From Sensitivity to Symptoms: Understanding the Intricate Pathways of Visceral Hypersensitivity in Irritable Bowel Syndrome

Faisal Ayub Kiani[1], Li hao[2,] Muhammad Usman Saleem[3], Suliman khan[4], Zulfiqar Ahmed[5], Faisal Rasool[6]

[1]Lecturer Department of Clinical Sciences, Bahauddin Zakariya University Multan, Pakistan & College of Veterinary Medicine, Huazhong Agricultural University, Wuhan, China

2College of Veterinary Medicine, Huazhong Agricultural University, Wuhan, China

[3]Department of Bio-Sciences, Faculty of Veterinary Sciences, Bahauddin Zakariya University, Multan Pakistan

[4]Lecturer Department of Veterinary Physiology and Biochemistry, Faculty of Veterinary and Animal Sciences, Lasbela University of Agriculture, Water and Marine Sciences, Uthal Balochistan

[5]Lecturer Department of Livestock & Poultry Production, Faculty of Veterinary &Animal Sciences, University of Poonch Rawalakot, Azad Kashmir

[6]Lecturer Department of Pathobiology, Faculty of Veterinary &Animal Sciences, University of Poonch Rawalakot, Azad Kashmir

Corresponding Email ID: drfakiani@bzu.edu.pk

Abstract:

A significant contributing factor to gastrointestinal diseases with mild or moderate symptoms is visceral hypersensitivity, which is present in IBS (irritable bowel syndrome). IBS is characterized by bloating, bowel irregularities, and pain or irritation in the abdomen. Irritable bowel syndrome is hypothesized to be caused by increased epithelial hyperpermeability, inflammation, dysbiosis, altered brain-gut interactions, epigenetics, genetics, and visceral hypersensitivity (VH). However, the specific pathophysiology is yet unknown. Visceral hypersensitivity to luminal stimuli results from many pathways at the peripheral, spinal, and supraspinal levels that lead to sensitizing receptors in visceral pain. The primary afferents of the vagus nerve and spinal nerve both innervate the gut viscera. The intestine's intrinsic enteric nervous system (ENS), which contains intrinsic primary afferent neurons, integrates gut motility and peristalsis (IPAN). In IBS patients, a persistently overactive afferent from the colon to the spinal cord causes secondary somatic hypersensitivity. Both human and animal models of visceral hypersensitivity have been used to investigate this process. A breach in the gut barrier can also result in systemic abnormalities and gastrointestinal dysfunction. According to clinical research, micro-RNA expression increases in the colon tissue in IBS models. It has been found that these microRNAs help IBS patients' epigenetic and genetic events. The fundamental elements that link gut somatic and visceral systems with IBS are covered in this review. The literature review highlights various phenomena of signals originating from the colon that affect the GIT of IBS

patients, such as changes in microRNA expression, changes in intestine permeability, and hypersensitivity in the GIT, as well as experimental exploration of VH in inflammatory bowel syndrome.
Key words: Visceral hypersensitivity, Irritable bowel syndrome, Gut microbiota, Permeability, miRNA expression

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Background:

Visceral hypersensitivity (VH), which emerges as increased sensitivity of the viscera to numerous stimuli, including elevated responses to painful and non-noxious stimuli, is a pathophysiological characteristic of many functional disorders of the gastrointestinal system. Visceral pain produced by inflammatory bowel disease significantly impairs the quality of life of those who suffer from it (Hao Jiang et al., 2023). Visceral hypersensitivity is thought to be a significant underlying mechanism that generates pain and is one of the most common types of pain linked with pathological disorders such as renal colic, dyspepsia, inflammatory bowel disease (IBD), angina, dysmenorrhoea, interstitial cystitis. In addition to physical discomfort, patients experiencing visceral pain often suffer from emotional distress, including anxiety and depression (Farrell KE et al., 2014; Farrokhyar F. et al., 2006). In 70% of IBD patients, continuous release of inflammatory mediators can result in enteric nerve-ending sensitization and abdominal discomfort, which is present not only during acute flares of disease but even during remission (Bielefeldt et al., 2009).

