NARRATIVE REVIEW

Intestinal Barrier Integrity: The Essential Role of Neuropeptides and Their Implications in the Pathogenesis of Gastrointestinal Diseases

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ABSTRACT

The intestinal barrier relies on tight junctions and proteins including claudins, occludins, and zonula occludens, helping to seal the epithelial cell gaps and hence controlling permeability. When tight junctions are disrupted, intestinal permeability increases, a condition recognised as "leaky gut." This condition is linked to gastrointestinal (GI) disorders including inflammatory bowel disease (IBD) and irritable bowel syndrome (IBS). Neuropeptides are crucial in modulating the tight junctions' integrity within the GI epithelial barrier. This review focuses on neuropeptide Y, vasoactive intestinal peptide, cholecystokinin, and substance P in regulating intestinal barrier integrity. Studies included in this narrative review were selected based on their relevance to the topic, identified through searches in databases such as Google Scholar, PubMed, and Mendeley using relevant keywords. Understanding the mechanisms of these neuropeptides may provide pathophysiological insights and potential treatment strategies for restoring intestinal barrier integrity in GI disorders.

Keywords
Intestinal barrier, neuropeptide Y, vasoactive intestinal peptide, cholecystokinin, substance P

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INTRODUCTION

The gastrointestinal tract (GIT) is a complex system essential for absorbing water and electrolytes to maintain fluid balance while efficiently processing and eliminating waste products. This process is carried out by a series of specialised organs which span between the mouth and the anus, each fulfilling a distinct role. The GIT also hosts a diverse microbiota that plays an integral part in maintaining digestive health.[1] Central to the function of the GIT is the intestinal barrier, a critical structure that divides the body's internal environment from the gut lumen.

The mucosal barrier of the GIT consists of three distinct layers: an outermost layer contains mucus, gut microbiota, and defense proteins such as secretory immunoglobulin and antimicrobial peptides. The middle layer is formed by intestinal epithelial cells, connected by junctional proteins such as tight and adherens junctions.[2] The innermost layer, the lamina propria, houses connective tissues, blood vessels, and immune cells. The principal role of this barrier is to selectively assimilate nutrients and other essential substances from the lumen while effectively blocking harmful foreign materials, food particles, microorganisms, and their byproducts from entering the body.[1]

The expansive surface area and high energy demands highlight the vital role of the GIT in nutrient absorption and safeguarding against harmful substances and pathogens.[2] This protective function is largely supported by tight junction proteins (TJPs) localised near the apical region of the epithelium between adjacent cells. These TJPs consist of dynamic structures comprised of at least 20 transmembrane proteins that continuously interact with their components to regulate the effectiveness of the gut barrier.[3] The key transmembrane proteins, including claudin, occludin, zonula occludens-1 (ZO-1), and cingulin, are necessary for sustaining the structural integrity and biological functions of intestinal epithelial cells.

An optimally functioning intestinal barrier is necessary for maintaining gut health. A dysregulated intestinal barrier is believed to contribute to various diseases, including GI disorders, and extend beyond the gut through interactions across the gut-brain axis.[4] The gut-brain axis is a bidirectional communication network involving neural, hormonal, immune, and microbiota pathways.[4] When this barrier function is compromised, it leads to amplified intestinal permeability called "leaky gut". This condition allows harmful substances such as toxins, bacteria, and other foreign molecules, which are normally restricted, to be excessively absorbed into the systemic vascular system.[5] It then triggers cascades of systemic effects that lead to extra-intestinal disorders, including metabolic disorders such as diabetes and obesity, neurodegeneration and neuropsychiatric conditions like depression and anxiety, as well as altered immune responses that may trigger inflammatory diseases.[2] A dysregulated intestinal barrier is believed to contribute to neurodegenerative and psychiatric disorders through interactions across the gut-brain axis.[45] These effects arise through mechanisms involving altered gut microbiota, disrupted intestinal barrier function, and changes in neuropeptide signalling pathways within the gut-brain axis.[2]

