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Title: **Psychoneuroimmunological Approach to Gastrointestinal Related Pain**

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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.

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 favorable 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 underexploited set of evidence-based tools is available for clinical use.

KEYWORDS: Psychoneuroimmunology, Microbiota, Inflammatory Bowel Disease, Functional Gastrointestinal Disorders, Pain

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 behavior such as ‘sickness behavior’[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 behavior 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 favorable 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 etiology-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 behavioral 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 pediatric 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 centers 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 Figure 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 diarrhea [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 [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 Meissners'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, fifteen including receptor subtypes, and most are present in the gut. Serotonin is a a key neurotransmitter necessary for inducing GI motility and ENS nerve growth [50]. Myenteric serotoninergic 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 serotoninergic 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 meager 10% of its metabolic fate, the majority or 90% of it being channeled 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 quinulinic 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 Figure 2). Microglia contain the enzyme indolamine dioxygenase (IDO), which favors the kynurenic pathway. It ultimately depletes the ENS of serotonin and creates a significant amount of kynurenic metabolites 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 tumor necrosis factor alpha (TNFα) 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 B_6, vitamin B_2, 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-fiber neurotransmission, evidence has confirmed all fibers 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 fibers 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-signaling 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 (TNFα, interleukin-1β, 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 center of pathophysiological investigation is the intestinal one, due to its length, surface, its role in nutrient resorption and the fact it's 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 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 TNFα 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 α2A 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 signaling 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 can't 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 aging. 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 TNFα and Interleukin-1β [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 favoring 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 behavior [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.

2.2.2. 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 TNFα being more expressed demonstrate the signaling 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 shouldn't 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’, unfavorable 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's 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 favorable 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 center. 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 neurogastroeneterology [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 ti 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 fecal 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 anemia [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 psychoneuroimmunologal therapy being precisely the epitome. Treating symptoms occurring in IBD and FGID such as diarrhea, 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 behavioral 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 behavioral [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 favorable 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 centers. 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 hese modalities are also a part of the chronic pain rehabilitation program, 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, fueled by growing understanding of the complex pathophysiologies, 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 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 signaling 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 behavioral 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 'homeopathic', since it's 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 signaling, 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.

List of abbreviations

ACC Anterior cingulate cortex; ATP Adenosine triphosphate; CB Cannabinoid receptor; CD Chron's disease; CGRP Calcitonin-gene related peptide; CNS Central nervous system; CRF Corticotropin releasing factor; ECC Enterochromaffin cell; ENS Enteric nervous system; FGID Functional gastrointestinal disorder; GI Gastrointestinal; GLP-2 Glucagon-like peptide-2; HPA Hypothalamus-pituitary-adrenals; IBD Inflammatory bowel disease; IBS Irritable bowel syndrome; IDO Indolamine dioxygenase; LDN Low-dose naltrexone; MT Melatonin receptor; NAD Nicotinamide dinucleotide; NMDA N-methyl-D-aspartate; NO Nitric oxide; NPY Neuropeptide Y; PAG Periaqueductal grey; PFC Prefrontal cortex; RNS Reactive nitrogen species; ROS Reactive oxygen species; TNF Tumor necrosis factor; TRPV Transient receptor potential cation channel subfamily V; UC Ulcerative colitis; VIP Vasoactive intestinal peptide.

