, but also one which could be comprehensively approached through a psychoneuroimmunological perspective. In light of the advanced findings in the underlying causes of chronic pain a novel, extended definition of pain has recently been proposed [20], one that includes cognitive and social components in addition to the classic definition which includes well-established sensory and emotional components [21]. By elucidating the complex relations between neurophysiological, endocrine and immunological mechanisms marked by characteristic behavioural traits, psychoneuroimmunology should represent a scientifically valid framework for an integrative and more effective approach in managing pain, e.g. as achievements in interdisciplinary pain management outcomes have noted [22–25].

1.2. 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. Finally, conclusions based on the read material have been formulated with additional suggestions for future considerations. Strengths and weaknesses of methodology are presented further in one of the last sections of this article.

1.3. Presenting a comprehensive model for managing gastrointestinal related pain

The aim of this article is to suggest a clinical approach based on a psychoneuroimmunological pathophysiological reasoning, when treating patients suffering from chronic non-malignant gastrointestinal (GI) pain. This type of pain is commonly present in inflammatory bowel diseases (IBD), namely ulcerative colitis (UC) [26,27] and Crohn's disease (CD) [27,28], but insufficiently dealt with since pain can arise both in exacerbating episodes and in complete clinical organic remission [29]. This makes it a challenge to find an effective long-term therapy. The article should provide a sound rationale for introducing novel clinical options. Another area of GI related pain that could benefit from the psychoneuroimmunological approach is the domain of functional gastrointestinal disorders (FGIDs) in which abdominal

pain is a hallmark and an inclusion criterion for the diagnosis according to authoritative Rome criteria. The latest guideline consensus Rome IV [30,31] from year 2016 features a prominent biopsychosocial model and dubs FGIDs as disorders of gut–brain interaction. According to the aforementioned criteria, FGIDs are divided anatomically (esophageal, gastroduodenal, bowel, centrally mediated, gallbladder, or anorectal disorders), as well as by age (adult, neonate/toddler, or child/adolescent category). It is striking that worldwide prevalence of FGIDs in children is 13.5%. The most common is irritable bowel syndrome (IBS) with a prevalence of 8.8% and girls are affected more often [32,33]. Unfortunately a negative feature of FGID is its persistence from childhood to later adulthood with a rate of more than 40% after 9 years of being diagnosed with a paediatric functional abdominal pain [33,34]. Additionally, anterior cutaneous nerve entrapment syndrome can cause category misdiagnosis by resembling symptomatology and as such is not considered in this manuscript [26].

1.4. Neuroanatomy of pain processing linked to gastrointestinal (GI) tract

Since pain is mediated by neural tissue, a basic division according to neuroanatomy may help direct the treatment. *En gros*, GI related pain may be divided into visceral (inflammation, strictures, adhesions) [35–37], somatic (musculoskeletal) [36,37] and centralized (neurobiological, psychological) [36–38]. Neuroanatomically, the division can be made on the intrinsic GI tract innervation which consists of the enteric nervous system (ENS), and the extrinsic GI tract innervation comprised of vagal, pelvic, and splanchnic nerves which terminate in central nervous system (CNS), i.e. spinal cord or the brain directly [35,36,38]. Spinal cord ascending pathways transmitting afferent pain-related information include the well-known anterolateral quadrant and the recently implicated important conduit for visceral nociception – dorsal funiculus [39–42]. Hierarchically higher centres involved in pain processing include primarily the thalamus, somatosensory, anterior cingulate, and insular cortex. Descending pathways originating from periaqueductal grey matter (PAG), raphe nuclei, and anterior cingulate cortex, represent an important antinociceptive route for exerting the effects of endogenously synthesized opioids (e.g. endorphins), and monoaminergic neurotransmitters such as serotonin, dopamine, and noradrenaline [36,38,42,43]. The anterior cingulate cortex projects to amygdala and PAG. This structural trio comprises salient components of the pain processing network. Following the introduction, pathophysiological mechanisms will be presented, proceeding to current peripheral and central therapeutic approaches (graphically presented by Fig. 1), ultimately mentioning future perspectives with concluding remarks.

2. Pathophysiological mechanisms

The importance of considering the peripheral and central pathophysiological mechanisms via a bidirectional gut–brain axis is a crucial step when investigating the phenomenon of GI related pain in IBD and FGIDs. Topographical division of mechanisms presumes peripheral (disturbances in enteric nervous system, gut epithelium, or microbiota), central (CNS structural and functional changes), and intermediary (immunological and endocrine imbalance) occurring disarrangements. The aforementioned chronic diseases that present with recurring GI pain are commonly accompanied by GI motility disruption in terms of constipation or diarrhoea [28,31]. This dysmotility may arise as a consequence of ongoing inflammation [44] or as a primary malfunction in ENS. The latter is being heavily investigated as a root cause in FGIDs according to a novel paradigm that brought the field of neurogastroenterology

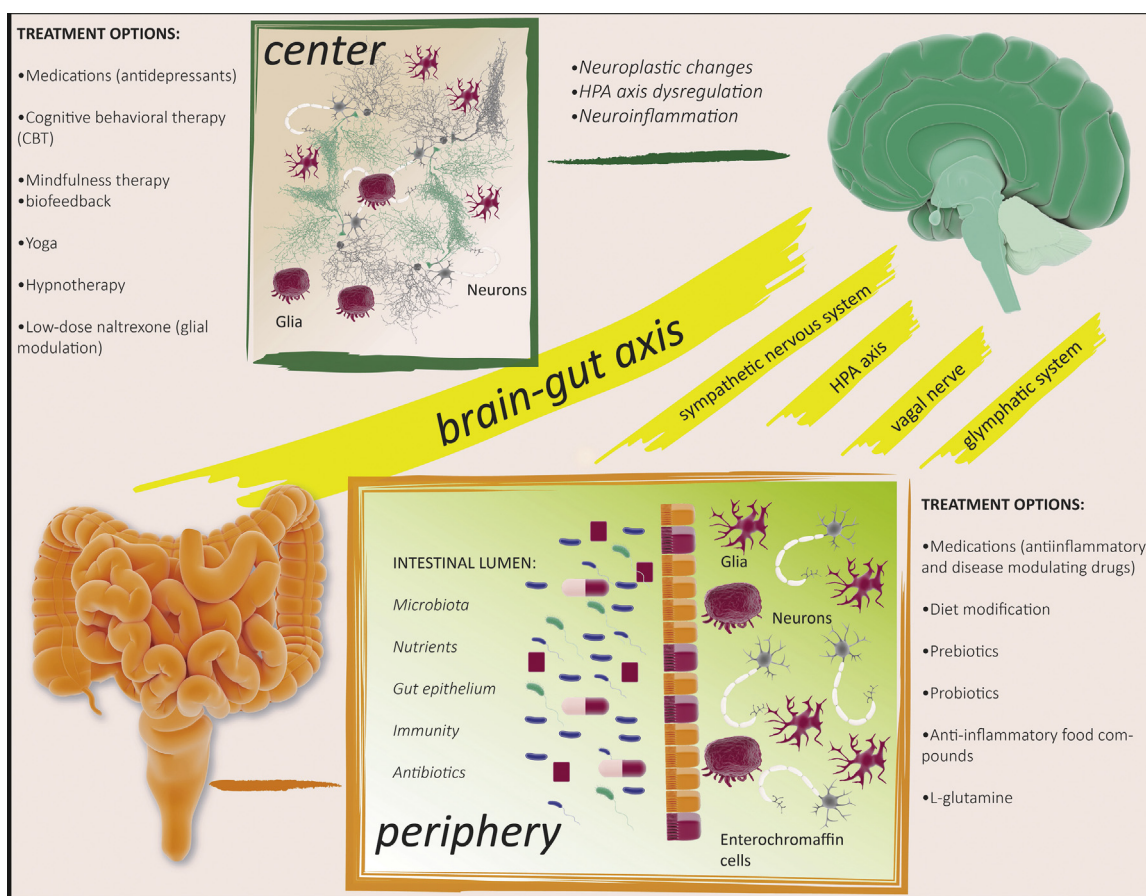


Fig. 1. An overview of pathophysiological components in the periphery and central nervous system with available treatments according to psychoneuroimmunological paradigm.

[45]. The intestinal epithelium is being constantly populated by host's own microbiota in an interactive manner. It represents a physical and immunological barrier for all the agents that arrive through ingestion, such as nutritive compounds, but also bacteria, viruses, and fungi. This leaves the GI tract in a constant process of balancing anti-inflammatory and pro-inflammatory signals. The immunomodulation occurring should keep homeostasis ideally, or if unable, then a dynamic balance with a higher expenditure of resources termed 'allostasis'.

2.1. Peripheral pathophysiological mechanisms

2.1.1. Enteric nervous system (ENS) as the third autonomic nervous component

In Langley's original division of autonomic system, ENS was the third entity among sympathetic and parasympathetic nervous systems. The term 'second brain', clearly depicts the highly complex and functionally important role in physiology and pathophysiology that falls upon this network of 100–500 million neurons spreading through the entire GI tract [46]. It is anatomically divided into two plexuses encircling the lumen of GI tract in two layers (myenteric Auerbach's and submucosal Meissner's, respectively). ENS coordinates the motility and secretion in the GI tract and interacts via same neurotransmitters as CNS, notably acetylcholine (ACh), dopamine and serotonin. It also serves as major pool for neurotransmitter synthesis. Almost 95% of serotonin [47] and 50% of dopamine [48] is synthesized in the ENS, hence its huge importance for entire organismic physiology. The production occurs in enteric neurons, enterochromaffin cells (ECC), epithelial cells and even lamina propria cells [47–49]. There are seven main types of

serotonin receptors, 15 including receptor subtypes, and most are present in the gut. Serotonin is a key neurotransmitter necessary for inducing GI motility and ENS nerve growth [50]. Myenteric serotonergic neurons project to cholinergic submucosal cells which ultimately induce the proliferation of stem cells destined for the epithelium [51]. On the other hand, ECC produced serotonin is pro-inflammatory while neuronal produced exerts protective effects on a cellular level [44].