Neuropeptides such as ghrelin, glucagon-like peptides, neuropeptide Y (NPY), vasoactive intestinal peptide (VIP), cholecystokinin (CCK), and substance P (SP) play an important role in regulating gut health.[6] Current research highlights the role of neuropeptides in facilitating communication between the gut microbiota and the host along this axis. These neuropeptides are secreted not only by neurons in both central and peripheral but also by the GIT, establishing an important bridge between the gut and the brain. Moreover, these peptides are essential to uphold the integrity of the intestinal barrier, which is vital for overall gastrointestinal health.[7] This review will emphasise the role of different neuropeptides, including NPY, VIP, CCK, and SP in regulating intestinal barrier integrity and their associated roles in disease pathogenesis. This narrative review incorporates studies considered relevant to the topic, identified through searches on Google Scholar, PubMed and Mendeley using keywords including "intestinal barrier", "neuropeptides", "gut-brain axis", and "intestinal permeability".

INVOLVEMENT OF GUT NEUROPEPTIDES IN INTESTINAL BARRIER INTEGRITY

Neuropeptide Y (NPY)

NPY is a 36-amino acid neuropeptide widely distributed throughout the body, including the central and peripheral nervous systems, and in organs associated with the cardiovascular, gastrointestinal, and genitourinary systems.[8] It is primarily expressed in the hypothalamus, playing a crucial role in responding to peripheral metabolic signals, thereby regulating food consumption and energy metabolism.[9] In the peripheral nervous system, it works with norepinephrine and adenosine triphosphate to modulate cardiovascular and other physiological functions.[8,9] Numerous studies highlight NPY's critical role in the GIT, particularly in regulating gastrointestinal motility through its effects on smooth muscle contractions, as well as mediating vasoconstriction in the gastrointestinal blood vessels.[10]

Additionally, NPY influences intestinal barrier permeability, contributing to the maintenance of the gut barrier function through various mechanisms.[8] The intestinal epithelium, which lines the small intestine, consists of structures such as the brush border, crypts, villi, and a basolateral plasma membrane.[2] This epithelium facilitates nutrient absorption and serves as a critical physical and biological barrier.[11] TJPs, such as occludins, claudins, and zonula occludens, are vital for preserving the integrity of the epithelial barrier by sealing the paracellular space between adjacent epithelial cells. This prevents the intrusion of external substances such as microorganisms, antigens, and xenobiotics.[2]

There is a significant connection between NPY and the regulation of TJPs. Claudin-2 which primarily serves as a marker of a leaky gut barrier, functions as the transmembrane protein responsible for channel formation, that allows the transport of small ions and water.[12] One study demonstrated that NPY increases epithelial monolayer permeability by upregulating the expression of claudin-2 through the phosphatidylinositol-

3-kinase (PI3K) pathway. In an experiment using colonic tissue cultures from the wild type and NPY knockdown mice, NPY was found to enhance epithelial permeability while NPY knockdown was demonstrated to improve intestinal integrity.[13]

Further evidence comes from another study, which found that overexpression of NPY leads to disrupted intestinal homeostasis, compromised barrier integrity, increased intestinal permeability, and elevated serum levels of inflammatory cytokines in the samples of ovariectomized rats.[14] These pathological changes are reversed by the NPY receptor antagonist (BIBO3304), implicating the involvement of NPY in the pathophysiology of leaky gut. Collectively, these findings underscore NPY's essential role in preserving intestinal permeability function, with its dysregulation potentially contributing to the development of intestinal disorders.