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Figures

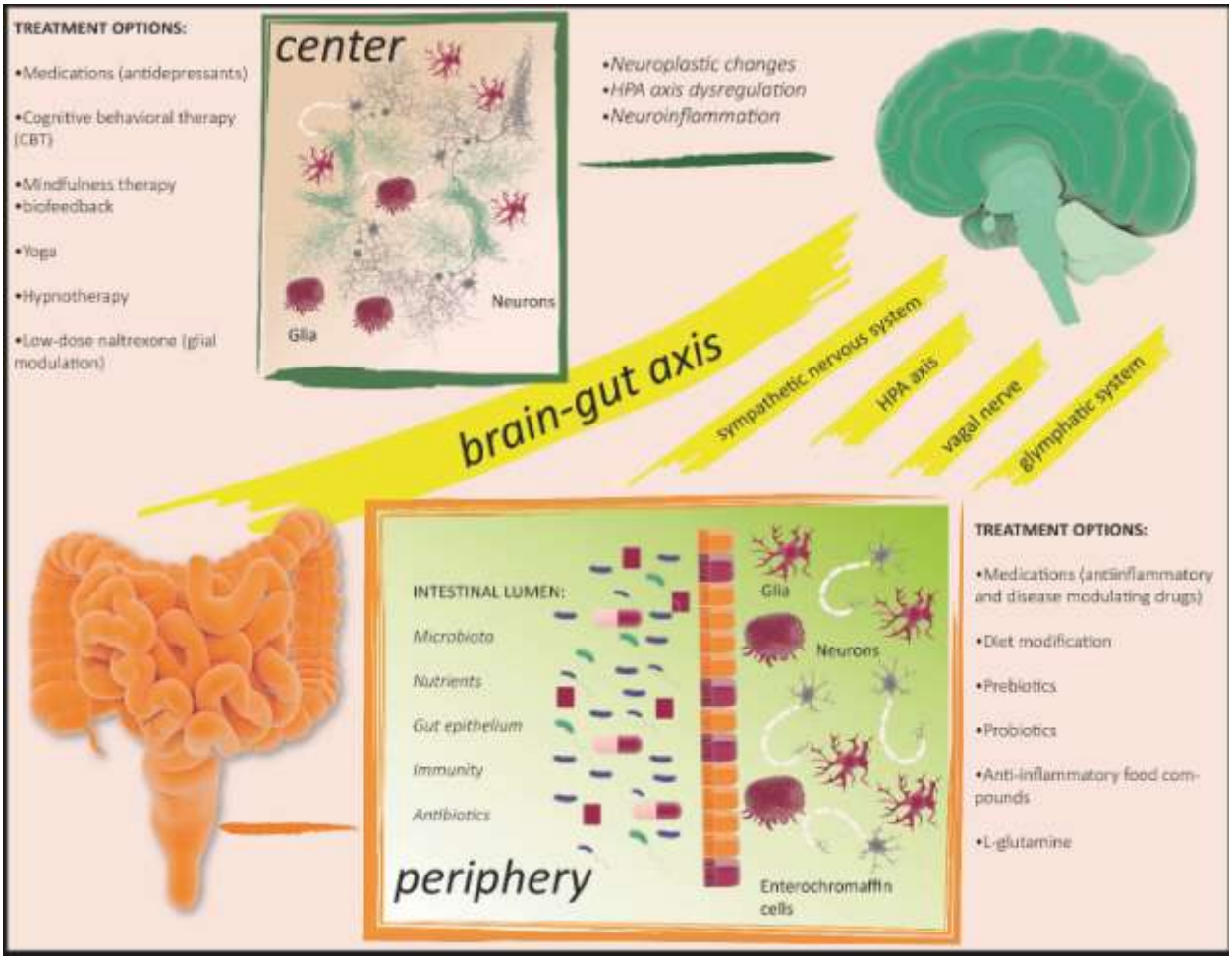

Figure 1. An overview of pathophysiological components in the periphery and central nervous system with available treatments according to psychoneuroimmunological paradigm

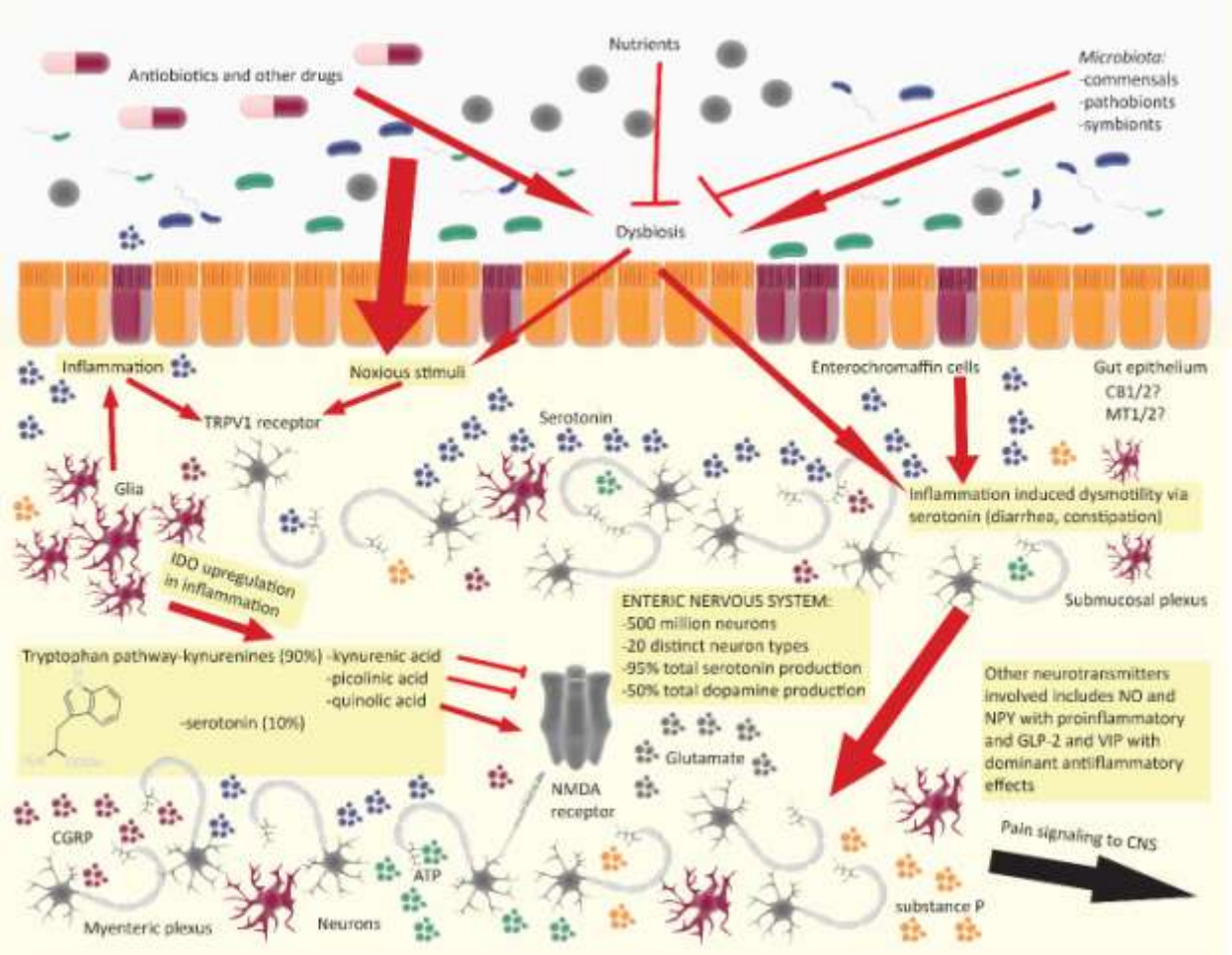

Figure 2. Pathophysiological process involving the enteric nervous system as an intermediary in the gut-brain axis. CGRP, calcitonin gene related peptide; ATP, adenosine triphosphate; IDO, indolamine dioxygenase; MT 1/2, melatonin 1/2 receptor; CB 1/2, cannabinoid 1/2 receptor; NPY, neuropeptide Y; GLP,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