2.1.2. GI tract dysmotility is influenced by kynurenic pathway

In addition to the cholinergic and serotonergic transmission, a pathophysiological role is especially studied for the effects of a neurotransmitter nitric oxide (NO) and glutamatergic N-methyl-D-aspartate (NMDA) receptors. Inflammation affects the metabolism of tryptophan. This essential amino acid is well known for being a precursor of serotonin, but that's only a meagre 10% of its metabolic fate, the majority or 90% of it being channelled to the kynurenic pathway [52,53]. The kynurenic pathway is immensely important for ultimately producing nicotinamide adenine dinucleotide (NAD), but other end- and side-products include kynurenic, picolinic, and quinolinic acid. These metabolites have an antagonistic (kynurenic and picolinic acid) and agonistic (quinolinic acid) effect on NMDA receptors, thus affecting the ENS neurotransmission and motility [52–54]. Physiological state is characterized by a balance in all metabolite quantities produced. However, by shifting the ENS to an inflammatory milieu and via activation of resident microglia, an imbalance occurs (the process depicted by Fig. 2). Microglia contain the enzyme indolamine dioxygenase (IDO), which favours the kynurenic pathway. It ultimately depletes the ENS of serotonin and creates a significant amount of kynurenic metabolites

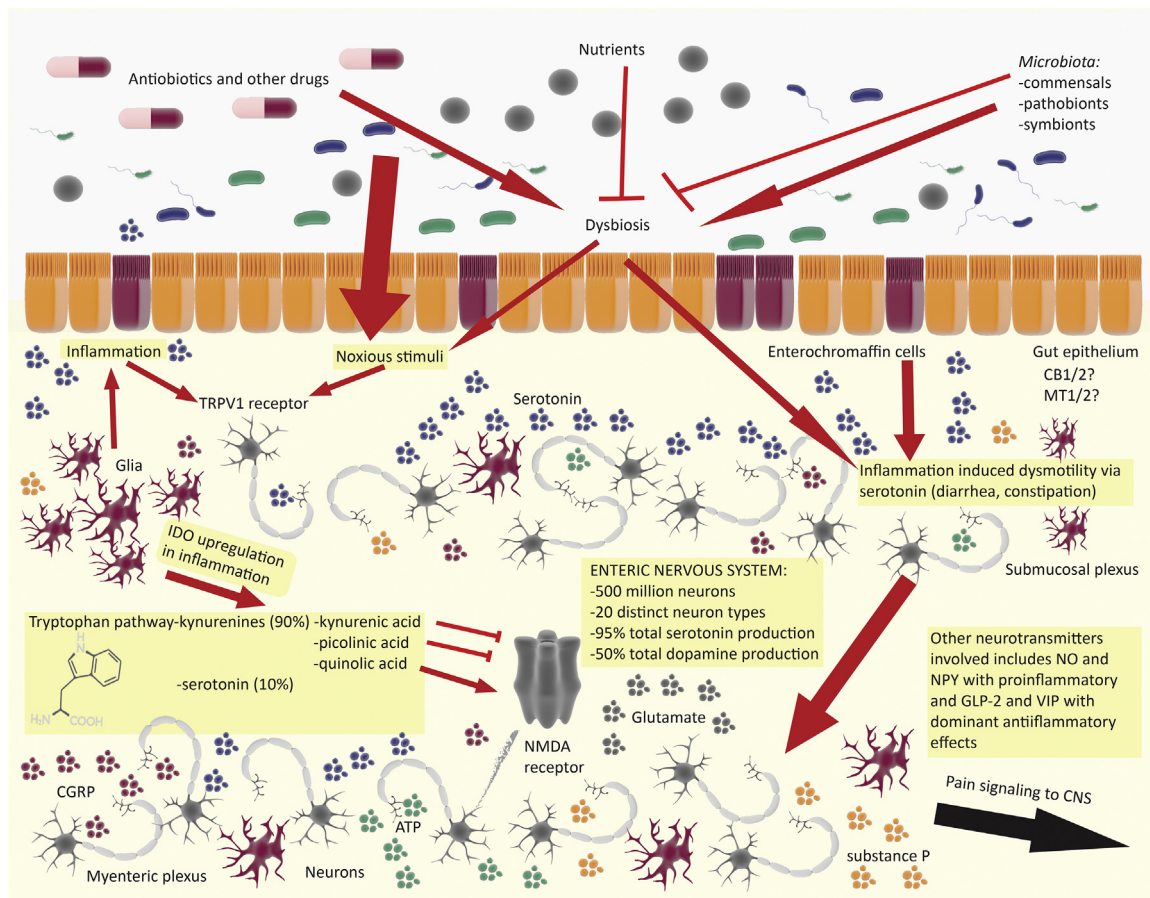


Fig. 2. Pathophysiological process involving the enteric nervous system as an intermediary in the gut–brain axis. CGRP, calcitonin gene related peptide; ATP, adenosine triphosphate; IDO, indolamine dioxygenase; MT 1/2, melatonin 1/2 receptor; CB 1/2, cannabinoid 1/2 receptor; NPY, neuropeptide Y; GLP, glucagon-like peptide; VIP, vasoactive intestinal peptide; NMDA, N-methyl-D-aspartate.

from all the tryptophan available. It has been shown that through these interactions by predominantly exerting NMDA antagonistic effects (via kynurenic acid) in acute inflammatory states, the ENS combats the enhanced motility induced by excitatory pro-inflammatory molecules [53]. The NMDA receptors present on NO emitting cells are the prime targets, so this is an indirect negative feedback mechanism, characteristic for complex regulation, i.e. another similarity of CNS and ENS. Cells secreting NO promote GI dysmotility and enhance the ongoing inflammation through production of reactive oxygen (ROS) and reactive nitrogen species (RNS) [53,55]. Turning down their activity is the goal of this acute regulation by kynurenines and NMDA antagonism. Kynurenic acid considerably downregulates the production of tumour necrosis factor alpha (TNF α) in immune cells [56]. On the other hand, a chronic inflammatory state leads to more NMDA agonistic effects, thus providing a positive feedback loop which represents a pathophysiological vicious cycle. This is the predominant effect of quinolinic acid [53,54]. Nutritional component is also vital for the regulation of these tryptophan metabolic pathways since it highly depends on vitamins and minerals as enzymatic co-factors, e.g. vitamin B₆, vitamin B₂, zinc, copper, manganese and cobalt [52]. Glutamatergic neurotransmission in ENS, previously more or less neglected, recently received much attention in studying certain gut pathophysiological states such as IBD and IBS [57]. Regarding visceral hypersensitivity and nociception in ENS specifically regarding C-fibre neurotransmission, evidence has confirmed all fibres respond to thermal, mechanical and chemical noxious stimuli via transient receptor potential receptors, largely by activation of vanilloid type I receptors (TRPV1) [35,57–59]. Additionally, half the fibres

contain calcitonin-gene related peptide (CGRP) and substance P, while the other half co-express purinergic P2X receptors responding to nucleotides such as ATP [58–62]. By releasing CGRP, a paracrine-signalling molecule with an adjunct vasodilatory effect, an effective communication of the ENS and immune system is achieved. It acts as a crucial signal in the neuro-immune axis [60] and modulates the production, differentiation, and function of all classes of immune cells, i.e. the ongoing research of the ENS is uncovering roles for other peptides in gut-associated inflammatory cascades. It was shown that vasoactive intestinal peptide (VIP) and glucagon-like peptide 2 (GLP-2) promote an anti-inflammatory response by reducing the glial secretion of cytokines (TNF α , interleukin-1 β , interferon- γ) and RNS, while neuropeptide Y (NPY) does the opposite [63,64]. The ENS is contained within the gut and is receiving stimuli highly dependent on the state of the epithelium, which is the barrier to the lumen.

2.1.3. Integrity of gut epithelium is affected by inflammation

The part of the gut epithelium that is in the centre of pathophysiological investigation is the intestinal one, due to its length, surface, its role in nutrient resorption and the fact it is housing the largest part of the microbiota [45]. The epithelial surface represents an essential physiological barrier, while losing its continuity leads to a state of pathological permeability, a phenomenon popularly called 'leaky-gut syndrome' [65]. The 'leaky-gut' permits various exogenous substances, e.g. sugars, peptides, bacteria, to enter the inner layers of the GI tract or even bloodstream, after which they spread across the body. A state of overt generalized or localized inflammation may ensue, in acute or chronic form, consequentially

aggravating present diseases or inducing new ones by potentiating pathophysiological inflammatory reactions [66]. Some of the causes for a greater intestinal permeability can be found in primary inflammatory processes affecting the epithelium (as in UC or CD) [67], the overgrowth of pathogenic bacteria from microbiota [68,69], viruses [68], autoimmune diseases such as Coeliac disease [70], and novel causes that could be linked directly to gluten regardless of the autoimmune response [71,72]. The average epithelial cell survives for five days, after which it is replaced by a matured stem cell. Inflammatory cytokines such as TNF α increase the shedding of epithelial cells and the newly formed gaps are not always sealed as they physiologically should be via tight junctions [73].

2.1.4. Serotonin is the ultimate product of an inflammatory cascade in gut epithelium

Enterochromaffin cells (ECCs), being a part of the gut lining and containing voltage gated sodium and calcium channels as well as α 2A adrenoreceptors [74] that characterize them as sensory components, are fully implicated in pathophysiological processes affecting the epithelium. The connection of ECC, microglia and ENS provides a basis for the interaction of the specified epithelium, immune and neural system. By producing serotonin, ECCs exhibit a major signalling cascade which ultimately leads to a pro-inflammatory response mediated by the aforementioned tricellular connection. ECCs are proliferating in inflammatory conditions [75,76]. Recently, it has been demonstrated that ECCs and peripheral nervous terminals communicate with synapse-like connections [74]. This represents the gut–brain axis as a direct continuum and indicates a direct role of microbiota and peripheral immune status in potentiating visceral hyperalgesia. Furthermore, melatonin is another metabolite derived from serotonin and its role is still largely unknown in the GI tract [77]. It has been shown recently that melatonin receptors MT1 and MT2 are highly spread throughout gut epithelial cells and ENS [78]. The exact mechanisms and physiological role for these still remains to be explained. Endogenous cannabinoid system may also prove salient in future research as more aspects are being uncovered. The specific cannabinoid receptor CB1 is present in the gut and once activated, demonstrates a protective effect measured by inflammatory products, IgA secretion and intestinal permeability [79]. Also, cannabinoid receptor CB2 emerges as an interesting pharmacological therapeutic target according to recent experimental data [59]. The gut lining is definitely a physical membrane, nevertheless it should always be considered as a part of a functional one, in unity with the immune component, the ENS and gut microbiota.

2.1.5. Microbiota is a salient component in health and disease

Bacteria residing in each human individual account for at least 100 trillion cells [80], the number being three times greater than the entire sum of own human cells which has recently been counted to a value of 37.2 trillion [81]. The enormous contribution of microbiota to genetic interactions with and within the host is demonstrated by the fact that these bacteria encode genes in a 100-fold greater amount than the entire human genome [82]. This genetic pool is termed microbiome and when considering it in an interactive relation with the human genome the term 'holobiome' is used. From the functional perspective, the microbiota can be considered as an organ located in the GI lumen. It consists of commensals, symbionts and pathobionts. Maintaining a constant dynamic balance between the three is crucial for health and if an imbalance occurs, termed dysbiosis, serious pathophysiological processes are started. Microbiota is modified by dietary habits, the surrounding habitat and interaction with the environment such as other people, animals, plants, etc. Since year 2007 and the NIH microbiome initiative [83], a staggering rise in research regarding microbiota is noted, with more than 2000 articles being published in the last few

consecutive years. As evidence are gathered, microbiota emerges as an important contributor to physiology and pathophysiology in most, if not all diseases, ranging from neuropsychiatric to metabolic ones [84,85]. With the recognition of the various axes in the body, e.g. brain–gut [86], brain–heart [87], liver–brain [66], and by combining it with the microbiota as a salient component to organismic immunology and metabolism, an inevitable road is paved for the integrative approach in medicine. Psychoneuroimmunology as a conceptual scientific backbone in ongoing research, devised years before any of this was known, testifies Ader's framework is bound to increasingly enter the clinical practice in order to achieve better treatment outcomes. Research on microbiota yields findings that correlate microbial contents with health or disease. It still remains to fully elucidate the cause–effect relationship with the correlation, i.e. does the dysbiosis cause the disease or the other way around. However, the microbial influence in an ongoing pathophysiological process cannot be ignored. There are approximately 1000 strains of bacteria present in the GI tract, most of those being anaerobic [80]. Microbiota varies across life and established findings point to a physiological loss of microbial biodiversity with ageing. Two most represented phyla are *Firmicutes* and *Bacteroidetes* [80]. The ratio between microbial phyla has been studied in various diseases. It has been shown that a dysbiosis linked with Western-diet eating habits causing a *Firmicutes* prevalence and decreasing *Bacteroides* and *Lactobacilli* levels (both *Bacteroidetes* phyla) [88], is correlated with IBS [89]. In patients suffering from acute episode of UC, a lower level of microbial diversity has been noted as well as an absolute and relative increase in the amount of pathobionts such as *E. coli* and *Campylobacter* with a restitution of symbionts once disease remission was achieved [90]. In analysis of patients suffering from CD, a significant predomination of *Firmicutes* phyla has been marked in the mucosal and even submucosal layers [91]. The presence of pathobionts has a direct pathological effect and an indirect one in exacerbating or prolonging the acute inflammatory episode and concurrent pain [92]. Microbiota serves a prominent metabolic role as a source of essential vitamins and short-chain fatty acids (SCFA), which enterocytes and further 'upstream' hepatocytes use for energetic purposes. In that sense dysbiosis could potentially lead to malnutrition and further aggravate the effects of the primary disease. Microbiota is closely involved directly with modulating the immune pattern and interacts bidirectional with Th1, Th2, Th17 and T_{reg} cells, also influencing the production of TNF α and Interleukin-1 β [91].