Vasoactive Intestinal Peptide (VIP)

VIP belongs to the secretin-glucagon peptide family and is a 28-amino acid peptide secreted through the proteolytic cleavage of its precursor, preproVIP195, a 170 -amino acid protein. VIP exerts diverse roles in both physiological and pathological conditions, affecting the growth, development, and regulation of epithelial, neuronal, and endocrine cells.[15] VIP is present in mast cells and lymphoid cells, with primary localisation in the neurons of the GIT.[16] In the gastrointestinal system, VIP serves various functions, including stimulating growth, regulating intestinal blood flow, controlling gut motility, relaxing sphincters, managing secretion activities, and modulating intestinal inflammatory response.[1]

Extensive research has highlighted the protective role of VIP in maintaining intestinal barrier integrity. It prevents increased intestinal permeability by enhancing TJPs.[17] Intestinal permeability is controlled by TJPs located between intestinal epithelial cells at the uppermost part of the intestinal epithelium.[17] Moreover, immunoreactive claudin-3 was observed within the intestinal crypts during necrotizing enterocolitis (NEC), and administration of VIP helped preserve the distribution and expression of TJPs.[18] The expression of claudin-3 was markedly elevated in the NEC+VIP group in juxtaposition with the solitary NEC group, suggesting that exogenous delivery of VIP reduces tight junction impairment.

Despite its protective roles in the barrier function, VIP is also implicated in the pathology of IBS, with studies showing that IBS patients exhibit significantly higher plasma levels of VIP compared to healthy controls.[19] Additionally, a separate study revealed that irregular food intake impairs barrier functions and causes dysbiosis, contributing to metabolic imbalance. This disruption is linked to chronic activation of VIP-producing neurons, suggesting the potential use of VPAC2 inhibitors to enhance barrier function.[20] These findings suggest that while VIP typically supports gut health via maintaining intestinal barrier function, its protective role may also be overwhelmed by other factors such as inflammation and altered microbial composition. In addition, elevated levels may represent a compensatory mechanism, underscoring its complex role in the disease's pathology.[21] Further investigations are required to understand the apparent contradiction between VIP's protective roles and its increased levels in IBS for better understanding of underlying mechanisms involved in the disease pathogenesis.

Cholecystokinin (CCK)

CCK is a hormone released by the gut endocrine cells that facilitates bile secretion from the gallbladder into the small intestine. CCK is synthesized from a 115-amino acid precursor molecule that undergoes various modifications to generate several isoforms ranging from 4 to 58 amino acids.[22] The main fragments present in the human body include CCK-58, CCK-22, CCK-33, and CCK-8. Of these, CCK-8 is the smallest active form and is recognised as a potent neurotransmitter.[23] Notably, CCK-8 has remained largely unchanged across species, retaining its biological functions through interaction with its receptors present in both the central nervous system (CNS) and GIT.[22]

CCK regulates GIT motor functions by inhibiting gastric emptying and stimulating gut motility. It induces smooth muscle contraction in the gallbladder and GIT while also

enhancing glandular excretion in the liver, pancreas, small intestine, and other organs.[23] CCK has been demonstrated to protect the colonic mucosal barrier by regulating TJPs and preventing damage in sepsis.[24] Intervention with CCK supports the integrity of the intestinal barrier by preventing excessive permeability and inhibiting the translocation of bacteria from the gut into the bloodstream. This protective function is vital in safeguarding the body from complications associated with a condition termed endotoxemia.

Substance P (SP)

SP is an excitatory neurotransmitter composed of 11 amino acids, produced by motor neurons in the central and peripheral nervous systems as well as in immune cells.[25] It belongs to the tachykinin (TAC) peptide hormone family, which is encoded by the TAC1 gene. SP serves dual functions as a neurotransmitter and a neuromodulator, with its highest concentration found in the mucosa of the GIT and its lower concentration in the lamina propria of the intestinal muscular membrane. In addition to its involvement in gastrointestinal inflammation, SP also affects the musculoskeletal and respiratory systems.[26] As a pro-inflammatory chemical messenger, SP is frequently activated during intestinal inflammation, contributing to altered gut motility.[26]

The significance of SP in gastrointestinal function is highlighted by research showing that patients experiencing constipation exhibited abnormal neurotransmitter levels, including a deficiency of SP, in the muscular layer of the intestinal walls.[27] Evidence suggests that SP may also influence intestinal activity through broad-spectrum action on the cationic transport channel in Cajal's interstitial cells, which is mediated by the release of intracellular calcium ions triggered by the stimulation of tachykinin NK1 receptors.[28] This interaction influences multiple processes beyond gastrointestinal motility, including secretion from glands, vascular membrane permeability, and pain responsiveness.