Abdominal pain/colic or discomfort, irregularities in defecation & bloating are the first clinical complaints of Irritable bowel syndrome (IBS). Many people with IBS experience severe symptoms, although some people only experience mild to moderate symptoms. IBS is frequently linked to various conditions such as pain syndromes, overactive bladder, migraine, depression, anxiety, and visceral hypersensitivity. Various factors cause IBS in animals and humans, with complex underlying pathophysiology, and the exact molecular pathophysiology is yet unknown. Many alterations, such as visceral hypersensitivity, some cerebral abnormalities, intestinal motility, and secretory problems, have been identified in IBS. Among the most profound symptoms of Irritable bowel syndrome is visceral hypersensitivity. In inflammatory bowel syndrome patients, distal rectosigmoid distension of the colon with a balloon catheter defines the VH as a reduced pain tolerance (Whitehead WE. et al., 1990; Poitras P. et al., 2002). Several gastrointestinal disorders have been linked to irritable bowel syndrome (IBS), including immune activation, altered gut microbiota, mucosal absorptions, nerve sensitization, mucosal and immune mediator expression and release, and gene expression profiles (Paul Enck et al., 2016). Although several processes, such as inflammation or sensitization following any biological or chemical insult, were reported by Mayer, E. A., and Gebhart, G. F., 1994, the specific etiology of

visceral hypersensitivity is still unknown. Some patients exhibit IBS symptoms due to an infection in the bowel, according to studies conducted by Spiller R. C. et al., 2003, Mearin F. et al., 2005, and Dupont A.W. 2007.

Visceral hypersensitivity is a critical pathophysiological process involved in gastrointestinal disorders that causes patients to experience discomfort. Azpiroz F. et al., 2007 reported that 20%–90% of patients show signs of visceral hypersensitivity in Irritable Bowel Syndrome, which is characterized by CNS and Peripheral pathways. A. Akbar et al. (2009) proposed several factors, including intestinal neural activity, psychological processes, and inflammation. Visceral hypersensitivity's pathophysiology, however, is not fully understood. Visceral hypersensitivity has been connected to pain in GIT disturbances, even though the cause of stomach pain is uncertain (Farmer A.D. et al., 2013). Visceral pain receptors are sensitized via several pathways at the peripheral, spinal, and supraspinal levels, which causes visceral hypersensitivity to luminal stimuli.

In this Review, we explore the fundamental variables contributing to the relationship between gut somatic and visceral mechanisms in people with IBS. The reviewed literature presents the experimental exploration of VH in Inflammatory Bowel Syndrome, as well as highlighting the various phenomena of signals initiation from the colon causing alteration in GIT of IBS patients, such as changes in microRNA expression, intestine permeability, and hypersensitivity in GIT. These underlying mechanisms demonstrate a synergy between peripheral and CNS systems, which plays a vital role in the pathophysiology of pain.

Visceral Sensations:

Vagal and spinal visceral afferent neurons innervate visceral organs, bridging the visceral domain and the brain. Both vagal and spinal primary afferents innervate the stomach viscera. Gut motility and peristalsis are coordinated by the intestine's inherent Enteric Nervous System (ENS), which contains intrinsic primary afferent neurons (IPAN) (Delgado-Aros S et al., 2005). Afferent fibers are classified into three types: (wide myelinated, quickly conducting) Aβ fibers that detect harmless stimuli, (small myelinated) Aδ fibers that channel noxious stimuli, and (unmyelinated) C fibers that conduct noxious stimuli (Lewin GR and Barde YA.1996). These are responsible for conducting specific control reflexes for multiple organs, general neuroendocrine regulation, general & specific visceral stimuli such as visceral pain, forming emotional feelings, and other functions (Wilfrid Janig, 1996). Inflammatory alterations in various visceral organs, such as IBD, pancreatitis, appendicitis, nephrolithiasis, cholelithiasis, or other functional problems in visceral organs, maybe the cause of visceral pain (David R. Robinson and G.F. Gebhart 2008). Without any biological insult, some nociceptors remain mechanically insensitive; however, after suffering an injury, these nociceptors become sensitive (Su, X. & Gebhart, G. F, 1998). 70–80% of mechanosensitive visceral afferents have low physiological activation thresholds, but some have high thresholds that are assumed to be common visceral nociceptors.