2.2. Intermediary pathophysiological mechanisms

2.2.1. Peripheral immune system alterations affect the central nervous system

The immune system is especially salient for proper functioning of the GI tract. By keeping the possible noxious bacterial products or the bacteria itself away from entering the bloodstream, a powerful role is being fulfilled. The GI lymphatic tissue represents the largest peripheral one, the appendix even being called the intestinal tonsil. It is connected with central and other peripheral lymphoid tissues and that is how a localized immune-mediated response in the GI tract can elicit systemic effects. By constantly interacting with the content of the gut lumen depending on the state of the epithelium, immunosurveillance has a crucial adaptive role. The potential unwanted too-revved up inflammatory process can become counterproductive, affecting the GI organs and the ENS. The peripheral neuroinflammation perpetuated by microglia disrupts the CNS balance as well. Directly, autonomic nervous tissue such as the vagal nerve, mediates the thrombin induced apoptosis in the CNS which is linked with central microglial and astrocyte activation [93]. This comes from the standard model of experimentally induced colitis where a marked decrease of neurons in efferent vagal nuclei

has been noted. Indirectly, peripheral neurotransmitter synthesis is disrupted. This leads to depletion of CNS serotonin or dopamine and the metabolic shift to kynurenic profile enlarges the pool of neuroexcitatory and neuroinflammatory derivatives with a potential neurotoxic epilogue [53].

2.2.2. Chronic pain results from a heterogenic immune cell activation profile

Other than microglia, another class of immune cells have been implicated in IBD pathology. Mast cells tend to proliferate significantly in IBD [94,95] and IBS [96,97]. The secretion of histamine, tryptase, and serotonin initiates and maintains a vicious cycle by these being both activating and secretory factors for mast cells in particular, but other immune cells also [94]. Mast cells are also interacting with the ENS and even CNS [98], therefore eliciting an influence far away from the primary focus of inflammation [99]. T-cells are also implicated in inflammatory GI pathology. Current knowledge recognizes the characteristic hallmarks of CD being linked to Th1 and Th17 cell profile differentiation, accompanied by cytokines such as IL-12, IL-23 and interferon-gamma [100,101]. On the other hand, in UC, a typical profile of immune response is favouring Th2 response together with IL-4 and IL-13, the latter being heftily produced by natural killer T-cells [101–103]. This points to various immune mechanisms leading to respective clinical presentations and histopathological findings, but ultimately inducing chronic GI pain as a common symptom. Finally the response of macrophages can either promote inflammation by being polarized to a M1 profile, or exert an anti-inflammatory effect by polarizing to M2 profile [104]. This has recently gained a lot of attention, since it is valid for both peripheral macrophages as well as microglial cells [104,105]. New evidence for the existence of a unique CNS lymphatic system connected to the peripheral lymph drainage, dubbed 'the glymphatic' one, extends the connection of peripheral and central immunity [106]. The glymphatic system is a conduit connecting the perivascular spaces of cerebral arteries and veins. The path is made by astrocytes and serves as a clearance mechanism parallel to the veins. Cerebrospinal fluid and arterial blood filtrate flow into the arterial perivascular space. Its flow, regulated by astroglia, continues via venous perivascular space until ultimately reaching proper lymphatic drainage. This also redefines the old paradigms of the brain being an immunoprivileged site. Acute and chronic inflammation alters behaviour [107]. Accordingly, hormonal changes are also noted. This points to the other main intermediary pathophysiological route, namely the hormonal system, one which is often disrupted in any chronic disease.

2.2.3. Hormonal dysregulation as a consequence of chronic aberrations

The main neurohormonal axes are consisted of the hypothalamus–pituitary–target organ/tissue model. The main axis thoroughly investigated in psychoneuroimmunological research is the hypothalamus–pituitary–adrenals (HPA) axis [2]. It mediates the acute and chronic stress response changes by directly freeing substantial amounts of cortisol and catecholamines from the adrenal cortex and medulla, respectively [108]. Acutely, a state of higher immunoreactivity is noted, but chronically it leads to a higher level of pro-inflammatory cytokines. Corticotropin releasing factor (CRF), IL-6 and TNF α being more expressed demonstrate the signalling interconnectedness of the immunological and neuroendocrine systems [109]. Indirectly, the HPA activation disrupts all other hormonal axes, such as the gonadal or growth axes, with multiple pathophysiological cycles started in order to achieve an allostasis – a defective homeostasis [110]. The aforementioned GI pathologies with pain as a prominent presenting component are proven to be linked with hormonal imbalances as well. Furthermore, GI related pathology impacts the dietary habits and

digestion in the affected people, leading to malnutrition, vitamin deficiencies, especially lipid soluble ones, and shortage of macro and micronutrients necessary for proper hormone production (e.g. folates, K, Fe, Ca, Mg, Zn, Se, vitamin A, vitamin D, vitamin B12) [111,112]. Hormonal imbalance can further lead to osteoporosis, hypothyroidism, hypogonadism, and glucose and insulin dysregulation [113–115]. All of these perpetuate the pain component, since pain is perceived from a cognitive and social aspect as noted before. The long term application of drugs used to treat IBD or FGID can further predispose patients to hormonal imbalances (e.g. steroids [116]) or nutritional deficiencies (e.g. proton-pump inhibitors impairing calcium absorption [117,118]). The disease per se carries the negative impact on overall health, but the iatrogenic effects should not be disregarded as GI disorders linked to pain are significantly present in the population [119]. The immunological and hormonal regulation are intertwined and they cover the entire organism, however the penultimate pathophysiological mechanism encompasses the CNS as the key cognitive and bodily integrator where the pain is indeed consciously experienced.

2.3. Central pathophysiological mechanisms

2.3.1. Neuroplastic modifications lead to functional changes of central nervous system

In chronic pain, various pathophysiological processes take place at the level of spinal cord and the brain. From a psychoneuroimmunological standpoint, the affection of CNS is not representing these central structures solely as a target, but also as a source for contributing pathophysiological stimuli and changes affecting the neuro-immune axis. With ongoing chronic pain and inflammatory cascades, multiple typical symptoms such as hyperalgesia or allodynia are noted [35,120,121]. Peripheral sensitization at the level of afferents and central sensitization at the level of higher cortical structures represent key chronic pain-related mechanisms occurring in CNS [122]. Due to the ability of the nervous system to rewire itself constantly, also known as 'neuroplasticity', unfavourable consequences may be elicited and chronic pain is a typical example of such improper adaptation [123]. From an evolutionary point of view, chronic pain may have been useful to provide the necessary sparing of the injured body part for a longer period of time in order to heal. However, with drastic evolutionary leaps and environmental changes, chronic pain is presently regarded as a maladaptive mechanism, in essence being an evolutionary mismatch mechanism for current conditions. After a prolonged period of peripheral nervous stimulation with a nociceptive or inflammatory process, central structures tend to succumb to neuroplastic modulation. Neuroplasticity, usually described as an effective tool for motor learning and rehabilitation, may display both positive and negative features when considering pain since it is inherently a neutral phenomenon. The pain matrix is a complex of CNS structures important for processing pain [123,124], namely the somatosensory cortex (S1,S2), insular cortex, anterior cingulate cortex (ACC), amygdala, prefrontal cortex (PFC), and thalamus. The PFC is important for emotional and cognitive processing of pain, whereas amygdala and ACC for noting pain as an unpleasant experience [123–125]. The other structures of the pain matrix are primarily providing sensorial discrimination of painful stimuli. Even though various triggers and diseases may lead to chronic pain neuroplastic changes, it mostly ends with uniform alterations in the pain matrix. The continuous neuronal excitation leads to diminished grey matter volume in amygdala, ACC and insular cortex [126–129]. The functioning of the brain measured via functional magnetic resonance imaging (fMRI) without any particular task is known as the default mode network (DMN). Its counterpart is the attention system, it being the fMRI pattern of activation when person is presented with a novel task or stimulus that requires active involvement. With fMRI

studies that had been conducted in people affected by chronic pain, evidence is provided that there is a notable and distinct shift in the DMN and attention system functioning, thusly displaying a feature of a possible biomarker [123,130]. The pathological activation pattern linked with neuroplastic changes shows a receptivity for heteronymous set of stimuli, i.e. once these troublesome alterations occur, a person might react to different provoking stimuli with an exaggerated central response [121]. The primary peripheral input may even be absent, but the pain symptomatology will persist. In such cases, the pathophysiology extends further from the immunological and neurological substrates, reaching the domain of psychological. As mentioned before, when considering FGID in accordance with Rome IV criteria, a prominent role for functional disruption of CNS is introduced [30,128]. Following treatment these pathological neuroplastic changes measured by fMRI should reduce or revert to the activation pattern of normal, non-affected individuals'.

3. Therapeutic approaches

Respecting the psychoneuroimmunological therapeutic approach it is vital to keep the holistic perspective in mind. However, that does not mean conventional symptom-orientated medicine does not provide benefits for the patient. It most certainly leads to favourable outcomes. Additionally, by addressing the entire spectrum of aforementioned pathophysiological alterations taking place, even more effective results may be achieved. Treatments can be roughly divided in those acting primarily on the periphery or the centre. The periphery as a single target is a more sound option for IBD-spectrum of diseases, since the GI tract represents the pathophysiological crucial origin. CNS and the neural axis are major targets for cases of FGID, this being confirmed by a paradigm shift in gastroenterology with the introduction of Rome IV criteria and the stressing of the novel discipline of neurogastroenterology [30,31]. The best practice would be to combine both, i.e. taking the bottom-up and top-down approach in managing the diseases. This does not only involve the healthcare providers, but a very prominent active role is reserved for the patient, especially regarding acquiring coping skills and making an effort to engage with the psychodynamics. Even though the organism is a unity and no true division on peripheral and central structures is possible in terms of imposing treatment on one while excluding the other, a perspective taken here emphasizes the predominant target being either the GI tract and its relating structures or the CNS.

