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Contribution of Neuropeptides and Neurotransmitters in colitis

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Abbreviations: ANS: Autonomic Nervous System; ENS: Enteric Nervous System; SChG: Sympathetic Chain Ganglia; IMG: Inferior Mesenteric Ganglion; CD: Crohn's Disease; UC: Ulcerative Colitis; IBD: Inflammatory Bowel Disease; IBS: Irritable Bowel Syndrome; CRH: Corticotropin-Releasing Hormone; NA: Noradrenaline; NPY: Neuropeptide Y; NO: Nitric oxide; NOS: Nitric oxide Synthase; SP: Substance P; CGRP: Calcitonin Gene-Related Peptide; VIP: Vasoactive Intestinal Peptide; 5-HT: Serotonin; CART: Cocaine and Amphetamine Regulated Transcript

Introduction

Colitis is a chronic, relapsing, and remitting disease involving complex interactions between genes, immune system, and neuroendocrine feedback. Important advances have been recently made to support the awareness that neuroendocrine factors can significantly impact the immune response in the gut [1]. Unlike the other nervous systems of the body, the enteric nervous system (ENS) can work without central input from the brain and is often considered as "the brain-in-the gut"[2]. However, both the ENS and the central nervous system (CNS) can amplify or modulate aspects of intestinal inflammation through secretion of neuropeptides and non-peptide neurotransmitters that serve as a link between the ENS and CNS. Neuropeptides are defined as any peptide released from the nervous system that serves as an intercellular signaling molecule [3]. Neuropeptides and other neurotransmitters, when released at the nerve endings in the colon side, diffuse into surrounding tissues and bind to their corresponding receptors affecting peristalsis, fluid secretion, and digestive processes [3,4]. Locally released neurotransmitters act also directly on contiguous vasculature, mast cells and muscles, prompting their release of proinflammatory factors [5,6]. Immune cells localized in the colon wall express various neurotransmitter receptors, and they produce cytokines and other immune/inflammatory mediators like chemokines and free radicals. Once the neurotransmitter has reached targeted cells and occupied appropriate receptors the initiated signal transduction pathways of cytokine production has been started [7]. On the other hand, regulatory cytokines released on colon wall can bind to specific receptors localized on sensory nerve fibers and trigger neuronal response. This bidirectional cross-talk between neuronal and immune factors is crucial to maintenance the visceral homeostasis and also plays an important role during colitis. Neuropeptides thought to play key roles in colitis include substance P (SP), calcitonine gene-related peptide (CGRP), neuropeptide Y (NPY), corticotropin-releasing hormone (CRH), vasoactive intestinal peptide (VIP), galanin (GAL) and cocaine and amphetamine regulated transcript (CART). Furthermore, neurotransmitters like noradrenaline (NA), serotonin (5-HT), and gaseous nitric oxide (NO). All above mentioned substances can control a variety of functions within the gastrointestinal (GI) tract under physiological and pathological conditions [8]. Neurotransmitters may evoke remarkably different and even opposing effects depending on the concentration of released neurotransmitter/co-transmitters, receptor expression levels, affinity, and timing of neurosecretory activity in relation to the inflammatory course [4,9]. The enhanced neuropeptide release has been reported in the colon during inflammation accompanying ulcerative colitis (UC), Crohn disease (CD) and irritable bowel syndrome (IBS) (Figure 1).

Substance P (SP) and calcitonin gene-related peptide (CGRP)

Sensory innervation of colon comprise of intrinsic primary afferent neurons (IPANs), whose cell bodies are located in the myenteric or submucosal plexuses and extrinsic primary afferent neurons (EPANs), with their somata in the dorsal root ganglia (DRG). These neuronal populations contain mainly neuropeptides, such as SP and CGRP, stored in vesicles that are released upon depolarization. SP- and CGRP-positive DRG neurons often co-express transient receptor potential vanilloid (TRPV1) channel. TRPV1 is one of the key components of nociceptive signal transduction pathways and is widely distributed throughout the GI tract as well. In experimentally induced colitis in rats activation of TRPV1 nociceptive afferent nerve terminals, lead to enhanced release of CGRP and SP not only at the inflammation side but also in adjacent visceral organs [10]. The liberation of CGRP and SP results in vasodilatation, plasma extravasation, and leukocyte migration, which is commonly referred to as neurogenic inflammation