Besides its role in regulating gut motility, recent findings suggest that SP can enhance epithelial cell expansion and exert an apoptosis-inhibiting effect at injury sites in the colon by interacting with its high receptor affinity neurokinin-1 receptor, NK-1R.[29] In terms of TJPs, SP accelerates intestinal healing by increasing the expression rate of ZO-1.[30] SP has also been shown to protect against sodium lauryl sulphate (SLS)-induced toxicity by sustaining the expression of E-cadherin at adherens junctions and providing anti-inflammatory effects.[31]

On the flip side, excessive expression of SP can disrupt normal gastrointestinal function. In a related case study, elevated serum levels of SP were observed in infants with acute intussusception, a condition characterised by a section of the intestine folding into another segment. This primarily occurs in the small bowel, while isolated cases involving only the large bowel are relatively rare.[32] The involvement of neuropeptides in the integrity of the intestinal barrier was summarised in **Table I** and illustrated in Figure 1.

Table I: Roles of Neuropeptides in Intestinal Barrier Integrity

Neuropeptides	Roles in Intestinal Barrier Integrity	Mechanisms	Study
NPY	Increases permeability	Upregulates claudin-2 expression via PI3K pathway	11–13
VIP	Enhances tight junction proteins but may disrupt barrier at high levels	Improves claudin-3 expression; protective against NEC	17–20
CCK	Regulates motility and protects barrier integrity	Enhances tight junction proteins; exhibits anti-inflammatory	24
SP	Promotes healing and tight junction maintenance but disrupts function at excess levels	Enhances ZO-1 expression, maintains E-cadherin	27–32

Abbreviations: CCK, cholecystokinin; NEC, necrotizing enterocolitis; NPY, neuropeptide Y; PI3K, phosphatidylinositol-3-kinase; SP, substance P; VIP, vasoactive intestinal peptide; ZO-1, zonula occludens-1

INVOLVEMENT OF GUT NEUROPEPTIDES IN GASTROINTESTINAL DISEASES AND DISORDERS

Irritable Bowel Syndrome (IBS)

IBS is a chronic GI disorder defined by disturbances in the complex brain-gut axis. Patients typically experience abdominal pain along with alterations in faeces consistency, immune response initiation, dysregulated intestinal motility, augmented intestinal barrier permeability, and enhanced vulnerability to psychosocial stressors.[33] Globally, IBS affects approximately 11.2% of the populace, making it the most prevalent functional gastrointestinal disorder.[34] Although the well-defined aetiology of IBS continues to be elusive, it is postulated to

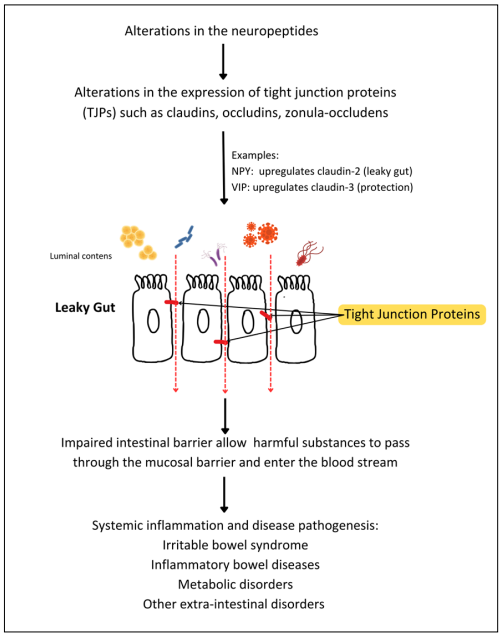

Figure I: The association between the gut-brain axis dysregulation and neuropeptide alterations in leaky gut and gastrointestinal disorders.

involve a complex interplay of various contributing factors. Dysfunction of the brain-gut axis is growingly acknowledged as a significant factor in the development of IBS.