3.1. Treatment focusing on the periphery

3.1.1. Reducing inflammation is possible with medications and lifestyle modifications

The main goal would be to lower any present inflammation in the GI tract, a hallmark of IBD or states with increased intestinal permeability. This can be achieved effectively by applying pharmacotherapy, namely drugs such as 5-aminosalicylates, corticosteroids, thiopurines, methotrexate, calcineurin inhibitors, anti-TNF agents (infliximab, adalimumab), anti-adhesion agents (vedolizumab, etrolizumab), JAK inhibitors and antibiotics [131]. Most patients respond well to a combination of more than one, but in the long-run the response rate drops and this makes unlikely for pharmacotherapy to ever exist as a single modality when treating IBD [132]. With ongoing discoveries in the area of microbiomics, adding prebiotics, probiotics and antibiotics as adjunct therapeutics proved to be useful for modulating the dysbiosis and restoring GI luminal homeostasis [85,133,134]. Strong evidence for the latter are still lacking, but ongoing research show the importance

of microbiota-gut-brain axis in numerous diseases including neuropsychiatric, cardiovascular and GI-related ones [85]. Following the success in treating *C. difficile* [135], drastic experiments are being made in the area of faecal transplants, but of no clinically confirmed value in treating IBD for now [136,137]. Nutritional component is extremely important and should never be neglected in chronic GI-related pathology. Due to the nutritional imbalances mentioned earlier, a special focus should be brought to the current nutritional status of the patient in order to correct vitamin and mineral deficiencies or even overt symptoms such as anaemia [138]. Anti-inflammatory diet should also be implemented, one especially rich in essential fatty acids while keeping even the omega-3 to omega-6 ratio, something that's a rarity with Western-diet habits [139]. Additionally, anti-oxidative and hormetic food compounds such as curcumin [140,141], allicin [142], resveratrol [143], and quercetin [144,145] may also provide beneficial effects for the GI epithelium. An adequate intake of L-glutamine provides a substrate of great value for enterocytes [146,147]. By reducing inflammation in the GI tract, a direct origin for IBD-related pathology is covered. Secondly, by reducing glial activation in the ENS and with established homeostasis of 'the second brain', a prerequisite for adequate neurotransmitter synthesis is ascertained. This extends further to the CNS via the neuronal and immunological connections explained earlier in the context of pathophysiology.

3.1.2. Pain associated symptoms are ameliorated by concurrently addressing multiple targets

The intermediary systems, namely the hormonal and autonomic nervous, are also in the need for balancing in order to achieve a more robust organismic state. Proper functioning of the HPA axis, melatonin secretion, gonadal axes, and growth hormone and glucoregulatory mechanisms is in order, as well as the balance between the sympathetic and parasympathetic drives. The imbalance of these systems is most definitely visible in sleep disturbances, fatigue, irritability, weight gain, and similar complaints which are often linked with chronic pain as additional symptoms, in this case being both the end-results and pathophysiological contributors on their own, respectively [148–150]. To break these vicious cycles, centrally orientated therapy is something that comes adjunctively in an integrative approach, with psychoneuroimmunological therapy being precisely the epitome. Treating symptoms occurring in IBD and FGID such as diarrhoea, constipation, fatigue, nausea or vomiting, and reduction in appetite with conventional pharmacotherapy and interventional procedures may be useful for short-term relief, but regulating the underlying pathophysiological mechanisms and possibly covering as much pathways as possible should provide long-term improvements [151]. Even though the therapy of GI-related pain should be guided according to the exact cause, oftentimes it remains difficult to identify the full extent of pathophysiological process and advance beyond symptomatic treatment. Unfortunately analgesics do not represent a permanently effective solution, even leading to heavy opioid usage among patients with IBD [152]. Novel effective pharmacotherapeutic options could include cannabis derivatives, since recent studies give encouraging results [153–155]. Nonetheless, drawbacks are also to be taken into account and currently no sound evidence that support cannabinoid use as a conventional clinical option exist. With emerging knowledge that neurogastroenterology provides, the psychoneuroimmunological approach currently represents a promising direction and offers, but also demands multiple therapeutic modalities. Genetic factors, previously thought to be an unmodifiable component, gain new dynamic features with the growing knowledge supporting epigenetic modifications as a fluctuating influence [156,157].

3.2. Treatment focusing on central components

3.2.1. Reducing central neuroinflammation can be achieved by various modalities

Centrally targeted pharmacotherapy for GI-related pain [38] should seem inevitable after the considerable elaboration of the physiological and pathophysiological connection of the CNS and periphery. With chronic abdominal pain which leads to alterations in neural-circuitry, neuroplastic changes with significant anatomical and ultimately behavioural changes in a patient [158–160]. In IBD and similar primary peripheral inflammatory pathologies, these changes are presumably secondary. This leads to focusing the therapy primarily on the peripheral GI inflammation. However, with chronic persisting disease, even under pharmacotherapy, CNS changes that significantly contribute to the gravity of flare-ups cannot be ignored [109]. High perception of stress is a hugely important predictor of a symptomatic flare [161]. Therefore, with the longer duration of the disease, the stress-resilience lowers and the patient suffers stronger and longer-lasting relapses. On the other hand, FGID-spectrum is recently considered a gut–brain disorder in definition by authoritative Rome IV [30,31], thus a centrally based approach seems vital and can even be considered etiological in its essence. By implementing cognitive behavioural [162–165] or mindfulness psychotherapy [166,167], various relaxation techniques such as yoga [168], biofeedback [169,170], and hypnotherapy [171–173], much can be done to alleviate the central component in IBD and FGID pathology. It has been shown that all of the aforementioned reduce stress, inflammatory cytokines and disease symptoms. The use of psychobiotics, i.e. probiotics that influence the CNS via microbiota–gut–brain axis, may also add a beneficial effect [133]. The use of antidepressant drugs which effectively aid patients with chronic abdominal pain [38] signifies that a dysregulation of neurotransmitters undoubtedly occurs. By reducing the activation of microglia, mediating the neuroinflammatory reactions in the ENS and the CNS [174], a proportion of pain generating cytokines affecting the neurons could be reduced. This glial modulation to a more favourable non-inflammatory profile should happen after reducing the general amount of inflammation in the body, i.e. by restoring ‘peripheral’ homeostasis [105]. With the healthy functioning ENS, the neurotransmitter pool for serotonin and dopamine ought to be replenished and kynurenic metabolites accordingly balanced ultimately decreasing the amount of activated microglia.

3.2.2. Psychotherapy relies on hierarchical organization of CNS

The function of all psychodynamically orientated therapy is to activate the prefrontal cortex, which drives inhibitory projections to ‘hierarchically lower’ anxiety-causing centres. The goal is to lower the negative rumination which leads to arousal of central pain-matrix, mostly reducing amygdala and insular over-activation [175]. These structures are related to limbic areas and activation of autonomic system, both commonly linked to most, if not all, anxiety and chronic-stress states [176]. Patients with chronic abdominal discomfort desperately seek therapies, hence ending as users of complementary and alternative medicine [177–179]. It includes physiotherapy, chiropractic, acupuncture, homeopathy, and massage therapy. Some of these modalities are also a part of the chronic pain rehabilitation programme, which represents an effective holistic approach for most kinds of chronic pain [180,181]. Lastly, the powerful phenomenon of placebo should not be neglected when considering psychoneuroimmunology and GI-related pain [19,182–184]. The healthcare provider–patient relationship appears to be therapeutic in itself and the belief in a good outcome boosts the mighty endogenous mechanisms that aid healing and data even show that the more frequent patient visits were, the more predictive it was a measure of a placebo response

[184]. Endogenous analgesics, endorphins, are being released from the brain. The stimulation of the central structure PAG sends mighty descending analgesic projections and elicits pain relief [43]. However, placebo extends beyond pain relief, it implicates the partial or even full remission of the disease. In terms of IBD, this especially depicts the impact of the *psyche* and *neuro* on the *immuno*. The bottom-up based treatments and the top-down intertwine exactly at the CNS. This has been recognized by gastroenterologists and other medical specialists respectively, by adopting the integrative approach. Future perspectives, fuelled by growing understanding of the complex pathophysiology, as cases of chronic abdominal pain are, point to inclusion of the CNS as the linking central chain in any disease that is being studied integratively.

4. Conclusions

4.1. Strength and limitations of the article

By providing a comprehensive compilation based on findings from multiple research fields, the article should provide an extensive resource for clinicians interested in up-to-date evidence. The large area covered yields new pain treatment strategies and presents an integrative line of thought that may be implemented clinically. The article benefits as much as it suffers in regard to the used methodology. Primarily it could have led to biased presenting of facts. However, that is consistent with the true nature of a narrative article. From authors' perspective, best available evidence were used in order to support an approach that may be considered as an upgrade to the current standard of pain management care.

4.2. Future perspectives

4.2.1. Glial cells as novel targets for treating pain

The past few years mark a shift in traditional allopathic approach to combating pain. Instead of utilizing just pharmacotherapy that consists of well-known traditional analgesics and anti-inflammatories as well as adjunctive medication such as antidepressants and anti-epileptics, immunomodulation seems to be entering as the next step in pain-research and clinical practice also [185–187]. By understanding the intercellular and intracellular signalling in chronic pain, the traditional paradigm of considering just the neuronal component is expanding heavily to include the area of glia [188,189]. Chronic pain leads to revved up microglia, a state which does not need the peripheral initial trigger to cause CNS functional alterations, but is a self-perpetuating process [105,190,191]. On top of that, microglia is also involved in the pathogenesis of opioid induced hyperalgesia [192], a phenomenon at the other end of the spectrum. When treating chronic pain iatrogenic consequences should also be considered, remembering that certain long-term medical treatments may worsen initial symptomatology. Glial modulation is pharmacologically possible by a well-used drug, an opioid antagonist naltrexone [193]. The dosage used for this indication is lesser than the standard dose of 50–100 mg. In the range 1.5–4.5 mg which has been clinically tested for now, termed as low-dose naltrexone or LDN therapy, considerable pain relief was achieved in patients with chronic pain including fibromyalgia, IBS and IBD [194–196]. Further scientific research in area of LDN is needed, since the current ones happening are too few. A reasonable amount of evidence points that LDN's target is the Toll-like 4 receptor found on proinflammatory microglia phenotype [105,188,194–197]. This goes in hand with the observed immunomodulatory effects, rather than immunosuppressive, as traditional anti-inflammatories cause. Other than LDN therapy, glial modulation is possible by reducing general levels of

inflammation in the body through dietary and behavioural modifications, most of those mentioned earlier [198–200].

4.2.2. Clinical psychoneuroimmunology supports modulation of pathophysiology

Immune modulation, glial modulation, as well as microbiota modulation, illustrate that homeostatic principles are respected as the way of combating chronic pain. Psychoneuroimmunology shows that in health and disease it is all about fine tuning the processes occurring, never to extinguish them entirely. This approach could also be defined as a one between what has traditionally been named the ‘allopathic’ and the ‘homoeopathic’, since it is applying neither disease-opposing nor disease-causing agents. The suitable name would be modulopathy, thus describing the true nature of practical psychoneuroimmunology. Modulating patient’s psychological responses, neural plasticity and signalling, and immunological responses in a manner that will gradually calm vicious cycles and possibly restore the homeostasis, is the goal for the discussed therapeutic approach. It might be considered an arduous path, but more importantly, as a solid one to attain long-term amelioration of chronic pain.

Ethical issues

None.

Conflicts of interest

The authors declare no conflict of interest.