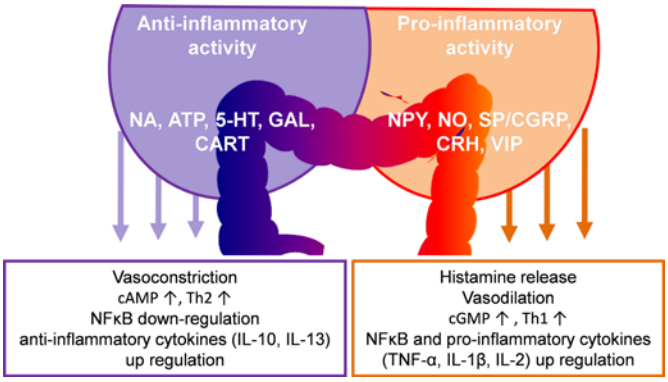

Figure 1: The contribution of particular neurotransmitters in colonic homeostasis. The homeostasis of colon activity is regulated by vasoconstrictory stimuli, including cAMP, anti-inflammatory cytokines, inhibition of NF-κB and Th-2 mode of immune response (left side of figure) and vasodilatory stimuli, including cGMP, pro-inflammatory cytokines, activation of NF-κB and Th-1 mode of immune response (right side of the figure).

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and is related to the axon reflex phenomenon. SP and CGRP stimulate T-cell migration, induce secretion of the proinflammatory cytokines like IL-1β, interferon gamma (IFN-γ), and tumor necrosis factor alpha (TNF-α) [9]. The molecular mechanism underlying this inflammatory response involves, in part, the activation of the nuclear transcription factor (NF-κB) system and the consequent inflammatory cascade [11]. In conclusion, the role of sensory neuronal activation and consecutive neuropeptide release with respect to protection or aggression in colonic inflammation seems to remain a double-edged sword. For example, release of SP/CGRP from afferent terminals triggers mRNA up-regulation followed by secondary increase in the release of SP/CGRP in the colon at later time [10].

Noradrenaline (NA)

The sympathetic nervous system (SNS), with its main neurotransmitter NA, which is released from postganglionic varicosities innervating the peripheral lymphoid organs, provides the primary pathway for the neural regulation of immune function [6,7]. There is ample evidence that the immunomodulatory effect of NA is mediated through cAMP. NA and the adrenergic agonists may influence the immune response directly, through adrenergic β-receptors expressed on macrophages and other immunologically competent cells, as well as indirectly via alteration of endogenous NA levels by influencing the activity of release-regulating presynaptic α2-adrenoceptors located on sympathetic nerve terminals. Activation of latter receptors results in a negative feedback effect on NA release, leading to decreased extracellular NA concentration. On the other hand, activation of neurotransmitter receptors that stimulate adenylate-cyclase leads to a shift toward T helper 2 (Th2)-type responses, which are both neuroprotective and anti-inflammatory, whereas down regulation of intracellular cAMP stimulates a T helper 1 (Th1)-type response, resulting in cell destructive effects and inflammation [7]. Prior studies have shown that the loss of noradrenergic fiber density during colitis is due to inhibition of N-type voltage-gated Ca^{2+} current in postganglionic sympathetic neurons [12,13]. Furthermore, during experimental colitis, the axotomy of sympathetic *nervii* supplying the descending colon in pigs are showed to decrease in the number of catecholamine-containing perikarya localized in sympathetic chain ganglia (SChG) and inferior mesenteric ganglion (IMG) – the main sources of sympathetic innervation of the colon [14,15]. These findings provide evidence that inflammation at colon wall influences the chemical coding of sympathetic neurons affecting neuronal plasticity.