David R. R. & G.F. Gebhart (2008) explored the location of pain and enlightened that cutaneous pain determination is excellent, and determination of joint and muscle pain is good. In contrast, the cognition to determine the spatial location of internal pain is diffuse and less localized. Colonic distension due to excessive bile salts instillation into the colon enhances mechano-sensitive colon afferent's action (Paul Enck et al., 2016). Activation of silent nociceptors eventually results in chronic visceral sensitivity through CNS and peripheral system mechanisms. The phenomenon behind chronic hypersensitivity from viscera has been thought to be well understood from primary visceral afferent physiology.

The physiological aberrations in bowel diseases were highlighted by Mayer E. A. 1994 and Gebhart G. F. 2000 as altered sensations and interstitial cystitis in IBS patients. In the same way that persistent tissue damage can lead to chronic hyperalgesia, acute mechano-sensitization can develop following an acute visceral afferent injury. Animal study models for VH have been described by Zhou Q. et al. (2008), Al Chaer et al. (2000), and Mayer E. A. et al. (2002). They concluded that central sensitization causes allodynia and hyperalgesia, while colon irritation causes chronic visceral hypersensitivity. On the other hand, it is still unclear how sensitization of peripheral and colonic afferents results in chronic visceral hypersensitivity. In hyperalgesia central and peripheral nervous system completely controls the elements through peripheral and central mechanisms.

Somatic & Visceral Hypersensitivity In Ibs:

The gastrointestinal tract has several afferent innervations that enable it to detect mechanical, chemical, and temperature stimuli. Whether they are unpleasant, sensory data that reaches the cortex can result in conscious experiences. When visceral hypersensitivity is abnormally elevated, which is now understood to be a significant pathophysiological component, it might result in functional gastrointestinal difficulties (Adrian Miranda, 2023). According to Giovanni Barbara et al. (2011), a significant portion of IBS patients experience visceral hypersensitivity, which is the most frequent cause of abdominal pain in such patients. While additional psychological issues like anxiety can increase this aberrant sensory perception, peripheral objective elements such as entero-endocrine factors, neuron plasticity, and immunological activation have been found in a subgroup of patients. They are most likely influenced by each other, as well as the gut microbiota (Cremon C. et al., 2010) and the mucosal barrier (Camilleri M. & Gorman H., 2007; Piche T. et al., 2009). Changes are acknowledged as key players in this complex situation. According to Liu et al. (2014), significant relationships were observed between somatic and visceral hypersensitivity, autonomic cardiovascular dysfunction and visceral hyper-sensitivity, and somatic hyper-sensitivity and autonomic cardiovascular dysfunction. Accarino et al., 1995, and Zighelboim J. et al., 1995 studied the somatic hypersensitivity of IBS patients. They concluded that hypersensitivity was confined to the gut and diminished or impermeable in other body parts in IBS patients compared to healthy control people. According to Zhou Q. et al., 2009, inadequate stimuli may be required for