Acknowledgments

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

- [1] Ader R. On the development of psychoneuroimmunology. *Eur J Pharmacol* 2000;405:167–76.
- [2] Irwin MR. Human psychoneuroimmunology: 20 years of discovery. *Brain Behav Immun* 2008;22:129–39.
- [3] Zachariae R. Psychoneuroimmunology: a bio-psycho-social approach to health and disease. *Scand J Psychol* 2009;50:645–51.
- [4] Ziemssen T, Kern S. Psychoneuroimmunology – cross-talk between the immune and nervous systems. *J Neurol* 2007;254(Suppl.):8–11.
- [5] Kelley KW, Bluth RM, Dantzer R, Zhou JH, Shen WH, Johnson RW, Broussard SR. Cytokine-induced sickness behavior. *Brain Behav Immun* 2003;17(Suppl.):112–8.
- [6] Eisenberger NI, Moieni M, Inagaki TK, Muscatell KA, Irwin MR. In sickness and in health: the co-regulation of inflammation and social behavior. *Neuropsychopharmacology* 2016;1–38.
- [7] Patarca R. Cytokines and chronic fatigue syndrome. *Ann N Y Acad Sci* 2001;933:185–200.
- [8] Black DS, Slavich GM. Mindfulness meditation and the immune system: a systematic review of randomized controlled trials. *Ann N Y Acad Sci* 2016;1–12.
- [9] Hulett JM, Armer JM. A systematic review of spiritually based interventions and psychoneuroimmunological outcomes in breast cancer survivorship. *Integr Cancer Ther* 2016.
- [10] Minelli A. Brief training of psychoneuroendocrinology-based meditation (PNEIMED) reduces stress symptom ratings and improves control on salivary cortisol secretion under basal and stimulated conditions. *Explore* 2014;10:170–9.
- [11] Irwin MR, Robert Ader: psychologist, past president of the American Psychosomatic Society, and pioneer in psychoneuroimmunology research. *Psychosom Med* 2012;74:783–4.
- [12] Leonard BE, Ayumu M. The psychoneuroimmunology of depression. *Hum Psychopharmacol Clin Exp* 2009;24:165–75.
- [13] Kern S, Ziemssen T. Brain – immune communication psychoneuroimmunology of multiple sclerosis. *Mult Scler* 2008;6–21.
- [14] Nassau JH, Tien K, Fritz GK. Review of the literature: integrating psychoneuroimmunology into pediatric chronic illness interventions. *J Pediatr Psychol* 2008;33:195–207.
- [15] Caine RM. Psychological influences in critical care: perspectives from psychoneuroimmunology. *Crit Care Nurse* 2003;23:60–70.
- [16] Denson TF, Spanovic M, Miller N. Cognitive appraisals and emotions predict cortisol and immune responses: a meta-analysis of acute laboratory social stressors and emotion inductions. *Psychol Bull* 2009;135:823–53.
- [17] Skinner R, Georgiou R, Thornton P, Rothwell N. Psychoneuroimmunology of stroke. *Immunol Allergy Clin N Am* 2009;29:359–79.
- [18] Uhlig T, Kallus KW. The brain: a psychoneuroimmunological approach. *Curr Opin Anaesthesiol* 2005;18:147–50.
- [19] Pacheco-López G, Engler H, Niemi MB, Schedlowski M. Expectations and associations that heal: immunomodulatory placebo effects and its neurobiology. *Brain Behav Immun* 2006;20:430–46.
- [20] de AC, Williams C, Craig KD. Updating the definition of pain. *Pain* 2016;1.
- [21] IASP Taxonomy Working Group. Pain terms a current list with definitions and notes on usage. *Pain* 1986;24:S215–21.
- [22] Clark T, Wakim J, Noe C. Getting ‘unstuck’: a multi-site evaluation of the efficacy of an interdisciplinary pain intervention program for chronic low back pain. *Healthcare* 2016;4:33.
- [23] Gagnon CM, Stanos SP, van der Ende G, Rader LR, Harden RN. Treatment outcomes for workers compensation patients in a US-based interdisciplinary pain management program. *Pain Pract* 2013;13:282–8.
- [24] Wellington J. Noninvasive and alternative management of chronic low back pain (efficacy and outcomes). *Neuromodulation* 2014;17(S2):24–30.
- [25] Bourgault P, Lacasse A, Marchand S, Courtemanche-Harel R, Charest J, Gaudon I, Barcellos de Souza J, Choinière M. Multicomponent interdisciplinary group intervention for self-management of fibromyalgia: a mixed-methods randomized controlled trial. *PLOS ONE* 2015;10:e0126324.
- [26] Coates M, Lahoti M, Binion D, Szigethy E, Regueiro M, Bielefeldt K. Abdominal pain in ulcerative colitis. *Inflamm Bowel Dis* 2013;19:2207–14.
- [27] Lemberg DA, Day AS. Crohn disease and ulcerative colitis in children: an update for 2014. *J Paediatr Child Health* 2015;51:266–70.
- [28] Laass MW, Roggenbuck D, Conrad K. Diagnosis and classification of Crohn’s disease. *Autoimmun Rev* 2014;13:467–71.
- [29] Zeitz J, Ak M, Müller-Mottet S, Scharl S, Biedermann L, Fournier N, Frei P, Pittet V, Scharl M, Fried M, Rogler G, Vavricka S. Pain in IBD patients: very frequent and frequently insufficiently taken into account. *PLOS ONE* 2016;11:e0156666.
- [30] Drossman DA, Hasler WL. Rome IV—functional GI disorders: disorders of gut–brain interaction. *Gastroenterology* 2016;150:1257–61.
- [31] Drossman DA. Functional gastrointestinal disorders: history, pathophysiology, clinical features, and Rome IV. *Gastroenterology* 2016;150:1262–79.e2.
- [32] Korterink JJ, Diederik K, Benninga MA, Tabbers MM. Epidemiology of pediatric functional abdominal pain disorders: a meta-analysis. *PLOS ONE* 2015;10:1–17.
- [33] Korterink J, Devanarayana NM, Rajindrajith S, Vlieger A, Benninga MA. Childhood functional abdominal pain: mechanisms and management. *Nat Rev Gastroenterol Hepatol* 2015;12:159–71.
- [34] Horst S, Shelby G, Anderson J, Acra S, Polk DB, Saville BR, Garber J, Walker LS. Predicting persistence of functional abdominal pain from childhood into young adulthood. *Clin Gastroenterol Hepatol* 2014;12:2026–32.
- [35] Bielefeldt K, Christianson JA, Davis RM. Basic and clinical aspects of visceral sensation: transmission in the CNS. *Neurogastroenterol Motil* 2005;17:488–99.
- [36] Vermeulen W, De Man JG, Pelckmans PA, De Winter BY. Neuroanatomy of lower gastrointestinal pain disorders. *World J Gastroenterol* 2014;20:1005–20.
- [37] Srinath AI, Walter C, Newara MC, Szigethy EM. Pain management in patients with inflammatory bowel disease: insights for the clinician. *Therap Adv Gastroenterol* 2012;5:339–57.
- [38] Tornblom H, Drossman DA. Centrally targeted pharmacotherapy for chronic abdominal pain. *Neurogastroenterol Motil* 2015;27:455–67.
- [39] Zhang Y, Zhao S, Takatoh J, Han B, Zhou X, Wang F. Identifying local and descending inputs for primary sensory neurons. *J Clin Invest* 2015;125:1–50.
- [40] Hong D, Andrén-Sandberg Å. Punctate midline myelotomy: a minimally invasive procedure for the treatment of pain in inextirpable abdominal and pelvic cancer. *J Pain Symptom Manag* 2007;33:99–109.
- [41] Arle JE, Carlson KW, Mei L, Iftimia N, Shiels JL. Mechanism of dorsal column stimulation to treat neuropathic but not nociceptive pain: analysis with a computational model. *Neuromodulation* 2014;17:642–54.
- [42] Boadas-Vaello P, Castany S, Homs J, Álvarez-Pérez B, Deulofeu M, Verdú E. Neuroplasticity of ascending and descending pathways after somatosensory system injury: reviewing knowledge to identify neuropathic pain therapeutic targets. *Spinal Cord* 2016;54:330–40.
- [43] Benarroch EE. Periaqueductal gray: an interface for behavioral control. *Neurology* 2012;78:210–7.
- [44] Margolis KG, Gershon MD. Enteric neuronal regulation of intestinal inflammation. *Trends Neurosci* 2016;xx:1–11.
- [45] Vanner SJ, Greenwood-Van Meerveld B, Mawe GM, Shea-Donohue T, Verdu EF, Wood J, Grundy D. Fundamentals of neurogastroenterology: basic science. *Gastroenterology* 2016;150:1280–91.
- [46] Grundy D, Schemann M. Enteric nervous system. *Curr Opin Gastroenterol* 2006;22:102–10.
- [47] Gershon MD. Review article: Roles played by 5-hydroxytryptamine in the physiology of the bowel. *Aliment Pharmacol Ther* 1999;13(Suppl. 2):15–30.
- [48] Eisenhofer G, Åneman A, Friberg P, Hunyady LA, Hooper D, Fändriks L, Lonroth H, Mezey EVA. Substantial production of dopamine in the human gastrointestinal tract. *J Clin Endocrinol Metab* 1997;82:3864–71.