Interest in the role of the SNS under inflammatory bowel disease (IBD) is rapidly increasing. However, much work needs to be done to enhance the understanding of how SNS function is altered during IBD and what contribution, if any, these changes make to pathogenesis [12]. One of the sympathetic co-transmitters, ATP, is also engaged during colitis, namely by the reduced purinergic transmission to submucosal arterioles that was noticed, and may be due to increased degradation of ATP throughout colitis [16]. On the other hand, venlafaxine, an 5-HT/NA reuptake inhibitor, alters colonic compliance and tone and tends to reduce sensation during colonic distention in healthy humans, showing usefulness in colonic disorders affecting motor and possibly sensory functions [17,18].

Neuropeptide Y (NPY)

NPY has been shown to elicit diverse biological functions including hypothalamic control of food intake, anxiety and sedation. This polypeptide is attached to heptahelical G-protein coupled receptors, which are widely distributed in the ENS and CNS. It has been found that NPY expression is up regulated in enteric neurons during experimental colitis in mice [19]. Thus, NPY is an inducible gene in enteric neurons that can promote inflammation. It has been demonstrated that NPY increases the number of NOS (nitric oxide synthase)-producing neurons in the murine ENS ganglia what can affect intestine vascularization and motility [20]. The administration of NPY antisense oligodeoxynucleotides (ODNs) in rats leads to an amelioration of experimentally-induced colitis, suggesting that NPY plays an important role in modulating of inflammation throughout colitis. Therefore, the NPY antisense ODNs may be a useful therapeutic approach to the treatment of ulcerative colitis (UC) and other intestinal diseases with inflammatory signs [21].

Nitric Oxide (NO)

NO is a gaseous mediator that exerts key regulatory functions in mammalian cells. Low levels of NO play homeostatic functions and counteract inflammation, whereas high amounts of NO cause tissue destruction and cellular death. NOS generates nitric oxide (NO), a major non-adrenergic non-cholinergic (NANC) neurotransmitter, which mediates relaxation responses of smooth muscle cells in the GI tract. NO has been identified to play a role in a variety of enteric neuropathies like Crohn's disease (CD), UC, Chagas disease, diabetic gastroparesis, achalasia and pyloric stenosis [20]. Inflammatory cytokines and infiltrating immune cells appear to be responsible for much of the colonic oxidative stress that is a hallmark of IBD and colonic nitrite levels serve as a sensitive marker of disease activity in colitis. When produced in small amounts, NO generally exerts positive effects in the gastrointestinal tract. However, under inflammatory colonic conditions, greatly increased NO levels have been reported, for example, in human IBD and in animal models of colitis [22]. It has been demonstrated that increased NO levels in the colon during UC is derived mostly from myenteric neurons than from epithelium [20]. Vascular resistance accompanying colitis is associated with higher levels of vasodilating NO in rat colonic mucosa [22]. Cytokines release during UC in rats induced expression of iNOS leading to a steep rise of NO synthesis [23]. In a rodent model of colitis, the new NO antagonists (NI-NOD1 and NI-NOD2) potently decreased inflammation. These data show that NI-NODs are effective in both *in vitro* and *in vivo* models of inflammation, mimicking the positive effects of low levels of NO and suppressing NOS-induced NO production [24].

Corticotropin-releasing hormone (CRH)

CRH is a 41-amino acid hypothalamic peptide that modulates the synthesis and release of adrenocorticotropic hormone (ACTH) from the pituitary, leading to release of anti-inflammatory corticosteroids from the adrenal glands. A major function of CRH is to coordinate the endocrine, behavioral, immune, and visceral responses to stress [25]. Emerging evidence also links activation of the CRH-dependent signaling pathways with modulation of intestinal inflammation [26]. There are functional differences between CRH receptor 1 (CRH-R1) and CRH-R2 activation. R1 stimulation evokes colonic motility, causes proinflammatory response with enhanced visceral nociception whereas R2 activation inhibits gastric emptying, reduces visceral perception and provokes anti-inflammatory changes reviewed in [27] CRH-R1 agonists promote intestinal inflammation, as well as endogenous inflammatory angiogenesis whereas CRH-R2 ones attenuate these features [28]. The enhanced expression of CRH and *c-fos* inside the hypothalamus (paraventricular nucleus) during experimentally induced acute colitis in rats has also been observed. This feature is probably evoked by the stimulatory effects of pro-inflammatory