nociceptive receptor activation. They further explained that the nociceptive stimulus studied in previous studies might not activate C fibers to generate active action potential/or neuronal mechanisms which involve (NMDA) receptors or other peptides. Prolonged nociceptive stimuli, such as heat pulses, activate cutaneous C fibers and NMDA receptors. Persistent nociceptive input from the GIT causes extensive hypersensitivity in IBS patients, as opposed to complicated regional pain syndrome, postherpetic neuralgia, and fibromyalgia, which may be caused by peripheral impulse input (Price D. et al., 2009). Zhou Q. et al. (2010) investigated somatic pain in IBS patients. They used varying levels of stimulation to the spines to elicit somatic pain in order to investigate different stimulus intensities and perceptual attributes. Some IBS patients showed increased sensitivity to somatic stimuli compared to controls. In somatic pain stimuli, such as cold and thermal presser stimuli, variation was evident for the foot but not for the hand; this could be explained by the fact that thermal hypersensitivity is organized somato-topically in IBS patients, with lower body dermatomes being more sensitive than upper body dermatomes. As a result, the IBS patients were more responsive to somatic stimuli than the control group. In the case of mechanical stimulation, no difference in somatic sensitivity was identified between the two groups. These findings are comparable to a recent study examining pain perception in IBS patients with and without fibromyalgia. When a mechanical stimulus (as an ascending sequence of pressure) was applied, IBS patients exhibited the same pain threshold as control individuals (Chang, L. et al. 2009). Variations in stimulus modalities could be one explanation for the outcome in IBS patients, which differs from the underlying reasons in reaction to different stimuli. Mechanical inputs trigger non-nociceptive mechanoreceptors at higher levels in the cerebral cortex, which may be compromised in IBS patients by continuous visceral nociceptive feedback (Price, D. D. et al., 2009). As a result, the overall nociceptive contribution from mechanical stimuli may be lower in IBS patients than in heat stimuli. The cold pressor procedure was already performed in patients with IBS to determine somatic hypersensitivity (Whitehead W. E. et al., 1990; Zighelboim J. et al., 1995). The pain perception was significantly higher when the cold pressor was applied to the foot rather than the side (Zhou Q. et al., 2010). In comparison, one study discovered hypersensitivity in IBS patients using cold pressor testing on the side. In contrast, two investigations discovered no hypersensitivity in IBS patients using cold pressor testing on the hand (Bouin M. et al., 2001; Whitehead, W. E. et al., 1990; Zighelboim J. et al., 1995). These differences may be explained by the fact that a small subset of IBS patients has a lower pain tolerance in the cold pressor test than the control group. In contrast, the rest of the IBS patients and subgroups have a closer pain threshold for cold water than the control group. Extensive studies into subsets of sensitive IBS patients could be fascinating and could lead to the detection of hypersensitivity transmission in IBS patients. Moore P. A. et al. (1979) employed an ischemia test called "the modified submaximal effort tourniquet technique" to assess somatic hypersensitivity in IBS patients. The ischemia test activates many muscle C fibers, resulting in diffuse and severe discomfort. The cutaneous stimulus differed from previous pain stimuli that activate A fibers because it was shorter than the ischemia stimulus (Moore, P. A.

et al. 1979, Carli, G. et al. 2002). The ischemia test revealed a large group of IBS patients hypersensitive to thermal and cold pressor stimuli (Zhou Q. et al., 2010). Investigations using the adapted submaximal effort tourniquet approach in individuals with temporomandibular disorders, interstitial cystitis, or fibromyalgia have verified ischemia hypersensitivity (Carli G. et al., 2002; Ness T. J. et al., 2005). Many of these illnesses share many comorbidities and symptoms with IBS. Zhou et al. (2010) investigated the levels and variations in adrenocorticotropic hormone (ACTH) and cortisol in a large group of IBS patients with hypersensitivity in the ischemia assessment. Cortisol and ACTH levels were significantly higher in IBS patients than in controls using an ischemia test. ACTH and Cortisol levels did not significantly change in response to cold pressor thermal stimulation. The cortisol and ACTH levels spike following an ischemia test suggests that IBS patients may find this stimulus more stressful than people without IBS (Posserud I. et al., 2004). These findings are similar to those of another study, which discovered differences in response to stress in healthy people versus the adreno-cortical response in IBS patients (Chang L. et al., 2009). The acquisition data support the concept that a subgroup of IBS patients has somatic hypersensitivity. Given that the somatic hypersensitivity of IBS patients is somato-topically structured, it is tempting to suppose that an afferent nociceptive response from the GIT will sensitize neurons in the spinal cord that are somato-topically close to the GIT. Several processes may be at work because there was only a modest degree of difference between IBS patient subgroups and hypersensitivity to ischemia, thermal, and cold pressor stimuli. Only a few IBS patients showed overlapping ischemia, thermal, and cold pressor hypersensitivity. The thermal and cold pressor trials revealed increased overlapping in somatic hypersensitivity in these patients. As a result, separate hypersensitivity phenomena may be underlying this discrete subset of people with IBS and somatic hypersensitivity.