- [49] Bellini M, Fornai M. Pharmacogenomics genetics and pharmacogenetics. *Pharmacogenomics* 2015;16:523–39.
- [50] Gershon MD. 5-Hydroxytryptamine (serotonin) in the gastrointestinal tract. *Curr Opin Endocrinol Diabetes Obes* 2013;20:14–21.
- [51] Gross ER, Gershon MD, Margolis KG, Gertsberg ZV, Cowles RA. Neuronal serotonin regulates growth of the intestinal mucosa in mice. *Gastroenterology* 2012;143:408–17.
- [52] Majewski M, Kozłowska A, Thoene M, Lepiarczyk E, Grzegorzewski WJ. Overview of the role of vitamins and minerals on the kynurenine pathway in health and disease. *J Physiol Pharmacol* 2016;67:3–20.
- [53] Kaszaki J, Erceg D, Varga G, Szabo A, Vecsei L, Boros M. Kynurenines and intestinal neurotransmission: the role of N-methyl-D-aspartate receptors. *J Neural Transm* 2012;121:211–23.
- [54] Stone TW, Forrest CM, Darlington LG. Kynurenine pathway inhibition as a therapeutic strategy for neuroprotection. *FEBS J* 2012;279:1386–97.
- [55] Venkataramana S, Lourenssen S, Miller KG, Blennerhassett MG. Early inflammatory damage to intestinal neurons occurs via inducible nitric oxide synthase. *Neurobiol Dis* 2015;75:40–52.
- [56] Tiszlavicz Z, Németh B, Fülöp F, Vécsei L, Tápai K, Ocsosvsky I, Mándi Y. Different inhibitory effects of kynurenic acid and a novel kynurenic acid analogue on tumour necrosis factor- α (TNF- α) production by mononuclear cells, HMGB1 production by monocytes and HNP1-3 secretion by neutrophils. *Naunyn Schmiedeberg Arch Pharmacol* 2011;383:447–55.
- [57] Filipa V, Moro E, Protasoni M, Crema F, Frigo G, Giaroni C. Role of glutamatergic neurotransmission in the enteric nervous system and brain–gut axis in health and disease. *Neuropharmacology* 2016;111:14–33.
- [58] Akbar A, Walters JRF, Ghosh S. Review article: Visceral hypersensitivity in irritable bowel syndrome: molecular mechanisms and therapeutic agents. *Aliment Pharmacol Ther* 2009;30:423–35.
- [59] Farzaei MH, Bahramsoltani R, Abdollahi M, Rahimi R. The role of visceral hypersensitivity in irritable bowel syndrome: pharmacological targets and novel treatments. *J Neurogastroenterol Motil* 2016;22:558–74.
- [60] Assas BM, Pennock JI, Miyaj JA. Calcitonin gene-related peptide is a key neurotransmitter in the neuro-immune axis. *Front Neurosci* 2014;8:1–9.
- [61] King BF. Purinergic signalling in the enteric nervous system (an overview of current perspectives). *Auton Neurosci Basic Clin* 2015;191:141–7.
- [62] Poole DP, Lieu T, Pelayo JC, Eriksson EM, Veldhuis NA, Bunnett NW. Inflammation-induced abnormalities in the subcellular localization and trafficking of the neurokinin 1 receptor in the enteric nervous system. *Am J Physiol Gastrointest Liver Physiol* 2015;309:G248–59.
- [63] Sharkey KA. Emerging roles for enteric glia in gastrointestinal disorders. *J Clin Invest* 2015;125:918–25.
- [64] Nezami BG, Srinivasan S. Enteric nervous system in the small intestine: pathophysiology and clinical implications. *Curr Gastroenterol Rep* 2010;12:358–65.
- [65] Odenwald MA, Turner JR. Intestinal permeability defects: is it time to treat? *Clin Gastroenterol Hepatol* 2013;11:1075–83.
- [66] Fukui H. Gut–liver axis in liver cirrhosis: how to manage leaky gut and endotoxemia. *World J Hepatol* 2015;7:425–42.
- [67] Michielan A, D'Inca R. Intestinal permeability in inflammatory bowel disease: pathogenesis, clinical evaluation, and therapy of leaky gut. *Mediators Inflamm* 2015;2015.
- [68] Lu Z, Ding L, Lu Q, Chen Y-H. Claudins in intestines. *Tissue Barriers* 2014;1:e24978.
- [69] Bures J, Cyrany J, Kohoutova D, Förstl M, Rejchrt S, Kvetina J, Vorisek V, Kopacova M. Small intestinal bacterial overgrowth syndrome. *World J Gastroenterol* 2010;16:2978–90.
- [70] van Elburg RM, Uil JJ, Mulder CJ, Heymans HS. Intestinal permeability in patients with coeliac disease and relatives of patients with coeliac disease. *Gut* 1993;34:354–7.
- [71] Hollon J, Puppa EL, Greenwald B, Goldberg E, Guerrero A, Fasano A. Effect of gliadin on permeability of intestinal biopsy explants from celiac disease patients and patients with non-celiac gluten sensitivity. *Nutrients* 2015;7:1565–76.
- [72] Catassi C, Bai JC, Bonaz B, Bouma G, Calabrò A, Carroccio A, Castillejo G, Ciacci C, Cristofori F, Dolinsek J, Francavilla R, Elli L, Green P, Holtmeier W, Koehler P, Koletzko S, Meinhold C, Sanders D, Schumann M, Schuppan D, Ullrich R, Vécsei A, Volta U, Zavallos V, Sapone A, Fasano A. Non-celiac gluten sensitivity: the new frontier of gluten related disorders. *Nutrients* 2013;5:3839–53.
- [73] Kiesslich R, Goetz M, Angus EM, Hu Q, Guan Y, Potten C, Allen T, Neurath MF, Shroyer NF, Montrose MH, Watson AJM. Identification of epithelial gaps in human small and large intestine by confocal endomicroscopy. *Gastroenterology* 2007;133:1769–78.
- [74] Bellono NW, Bayrer JR, Leitch DB, Castro J, Zhang C, O'Donnell TA, Brierley SM, Ingraham HA, Julius D. Enterochromaffin cells are gut chemosensors that couple to sensory neural pathways. *Cell* 2017;170:185–98.e16.
- [75] Motomura Y, Chia J-E, Wang H, Akiho H, El-Sharkawy RT, Collins M, Wan Y, McLaughlin JT, Khan WI. Enterochromaffin cell and 5-hydroxytryptamine responses to the same infectious agent differ in Th1 and Th2 dominant environments. *Gut* 2008;57:475–81.
- [76] Wang H, Steeds J, Motomura Y, Deng Y, Verma-Gandhu M, El-Sharkawy RT, McLaughlin JT, Grecis RK, Khan WI. CD4+ T cell-mediated immunological control of enterochromaffin cell hyperplasia and 5-hydroxytryptamine production in enteric infection. *Gut* 2007;56:949–57.
- [77] Homolák J. Melatonin: the immunology perspective. *Gyrus* 2015;3:72–80.
- [78] Söderquist F, Hellström PM, Cunningham JL. Human gastroenteropancreatic expression of melatonin and its receptors MT1 and MT2. *PLOS ONE* 2015;10:1–18.
- [79] Zoppi S, Madrigal JLM, Pérez-Nieves BG, Marín-Jiménez I, Caso JR, Alou L, García-Bueno B, Colón A, Manzanera J, Luisa Gómez-Lus M, Menchén L, Leza JC. Endogenous cannabinoid system regulates intestinal barrier function in vivo through cannabinoid type 1 receptor activation. *Am J Physiol Gastrointest Liver Physiol* 2012;302:G565–71.
- [80] Walsh CJ, Guinane CM, O'Toole PW, Cotter PD. Beneficial modulation of the gut microbiota. *FEBS Lett* 2014;588:4120–30.
- [81] Bianconi E, Piovesan A, Facchin F, Beraudi A, Casadei R, Frabetti F, Vitale L, Pelleri MC, Tassani S, Piva F, Perez-Amodio S, Strippoli P, Canaider S. An estimation of the number of cells in the human body. *Ann Hum Biol* 2013;40:463–71.
- [82] Huttenhower C, Fah Sathirapongsasuti J, Segata N, Gevers D, Earl AM, Fitzgerald MG, Young SK, Zeng Q, Alm EJ, Alvarado L, Anderson S, Arachchi BM, Bloom T, Ciulla DM, Erlich RL, Feldgarden M, Fisher S, Friedrich DC, Giannoukos G, Goldberg JM, Griggs A, Gujja S, Haas BJ, Hepburn TA, Howarth C, Huang KH, Kells C, Lennon N, Mehta T, Nussbaum C, Pearson M, Priest ME, Russ C, Shenoy N, Sykes SM, Tabbaa DG, Ward DV, Yandava C, Zucker JD, Birren BW, Knight R, Clemente JC, Lozupone CA, McDonald D, Abubucker S, Chinwalla AT, Fulton RS, Hallsworth-Pepin K, Lobos EA, Magrini V, Martin JC, Mitreva M, Sodergren EJ, Wollam AM, Appelbaum E, Bhonagiri V, Chen L, Clifton SW, Delehaunty KD, Dooling DJ, Farmer CN, Fronick CC, Fulton LL, Gao H, Herter B, Kota KC, Mardis ER, Mihindukulasuriya KA, Minx PJ, Oglaughlin M, Pohl C, Tomlinson CM, Walker J, Wang Z, Warren W, Wylie KM, Wylie T, Ye L, Zhou Y, Weinstock GM, Wilson RK, Badger JH, Madupu R, Bihan M, Busam DA, Scott Durkin A, Foster L, Goll J, Li K, McCorison JM, Miller JR, Rogers YH, Sanka RK, Singh I, Sutton GG, Thiagarajan M, Torralba M, Methé BA, Nelson KE, Creasy HH, Giglio MG, Wortman JR, Abolude OO, Arze CA, Cantarel BL, Crabtree J, Davidovics NJ, Felix VM, Jordan C, Mahurkar AA, Orvis J, Ravel J, Schriml L, White JR, White O, Muzny DM, Worley KC, Buhay CJ, Ding Y, Dugan SP, Holder ME, Jiang H, Joshi V, Kovar CL, Lee SL, Lewis L, Liu Y, Newsham I, Qin X, Reid JG, Wilczek-Boney K, Wu Y, Zhang L, Zhu Y, Gibbs RA, Highlander SK, Petrosino JF, Versalovic J, Aagaard KM, Allen-Vercos E, Andersen GL, Armitage G, Ayvaz T, Keitel WA, Ross MC, Youmans BP, Baker CC, Begg L, Belachew T, Campbell JL, Deal C, Di Francesco V, Giblin C, Giovanni MY, Blaser MJ, Bonazzi V, Chhibba S, McEwen J, Peterson J, Proctor LM, Schloss JA, Wang L, Wellington C, Wetterstrand KA, Paul Brooks J, Buck GA, Rivera MC, Sheth NU, Canon SR, Chain PSG, Lo CC, Scholz M, Kyrpides NC, Liolios K, Markowitz VM, Mavromatis K, Pagani I, Chen IMA, Chu K, Palaniappan K, Cutting MA, Hamilton HA, Harris EL, Dwayne Lunsford R, McInnes P, Davis CC, Desantis TZ, Dewhirst FE, Izard J, Lemon KP, Deych E, La Rosa PS, Shannon WD, Michael Dunne W, Watson MA, Edgar RC, Farrell RM, Sharp RR, Faust K, Raes J, Fodor AA, Forney LJ, Friedman J, Smillie CS, Garcia N, Gonzalez A, Knights D, Kinder Haake S, Hoffmann DE, Huse SM, Jansson JK, Katancik JA, Kelley ST, Rodriguez-Mueller B, King NB, Kong HH, Koren O, Ley RE, Koren S, Liu B, Pop M, Sommer DD, Lewis CM, Spicer P, Madden T, Mannon PJ, McGuire AL, Patel SM, Podar M, Vishnivetskaya TA, Pollard KS, Sharpston TJ, Truty RM, Rho M, Ye Y, Rhodes R, Riehle KP, Sankar P, Schloss PD, Schubert AM, Schmidt TM, Simone GA, Sobel JD, Treangen TJ, Yooseph S, Zoloth L, Conlan S, Segre JA. Structure, function and diversity of the healthy human microbiome. *Nature* 2012;486:207–14.
- [83] Turnbaugh PJ, Ley RE, Hamady M, Fraser-liggett C, Knight R, Gordon JL. The human microbiome project: exploring the microbial part of ourselves in a changing world. *Nature* 2007;449:804–10.
- [84] Janssen AWF, Kersten S. The role of the gut microbiota in metabolic health. *FASEB J* 2015;29:3111–23.
- [85] Zhou L, Foster JA. Psychobiotics and the gut–brain axis: in the pursuit of happiness. *Neuropsychiatr Dis Treat* 2015;11:715–23.
- [86] Mayer EA. The brain–gut axis in abdominal pain syndromes. *Annu Rev Med* 2011.
- [87] Silvani A, Calandra-buonaura G, Dampney RAL, Cortelli P, Cortelli P. Brain–heart interactions: physiology and clinical implications. *Philos Trans R Soc A* 2016;374.
- [88] Ley RE. Obesity and the human microbiome. *Curr Opin Gastroenterol* 2010;26:5–11.
- [89] Rajilić-Stojanović M, Biagi E, Heilig HGHJ, Kajander K, Kekkonen RA, Tims S, De Vos WM. Global and deep molecular analysis of microbiota signatures in fecal samples from patients with irritable bowel syndrome. *Gastroenterology* 2011;141:1792–801.
- [90] Ohkusa T, Koido S. Intestinal microbiota and ulcerative colitis. *J Infect Chemother* 2015;21:761–8.
- [91] Chiodini RJ, Dowd SE, Chamberlin WM, Galanduk S, Davis B, Glassing A. Microbial population differentials between mucosal and submucosal intestinal tissues in advanced Crohn's disease of the ileum. *PLOS ONE* 2015;10:1–19.
- [92] Chichłowski M, Rudolph C. Visceral pain and gastrointestinal microbiome. *J Neurogastroenterol Motil* 2015;21:172–81.
- [93] Fritze D, Zhang W, Li JY, Chai B, Mulholland M. Thrombin mediates vagal apoptosis and dysfunction in inflammatory bowel disease. *J Gastrointest Surg* 2014;18:1495–506.
- [94] He S-H. Key role of mast cells and their major secretory products in inflammatory bowel disease. *World J Gastroenterol* 2004;10:309–18.
- [95] Hamilton MJ, Frei SM, Stevens RL. The multifaceted mast cell in inflammatory bowel disease. *Inflamm Bowel Dis* 2014;12:2364–78.
- [96] Zhang L, Song J, Hou X. Mast cells and irritable bowel syndrome: from the bench to the bedside. *J Neurogastroenterol Motil* 2016;22:181–92.