cytokines on visceral sensory afferents what enhances the excitability and activity of the hypothalamus pituitary adrenal (HPA) axis [29,30]. In contrary to the anti-inflammatory effects of hypothalamic CRH through induction of glucocorticoids, CRH secreted peripherally by immune cells, nerve fibers, and possibly additional cell types may act locally as a proinflammatory mediator [31]. In a chronic colitis model in rats the over expression of CRH-RI has been noticed [32]. The worsening of colitis symptoms occurred during periods of emotional stress suggests that IBS may be, at least partially, the result of the central CRH excess [30]. IBS in human lead to a mild elevation of plasma cortisol and significantly blunted ACTH levels suggest a deregulation of the HPA axis [33]. As most recently shown, gut [32], similarly to skin [34] and joints [35], has formed a local equivalent of the HPA axis which contributes to the central one and modulates its activity.

Vasoactive intestinal peptide (VIP)

VIP is a potent neuroendocrine mediator of diverse physiological responses, and is expressed prominently in primary immune organs and neurons of ENS and CNS [36]. VIP inhibits inflammatory pathways by reducing production of TNF-α, IL-6 and IL-12. Other studies have shown that VIP enhances the differentiation of T helper cells and promotes release of histamine by mast cells, thereby inducing erythema [37]. Normal activity of VIP transmission is critical in maintaining the intestinal immune homeostasis and selective enhancement of VIP signaling activates cAMP/PKA signal transduction pathways sufficiently to enhance colitis in mice. Taken together these and other findings suggest that VIP may manifest either an inhibitory or stimulatory effect on immune and immunopathological reactions in intestine [38].

Galanin (GAL)

In humans, GAL is a 30-aa-long neuroendocrine peptide, for which its physiological functions are regulated by G protein-coupled receptors. GAL is found throughout the CNS and ENS, and its effects include a control of memory acquisition, modulation of appetite or sexual conduct, GI motion as well as effects on nociception during colitis. Both, colitis and the axotomy of colon wall cause an increase in GAL-immunoreactivity in the autonomic nervous system [14,15] and ENS in pigs [39]. Treatment with GAL is able to reduce the severity of the colitis by lowering the incidence of diarrhea, weight loss, infiltration of the inflammatory cells, mucosa disruption and edema [40]. GAL treatment has a significant preventive effect in TNBS-induced acute model of colitis in rats [41].

Serotonin (5-HT)

5-HT is a monoamine neurotransmitter that is classically recognized for its functions in the CNS, where it plays important roles in regulating mood, body temperature, sleep, sexuality, appetite, and metabolism. The vast majority of 5-HT (approximately 95%) is localized to the intestine, where is synthesized by serotoninergic neurons of ENS as well as in the enterochromaffin (EC) cells [42]. As a paracrine factor, 5-HT targets mucosal projections of intrinsic primary afferent neurons to initiate enteric peristaltic and secretory reflexes. 5-HT is likely to play a role in mucosal homeostasis. Mucosal 5-HT modulates the immune response, and thus, is able potentially influence intestinal inflammation. 5-HT has been shown to promote lymphocyte activation and secretion proinflammatory cytokines [43]. Moreover, dendritic cells, lymphocytes, macrophages, endothelial cells, and enteric epithelial cells all express 5-HT receptors. Additionally, activation of specific signaling molecules of the NF-κB pathway is mediated by 5-HT during intestinal inflammation [42]. Findings of a recent studies have provided a new mechanistic insights into anti-inflammatory and immunosuppressive activities of 5-HT3 receptor antagonist (tropisetron) during rat IBD [44].