Neuropeptides exacerbate intestinal barrier dysfunction, a critical component of IBS pathology. Research revealed significant alteration in the blood levels of neuropeptides, including SP and NPY, in different diarrhoea-predominant IBS rat models in comparison to the normal reference group. In the context of IBS, elevated SP levels indicate an increased perception of intestinal pain and visceral hypersensitivity, while reduced NPY levels suggest dysregulation of the stress response and an imbalance in gut homeostasis.[35] Similarly, increased SP and decreased NPY were reported in a retrospective cohort study involving IBS patients and in an animal study using IBS mouse models.[36,37] In contrast, a cross-sectional study reported higher NPY levels in IBS patients as opposed to healthy control subjects.[38] Differences in the physiological response to stress or inflammation among IBS patients might contribute to these contrasting findings.

The expression of VIP is reportedly elevated in IBS, as presented in an animal study using specific pathogen-free Sprague-Dawley rats and in a clinical study.[19,39] This points to the fact that increased VIP levels may contribute to the pathophysiology of IBS by influencing gastrointestinal motility and sensitivity. Conversely, another reported decreased VIP expression in IBS constipation patients, indicating that VIP expression may not consistently increase in IBS across different experimental conditions or models.[40] These discrepancies underscore the complexity of neuropeptide regulation in IBS and highlight the need for further research to clarify the role of VIP in this disorder.

A randomised comparative trial observed that IBS patients exhibited higher levels of cholecystokinin (CCK) than healthy individuals, with increased levels associated with constipation, while NPY levels were undetectable.[41] Additionally, a case study also indicated elevated CCK levels in IBS patients.[40] This study found direct correlations between CCK levels in both the mucosa and plasma and various pain metrics, including pain intensity, symptoms, and frequency. Conversely, the levels of CCK measured before meals were substantially reduced in individuals with IBS compared to controls. While baseline pre-prandial CCK levels in IBS patients were quite low, they surged nearly fourfold after eating. This suggests that IBS patients may respond differently to meals, potentially contributing to their symptoms and digestive issues.[40]

Inflammatory Bowel Disorders (IBD)

IBD is a recurring disorder of the digestive tract that progresses over time and is characterized by abnormal and persistent inflammation. It incorporates two major types: Crohn's disease and ulcerative colitis.[42] As indicated by the Global Burden of Disease Study, the IBD prevalence continues to rise, with an estimated 4.9 million cases worldwide in 2019.[43] Most IBD cases are diagnosed between the ages of 15 and 35 years old, with approximately 25–30% of patients under 20 years old diagnosed with Crohn's disease, while one-fifth are diagnosed with ulcerative colitis.[44] A significant factor in the development of IBD is a disproportionate immune reaction against microbes and disrupted gut microbiota in genetically susceptible individuals. IBD is associated with the integrity of the intestinal barrier, particularly the TJPs. Although IBD is classified as an idiopathic disorder,

numerous studies suggest that maintaining intestinal barrier integrity is vital to prevent its development. A compromised intestinal barrier leads to increased intestinal permeability, allowing the translocation of bacteria and toxins, which can trigger a series of immune and inflammatory responses. Alterations in TJPs are also observed in IBD. For instance, claudin-2, a tight junction protein essential for forming water channels in the space between cells, is often highly expressed in leaky epithelial tissues and enhanced in IBD. This excess of claudin-2 contributes to heightened intestinal permeability and worsens the inflammatory response associated with the disease.[45,46]