- [97] Barbara G, Cremon C, Carini G, Bellacosa L, Zecchi L, De Giorgio R, Corinaldesi R, Stanghellini V. The immune system in irritable bowel syndrome. *J Neurogastroenterol Motil* 2011;17:349–59.
- [98] Héron A, Dubayle D. A focus on mast cells and pain. *J Neuroimmunol* 2013;264:1–7.
- [99] Stoyanova II, Gulubova MV. Mast cells and inflammatory mediators in chronic ulcerative colitis. *Acta Histochem* 2002;104:185–92.
- [100] Brand S. Crohn's disease: Th1, Th17 or both? The change of a paradigm: new immunological and genetic insights implicate Th17 cells in the pathogenesis of Crohn's disease. *Gut* 2009;58:1152–67.
- [101] Fuss IJ. Is the Th1/Th2 paradigm of immune regulation applicable to IBD? *Inflamm Bowel Dis* 2008;14(Suppl. 2):S110–2.
- [102] Sfdqfupst D, Pg D, Tjodf D, Xbt U, Jodsfbtf OP, Dfmmt JO, Hbmbd C, Opodmbt-tjdbm BCZ, Qspvjdoh D, Ibwjoh BOE, Qpufoujbm D, Fqjuifmjbm GPS. Nonclassical CD1d-restricted NKT cells that produce IL-13 characterized an atypical Th2 response in ulcerative colitis. *J Clin Invest* 2004;113:1490–7.
- [103] Heller F, Florian P, Bojarski C, Richter J, Christ M, Hillenbrand B, Mankertz J, Gitter AH, Bürgel N, Fromm M, Zeitz M, Fuss I, Strober W, Schulzke JD. Interleukin-13 is the key effector Th2 cytokine in ulcerative colitis that affects epithelial tight junctions, apoptosis, and cell restitution. *Gastroenterology* 2005;129:550–64.
- [104] Murray PJ, Wynn TA. Protective and pathogenic functions of macrophage subsets. *Nat Rev Immunol* 2011;11:723–37.
- [105] Orihuela R, McPherson CA, Harry GJ. Microglial M1/M2 polarization and metabolic states. *Br J Pharmacol* 2016;173:649–65.
- [106] Jessen NA, Munk ASF, Lundgaard I, Nedergaard M. The glymphatic system: a beginner's guide. *Neurochem Res* 2015;40:2583–99.
- [107] Dantzer R. Cytokine-induced sickness behavior: where do we stand? *Brain Behav Immun* 2001;15:7–24.
- [108] Bengmark S. Acute and 'chronic' phase reaction – a mother of disease. *Clin Nutr* 2004;23:1256–66.
- [109] Mawdsley JE, Rampton DS. Psychological stress in IBD: new insights into pathogenic and therapeutic implications. *Gut* 2005;54:1481–91.
- [110] McEwen BS, Wingfield JC. The concept of allostasis in biology and biomedicine. *Horm Behav* 2003;43:2–15.
- [111] Stein J, Hartmann F, Dignass AU. Diagnosis and management of iron deficiency anemia in patients with IBD. *Nat Rev Gastroenterol Hepatol* 2010;7:599–610.
- [112] Massironi S, Rossi RE, Cavalloli FA, Della Valle S, Fraquelli M, Conte D. Nutritional deficiencies in inflammatory bowel disease: therapeutic approaches. *Clin Nutr* 2013;32:904–10.
- [113] Tigas S, Tsatsoulis A. Endocrine and metabolic manifestations in inflammatory bowel disease. *Ann Gastroenterol Q Publ Hell Soc Gastroenterol* 2012;25:37–44.
- [114] Shizuma T. Concomitant thyroid disorders and inflammatory bowel disease: a literature review. *Biomed Res Int* 2016;2016:5187061.
- [115] O'Toole A, Winter D, Friedman S. Review article: the psychosexual impact of inflammatory bowel disease in male patients. *Aliment Pharmacol Ther* 2014;39:1085–94.
- [116] Cronin E. Prednisolone in the management of patients with Crohn's disease. *Color Nurs* 2010;19:1333–6.
- [117] Corleto VD, Festa S, Di Giulio E, Annibale B. Proton pump inhibitor therapy and potential long-term harm. *Curr Opin Endocrinol Diabetes Obes* 2014;21:3–8.
- [118] Sheen E, Triadafilopoulos G. Adverse effects of long-term proton pump inhibitor therapy. *Dig Dis Sci* 2011;56:931–50.
- [119] Vinol A, Keunecke C, Biroga T, Stadje R, Dornieden K, Bösner S, Donner-Banzhoff N, Haasenritter J, Becker A. Studies of the symptom abdominal pain – a systematic review and meta-analysis. *Fam Pract* 2014;31:517–29.
- [120] Andresen T, Nilsson M, Nielsen AK, Lassen D, Arendt-Nielsen L, Drewes AM. Intradermal injection with nerve growth factor: a reproducible model to induce experimental allodynia and hyperalgesia. *Pain Pract* 2016;16:12–23.
- [121] Latremoliere A, Woolf CJ. Central sensitization: a generator of pain hypersensitivity by central neural plasticity. *J Pain* 2009;10:895–926.
- [122] Hobson AR, Aziz Q. Central nervous system processing of human visceral pain in health and disease. *News Physiol Sci* 2003;18:109–14.
- [123] Henry DE, Chiodo AE, Yang W. Central nervous system reorganization in a variety of chronic pain states: a review. *PM&R* 2011;3:1116–25.
- [124] Wager TD, Atlas LY, Lindquist MA, Matthieu R, Woo C-W, Kross E. An fMRI-based neurologic signature of physical pain. *N Engl J Med* 2013;368:1388–97.
- [125] Kucyi A, Moayed M, Weissman-Fogel I, Goldberg MB, Freeman BV, Tenenbaum HC, Davis KD. Enhanced medial prefrontal-default mode network functional connectivity in chronic pain and its association with pain rumination. *J Neurosci* 2014;34:3969–75.
- [126] Van Oudenhove L. Understanding gut–brain interactions in gastrointestinal pain by neuroimaging: lessons from somatic pain studies. *Neurogastroenterol Motil* 2011;23:292–302.
- [127] Agostini A, Filippini N, Benuzzi F, Bertani A, Scarcelli A, Leoni C, Farinelli V, Riso D, Tambasco R, Calabrese C, Rizzello F, Gionchetti P, Ercolani M, Nichelli P, Campieri M. Functional magnetic resonance imaging study reveals differences in the habituation to psychological stress in patients with Crohn's disease versus healthy controls. *J Behav Med* 2013;36:477–87.
- [128] Van Oudenhove L, Demyttenaere K, Tack J, Aziz Q. Central nervous system involvement in functional gastrointestinal disorders. *Best Pract Res Clin Gastroenterol* 2004;18:663–80.
- [129] Agostini A, Benuzzi F, Filippini N, Bertani A, Scarcelli A, Farinelli V, Marchetta C, Calabrese C, Rizzello F, Gionchetti P, Ercolani M, Campieri M, Nichelli P. New insights into the brain involvement in patients with Crohn's disease: a voxel-based morphometry study. *Neurogastroenterol Motil* 2013;25:1–8.
- [130] Salomons TV, Iannetti GD, Liang M, Wood JN. The 'pain matrix' in pain-free individuals. *JAMA Neurol* 2016;4–5.
- [131] Bernstein CN. Treatment of IBD: where we are and where we are going. *Am J Gastroenterol* 2015;110:114–26.
- [132] Martin TD, Chan SSM, Hart AR. Environmental factors in the relapse and recurrence of inflammatory bowel disease: a review of the literature. *Dig Dis Sci* 2015;60:1396–405.
- [133] Wasilewski A, Zielińska M, Storr M, Fichna J. Beneficial effects of probiotics, prebiotics, synbiotics, and psychobiotics in inflammatory bowel disease. *Inflamm Bowel Dis* 2015;0:1–9.
- [134] Bernstein CN. Antibiotics, probiotics and prebiotics in IBD. *Nestle Nutr Inst Workshop Ser* 2014;79:83–100.
- [135] Borody T, Peattie D, Mitchell S. Fecal microbiota transplantation: expanding horizons for *Clostridium difficile* infections and beyond. *Antibiotics* 2015;4:254–66.
- [136] Scaldaferrri F, Pecere S, Petito V, Zambrano D, Fiore L, Lopetuso LR, Schiavoni E, Bruno G, Gerardi V, Laterza L, Pizzoferrato M, Ianiro G, Stojanovic J, Poscia A, Papa A, Sterbini FP, Sanguinetti M, Masucci L, Cammarota G, Gasbarrini A. Efficacy and mechanisms of action of fecal microbiota transplantation in ulcerative colitis: pitfalls and promises from a first meta-analysis. *Transplant Proc* 2016;48:402–7.
- [137] Colman RJ, Rubin DT. Fecal microbiota transplantation as therapy for inflammatory bowel disease: a systematic review and meta-analysis. *J Crohns Colitis* 2014;8:1569–81.
- [138] Shah ND, Parian AM, Mullin GE, Limketkai BN. Oral diets and nutrition support for inflammatory bowel disease: what is the evidence? *Nutr Clin Pract* 2015;30:462–73.
- [139] Toljan K. Psychoneuroimmunological approach regarding the effects of dietary polyunsaturated fatty acid content. *Gyus* 2015;3:62–5.
- [140] Esatbeyoglu T, Ulbrich K, Rehberg C, Rohn S, Rimbach G. Thermal stability, antioxidant, and anti-inflammatory activity of curcumin and its degradation product 4-vinyl guaiaicol. *Food Funct* 2015;6:887–93.
- [141] Schaffer M, Schaffer PM, Zidan J, Bar Sela G. Curcuma as a functional food in the control of cancer and inflammation. *Curr Opin Clin Nutr Metab Care* 2011;14:588–97.
- [142] Chan JYY, Yuen ACY, Chan RYK, Chan SW. A review of the cardiovascular benefits and antioxidant properties of allicin. *Phyther Res* 2013;27:637–46.
- [143] Samsami-kor M, Daryani NE, Asl PR, Hekmatdoost A. Anti-inflammatory effects of resveratrol in patients with ulcerative colitis: a randomized, double-blind, placebo-controlled pilot study. *Arch Med Res* 2015;46:280–5.
- [144] Shibata T, Nakashima F, Honda K, Lu YJ, Kondo T, Ushida Y, Aizawa K, Suganuma H, Oe S, Tanaka H, Takahashi T, Uchida K. Toll-like receptors as a target of food-derived anti-inflammatory compounds. *J Biol Chem* 2014;289:32757–72.
- [145] Kawabata K, Kato Y, Sakano T, Baba N, Hagiwara K, Tamura A, Baba S, Natsume M, Ohgashi H. Effects of phytochemicals on in vitro anti-inflammatory activity of *Bifidobacterium adolescentis*. *Biosci Biotechnol Biochem* 2015;79:799–807.
- [146] Wang B, Wu G, Zhou Z, Dai Z, Sun Y, Ji Y, Li W, Wang W, Liu C, Han F, Wu Z. Glutamine and intestinal barrier function. *Amino Acids* 2014;47:2143–54.
- [147] Yi D, Hou Y, Wang L, Ouyang W, Long M, Zhao D, Ding B, Liu Y, Wu G. L-Glutamine enhances enterocyte growth via activation of the mTOR signaling pathway independently of AMPK. *Amino Acids* 2015;47:65–78.
- [148] Cheattle MD, Foster S, Pinkett A, Lesneski M, Qu D, Dhinra L. Assessing and managing sleep disturbance in patients with chronic pain. *Anesthesiol Clin* 2016;34:379–93.
- [149] Amy Janke E, Kozak AT. 'The more pain i have, the more i want to eat': obesity in the context of chronic pain. *Obesity* 2012;20:2027–34.
- [150] Walk D, Poliak-Tunis M. Chronic pain management: an overview of taxonomy, conditions commonly encountered, and assessment. *Med Clin N Am* 2016;100:1–16.
- [151] Dobrek L, Thor PJ. Pathophysiological concepts of functional dyspepsia and irritable bowel syndrome future pharmacotherapy. *Acta Pol Pharm Drug Res* 2009;66:447–60.
- [152] Targownik LE, Nugent Z, Singh H, Bugden S, Bernstein CN. The prevalence and predictors of opioid use in inflammatory bowel disease: a population-based analysis. *Am J Gastroenterol* 2014;109:1613–20.
- [153] Schicho R, Storr M. IBD patients find symptom relief in the Cannabis field. *Nat Rev Gastroenterol Hepatol* 2014;11:142–3.
- [154] Naftali T, Bar-Lev Schleider L, Dotan I, Lansky EP, Sklerovsky Benjaminov F, Konikoff FM. Cannabis induces a clinical response in patients with Crohn's disease: a prospective placebo-controlled study. *Clin Gastroenterol Hepatol* 2013;11.
- [155] Carter GT, Javaher SP, Nguyen MH, Garret S, Carlini BH. Re-branding cannabis: the next generation of chronic pain medicine? *Pain Manag* 2015;5:13–21.
- [156] Seo S, Grzenda A, Lomberg G, Ou X-M, Cruciani RA, Urrutia R. Epigenetics: a promising paradigm for better understanding and managing pain. *J Pain* 2013;14:549–57.
- [157] Tran L, Schulkin J, Ligon CO, Greenwood-Van Meerveld B. Epigenetic modulation of chronic anxiety and pain by histone deacetylation. *Mol Psychiatry* 2014;20:1–13.
- [158] Lomax AE, Fernández E, Sharkey KA. Plasticity of the enteric nervous system during intestinal inflammation. *Neurogastroenterol Motil* 2005;17:4–15.