Cocaine and amphetamine regulated transcript (CART)

CART was originally given a role in drug abuse but the current focus on CART-induced effects is feeding behavior and body weight regulation as well the neuromodulatory and/or neurotrophic effects in intestine [45]. The coexistence of CART with NOS and VIP in the same neural population inside GI indicates that this peptide may influence NO- and VIP-induced effects during colitis [46]. CART is also implicated in promoting the survival of animal ENS neurons and in the protection of enteric neurons in intestinal disorders, neuronal stress or injury [47,48]. Other study suggests that CART influences on GI function are mostly via CRH-dependent mechanism and peripheral cholinergic pathways [49]. Further examinations need to be undertaken to elicit the valuableness of CART in intestinal functions especially during colitis (Figure 2).

Conclusion

Colitis is a chronic multifactorial disease that targets the colon and as of recently afflicts more often the western population exacts a substantial toll on the economy with loss of productivity from disabilities and cost of medication. Despite advances in understanding of colitis pathogenesis and discovery of new treatments, the patients continue to suffer from this refractory disease [3]. Current treatment of colitis is expensive (antagonists of TNF-α; adalimumab, infliximab, certolizumab) and frequently toxic (5-aminosalicylates) [50]. Furthermore, they are not effective in all patients [51]. The inadequacy of conventional therapy has motivated investigators to develop a novel approach to treat colitis. For example, tachykinin NK receptors inhibitors [52,53] or natural products which inhibit the NF-κB activity [54] have been recently under intense investigation as the newest target for colitis treatment.

Colitis is an extremely complex illness involving multiple levels of interaction between the neural, immune, and endocrine systems. The close anatomical and functional association between nerves, lymphoid organs, and intestinal cells suggests multidirectional cross-talk between them, where neuropeptides and cytokines act as viable neuroendocrine

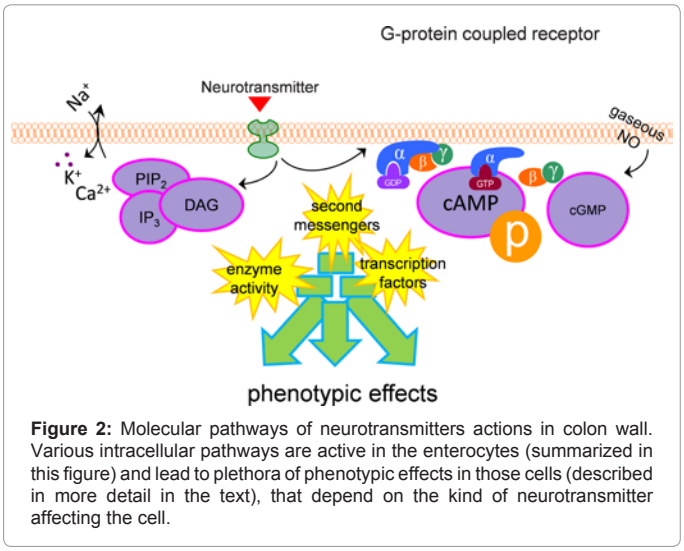

Figure 2: Molecular pathways of neurotransmitters actions in colon wall. Various intracellular pathways are active in the enterocytes (summarized in this figure) and lead to plethora of phenotypic effects in those cells (described in more detail in the text), that depend on the kind of neurotransmitter affecting the cell.

linkage between these systems. However, the complexity of interactions between neuropeptides, conflicting study results, and opposing mechanisms of action of the neuropeptides, discussed warrants research in this field. Further clarification of the molecular mechanisms of neuropeptides and their effects on human diseases may yield treatment options in the future. This review highlights some aspects of bidirectional co-operation of neuro-immune factors and their impact on etiopathogenesis and course of colitis, mainly in human and laboratory animals. However, data obtained from these animal models cannot be directly extra pooled to human regarding evident differences in colon anatomy and physiology between two. The promising prospective alternatives constitute experiments performed on pigs [14,39,55].

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