NPY acts as a pro-inflammatory molecule in IBD. In animal studies, NPY has been shown to increase epithelial permeability by activating the PI3-K pathway, leading to the intensified expression of claudin-2. This increased claudin-2 expression can compromise intestinal barrier integrity and potentially contribute to the onset and development of IBD.[14] Clinical studies using sigmoid colon biopsies further support these findings, showing elevated NPY expression in patients diagnosed with IBD.[47] Nevertheless, CCK has shown promise in reducing the inflammatory response in the compromised intestine while also enhancing the integrity of the intestinal epithelial barrier. *In vivo* studies suggest that CCK may effectively treat IBD due to its anti-inflammatory characteristics and its role in maintaining intestinal barrier function.[48,49]

The neuromodulator VIP is recognised for stimulating vasodilation of the intestinal barrier and has also been implicated in the progression of IBD. An animal study revealed significantly elevated VIP expression in dogs with severe IBD.[50] Similarly, a clinical study reported significantly intensified VIP levels in the plasma of those diagnosed with Crohn's disease and ulcerative colitis compared to controls.[51] A similar pattern is observed with SP, where another research found elevated serum levels and enhanced density of SP immunoreactive fibres in the lamina propria of IBD patients.[26] Furthermore, SP stimulates the expression of inflammation-associated cytokine mRNA and the excretion of inflammation-associated cytokines in mesenteric preadipocytes derived from individuals suffering from IBD.[52]

Table II highlights changes in the levels of neuropeptides and their roles in GI diseases such as IBS and IBD. The inconsistencies in results could be attributed to several reasons such as differences in experimental models, study duration, and variations in measurement techniques.[38,53] Further studies employing similar study populations, larger sample sizes, and standardized measurement protocols are warranted to address these discrepancies and to provide more relevant findings.

Table II: Roles of Neuropeptides in Gastrointestinal Disorders

GIT Diseases	Mechanisms	Pathogenesis	Study
IBS	Altered in IBS; SP associated with pain, NPY with stress response	Elevated SP, reduced NPY in IBS though some studies show higher NPY levels in IBS	24,35,37–39
IBD	NPY increases permeability; SP and VIP contribute to inflammation	NPY, VIP, and SP levels elevated in IBD, with roles in enhancing permeability and cytokine production.	16,41–50

Therapeutic Implications for GI Diseases

Understanding the underlying roles of each neuropeptide in modulating intestinal barrier function potentially offers prospective directions for clinical applications for GI disorders like IBS and IBD. For instance, the use of NPY receptor antagonists to block NPY signalling, NPY gene transcription inhibitors to reduce NPY transcription, and anorexigenic hormone analogues to reduce NPY-induced food intake are among potential strategies which target the NPY pathways.[8] Additionally, VIP and NPY are being explored for their roles in IBS and IBD, where VIP modulation can promote colonic crypt cell migration, proliferation, and repair, while NPY helps in tissue homeostasis.[15,54] NPY are also implicated in inflammation -induced tumorigenesis by modulating epithelial cell proliferation, survival, and apoptosis, through miRNA-dependent mechanisms, which may influence cancer progression.[13] These findings highlight the broad potential of neuropeptides in treating both GI and systematic conditions.

CONCLUSION

In conclusion, neuropeptides including NPY, VIP, CCK, and SP play a vital role in supporting the barrier function of the intestinal epithelium, and abnormalities in these peptides may contribute to the pathogenesis of diseases including IBD and IBS. The insights gained from this review may inform therapeutic strategies, such as developing neuropeptide analogs to restore intestinal barrier integrity by targeting pathways mediated by neuropeptides. Future studies should aim to test neuropeptide mechanisms in diverse populations or explore their roles beyond gut health including the gut-brain axis.

CONFLICT OF INTEREST

The authors declare no conflict of interest concerning this manuscript.

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