- [159] Brierley SM, Linden DR. Neuroplasticity and dysfunction after gastrointestinal inflammation. *Nat Rev Gastroenterol Hepatol* 2014;11:611–27.
- [160] Brierley S. Altered ion channel/receptor expression and function in extrinsic sensory neurons: the cause of and solution to chronic visceral pain? *Adv Exp Med Biol* 2016;75–90.
- [161] Bernstein CN, Singh S, Graff L, Walker JR, Miller N, Cheang M. A prospective population-based study of triggers of symptomatic flares in IBD. *Am J Gastroenterol* 2010;105:1994–2002.
- [162] Robins PM, Smith SM, Glutting JJ, Bishop CT. A randomized controlled trial of a cognitive-behavioral family intervention for pediatric recurrent abdominal pain. *J Pediatr Psychol* 2002;30:397–408.
- [163] van der Veek SMC, Derkx BHF, Benninga MA, Boer F, de Haan E. Cognitive behavior therapy for pediatric functional abdominal pain: a randomized controlled trial. *Pediatrics* 2013;132:1163–72.
- [164] McCombie AM, Mulder RT, Geary RB. Psychotherapy for inflammatory bowel disease: a review and update. *J Crohn's Colitis* 2013;7:935–49.
- [165] Mikocka-Walus A, Bampton P, Hetzel D, Hughes P, Esterman A, Andrews JM. Cognitive-behavioural therapy for inflammatory bowel disease: 24-month data from a randomised controlled trial. *Int J Behav Med* 2016.
- [166] Schoultz M, Atherton I, Watson A. Mindfulness-based cognitive therapy for inflammatory bowel disease patients: findings from an exploratory pilot randomised controlled trial. *Trials* 2015;16:379.
- [167] Berrill JW, Sadlier M, Hood K, Green JT. Mindfulness-based therapy for inflammatory bowel disease patients with functional abdominal symptoms or high perceived stress levels. *J Crohn's Colitis* 2014;8:945–55.
- [168] Korterink JJ, Ockeloen LE, Hilbink M, Benninga MA, Deckers-Kocken JM. Yoga therapy for abdominal pain related-functional gastrointestinal disorders in children. A randomized controlled trial. *J Pediatr Gastroenterol Nutr* 2016;1.
- [169] Stern MJ, Guiles RAF, Gevirtz R. HRV biofeedback for pediatric irritable bowel syndrome and functional abdominal pain: a clinical replication series. *Appl Psychophysiol Biofeedback* 2014;39:287–91.
- [170] Sowder E, Gevirtz R, Shapiro W, Ebert C. Restoration of vagal tone: a possible mechanism for functional abdominal pain. *Appl Psychophysiol Biofeedback* 2010;35:199–206.
- [171] Szigethy E. Hypnotherapy for inflammatory bowel disease across the lifespan. *Am J Clin Hypn* 2015;9157.
- [172] Rutten JMTM, Vlieger AM, Frankenhuys C, George EK, Groeneweg M, Norbruis OF, Tjon A Ten W, Van Wering H, Dijkgraaf MGW, Merkus MP, a Benninga M. Gut-directed hypnotherapy in children with irritable bowel syndrome or functional abdominal pain (syndrome): a randomized controlled trial on self exercises at home using CD versus individual therapy by qualified therapists. *BMC Pediatr* 2014;14:140.
- [173] Rutten JMTM, Reitsma JB, Vlieger AM, a Benninga M. Gut-directed hypnotherapy for functional abdominal pain or irritable bowel syndrome in children: a systematic review. *Arch Dis Child* 2013;98:252–7.
- [174] Malcangio M. Microglia and chronic pain. *Pain* 2016;157:1002–3.
- [175] Paret C, Ruf M, Gerchen MF, Kluetsch R, Demirakca T, Jungkunz M, Bertsch K, Schmahl C, Ende G. fMRI neurofeedback of amygdala response to aversive stimuli enhances prefrontal-limbic brain connectivity. *Neuroimage* 2016;125:182–8.
- [176] Baur V, Hänggi J, Langer N, Jäncke L. Resting-state functional and structural connectivity within an insula-amygdala route specifically index state and trait anxiety. *Biol Psychiatry* 2013;73:85–92.
- [177] Abitbol V, Lahmek P, Buisson A, Olympie A, Poupardin C, Chaussade S, Lesgourgues B, Nahon S. Impact of complementary and alternative medicine on the quality of life in inflammatory bowel disease. *Eur J Gastroenterol Hepatol* 2014;26:288–94.
- [178] Langhorst J, Wulfert H, Lauche R, Klose P, Cramer H, Dobos GJ, Korzenik J. Systematic review of complementary and alternative medicine treatments in inflammatory bowel diseases. *J Crohn's Colitis* 2015;9:86–106.
- [179] Lindberg A, Fossum B, Karlen P, Oxelmark L. Experiences of complementary and alternative medicine in patients with inflammatory bowel disease – a qualitative study. *BMC Complement Altern Med* 2014;14:407.
- [180] Kempert H, Benore E, Heines R. Easily administered patient-reported outcome measures: adolescents' perceived functional changes after completing an intensive chronic pain rehabilitation program. *Arch Phys Med Rehabil* 2017;98:58–63.
- [181] Landry BW, Fischer PR, Driscoll SW, Koch KM, Harbeck-Weber C, Mack KJ, Wilder RT, Bauer BA, Brandenburg JE. Current concepts in pediatric pain management managing chronic pain in children and adolescents: a clinical review. *PM&R J* 2015;7:S295–315.
- [182] Capurso G, Cocomello L, Benedetto U, Cammà C, Delle Fave G. Meta-analysis: the placebo rate of abdominal pain remission in clinical trials of chronic pancreatitis. *Pancreas* 2012;41:1125–31.
- [183] Schmid J, Langhorst J, Gaß F, Theysohn N. Placebo analgesia in patients with functional and organic abdominal pain: a fMRI study in IBS, UC and healthy volunteers. *Gut* 2014;2–3.
- [184] Bernstein CN. The placebo effect for gastroenterology: tool or torment. *Clin Gastroenterol Hepatol* 2006;4:1302–8.
- [185] Merighi A. Targeting the glial-derived neurotrophic factor and related molecules for controlling normal and pathologic pain. *Expert Opin Ther Targets* 2016;20:193–208.
- [186] Lu CL. Spinal microglia: a potential target in the treatment of chronic visceral pain. *J Chin Med Assoc* 2014;77:3–9.
- [187] Burke NN, Fan CY, Trang T. Microglia in health and pain: impact of noxious early life events. *Exp Physiol* 2016;101:1003–21.
- [188] Milligan ED, Sloane EM, Watkins LR. Glia in pathological pain: a role for fractalkine. *J Neuroimmunol* 2008;198:113–20.
- [189] Austin PJ, Moalem-Taylor G. The neuro-immune balance in neuropathic pain: involvement of inflammatory immune cells, immune-like glial cells and cytokines. *J Neuroimmunol* 2010;229:26–50.
- [190] Taylor AMW, Castonguay A, Taylor AJ, Murphy NP, Ghogha A, Cook C, Xue L, Olmstead MC, De Koninck Y, Evans CJ, Cahill CM. Microglia disrupt mesolimbic reward circuitry in chronic pain. *J Neurosci* 2015;35:8442–50.
- [191] Old EA, Clark AK, Malcangio M. *Pain Control*, vol. 227. Berlin, Heidelberg: Springer Berlin Heidelberg; 2015.
- [192] Ferrini F, Trang T, Mattioli T-AM, Laffray S, Del'Guidice T, Lorenzo L-E, Castonguay A, Doyon N, Zhang W, Godin AG, Mohr D, Beggs S, Vandal K, Beaulieu J-M, Cahill CM, Salter MW, De Koninck Y. Morphine hyperalgesia gated through microglia-mediated disruption of neuronal Cl^- homeostasis. *Nat Neurosci* 2013;16:183–92.
- [193] Younger J, Parkitny L, McLain D. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. *Clin Rheumatol* 2014;33:451–9.
- [194] Younger J, Noor N, McCue R, MacKey S. Low-dose naltrexone for the treatment of fibromyalgia: findings of a small, randomized, double-blind, placebo-controlled, counterbalanced, crossover trial assessing daily pain levels. *Arthritis Rheum* 2013;65:529–38.
- [195] Smith JP, Stock H, Bingaman S, Mauger D, Rogosnitzky M, Zagon IS. Low-dose naltrexone therapy improves active Crohn's disease. *Am J Gastroenterol* 2007;102:820–8.
- [196] Segal D, MacDonald JK, Chande N, MacDonald John K, Chande N. Low dose naltrexone for induction of remission in Crohn's disease. *Cochrane Database Syst Rev* 2014;10–3.
- [197] Hutchinson MR, Zhang Y, Brown K, Coats BD, Shridhar M, Sholar PW, Patel SJ, Crysdale NY, Harrison JA, Maier SF, Rice KC, Watkins LR. Non-stereoselective reversal of neuropathic pain by naloxone and naltrexone: involvement of toll-like receptor 4 (TLR4). *Eur J Neurosci* 2008;28:20–9.
- [198] Cianciulli A, Dragone T, Calvillo R, Porro C, Trotta T, Lofrumento DD, Panaro MA. IL-10 plays a pivotal role in anti-inflammatory effects of resveratrol in activated microglia cells. *Int Immunopharmacol* 2015;24:369–76.
- [199] Kurtys E, Eisel UL, Verkuyll JM, Broersen LM, Dierckx RA, de Vries EF. The combination of vitamins and omega-3 fatty acids has an enhanced anti-inflammatory effect on microglia. *Neurochem Int* 2016;99:206–14.
- [200] Lutz JA, Kulshreshtha M, Rogers DT, Littleton JM. A nicotinic receptor-mediated anti-inflammatory effect of the flavonoid rhamnetin in BV2 microglia. *Fitoterapia* 2014;11–21.