Afferent Feedback From Perepheral Sources In Ibs:

The spino-mesencephalic, spino-reticular, and spino-thalamic tracts are afferent nociceptive routes that project to the mid-cingulate cortex, anterior cingulate cortex, and primary somatosensory cortex (Aziz Q. et al., 1998; Van Oudenhove L. et al., 2004). The spino-thalamic circuit is required for sensory differentiation and localization of somatic and visceral inputs (Jones MP. et al., 2006). Some mechanisms producing visceral hypersensitivity and irregular referrals of visceral sensations are enteric neuron sensitization, spinal cord neuron sensitization, aberrant ascending route modulation, and abnormal cortical integration. In IBS patients, descending inhibitory influx is also essential in pain sensation control (Wilder-Smith CH. et al., 2004; Tracey I. et al., 2004)

Persistent afferent assault from the colon to the spinal cord is one potential source of hypersensitivity in irritable bowel syndrome patients. Research has been conducted to evaluate hypersensitivity using animal models. Repeated afferent stimulation from peripheral sources affects central processing, resulting in spontaneous motor abnormalities, hyperalgesia, allodynia,

and irritation (Zhou Q. et al., 2008, Mayer E. A. et al., 2002). Several models are based on the discovery that blocking nociceptive feedback from specific somatic foci with peripheral anesthetics improves allodynia and pain in individuals with complicated regional pain syndrome produced by cold or mechanical stimulation (Gracely R. H. et al. 1992). Nociceptive colonic afferent neuronal impulses can maintain hypersensitive zones in fibromyalgia, neuropathic pain, and VH in IBS patients. In two studies for colonic distension, the effect of a local anesthetic (lidocaine) was investigated. Rectal lidocaine did not affect the sensation of phasic or ramp rectum distension in IBS patients, according to Lembo T. et al., 1994. Sabate J. M. (2000) conducted a study and reported that lidocaine suppressed rectal sensitivity to the gradual ramp but not fast phasic distension in persons; however, patients with IBS were excluded from this investigation. Verne G. N. et al., 2003 studied the effect of tonic impulse from the gut in individuals with irritable bowel syndrome in a double-blind crossover research utilizing lidocaine jelly in the colon and found that intra-colonic lidocaine reduced hypersensitivity. Zhou Q. et al. (2008) discovered similar results in hypersensitive rats (IBS model) by normalizing thermal and intestinal sensitivities. Lidocaine levels in blood were not detected up to 50 minutes after injection in both trials, indicating that the outcome was not driven by lidocaine systemically absorbed. Some conditions exist in the gut where tonic impulses from a peripheral source dynamically sustain the primary hypersensitivity generated by gut input as well as the secondary somatic hypersensitivity that is distant (for example, in an extremity) from the peripheral source of impulse input (R. H. Gracely et al., 1992). There are a few approaches to assess the spinal cord mechanisms of hyper-sensitivity in individuals with irritable bowel syndrome. Coffin B. et al., 2004 investigated the effect of painful electric shocks in the foot field on colonic distension utilizing electro-myographic recordings of somatic nociceptive reflexes (R-III). Colon distension suppressed the nociceptive reflex in 10 healthy volunteers but accentuated it in 14 individuals with irritable bowel syndrome. These data suggest that IBS patients may have increased excitability of spinal nociceptive processing. According to Zhou Q. et al. (2011), some IBS patients experienced strong temporal summation of second pain in response to painful heat pulses with a modest peak intensity (47 °C). Windup was observed in IBS patients and was inhibited by the NMDA receptor antagonist dextromethorphan. Windup is essential for maintaining and producing chronic diseases such as allodynia and hyperalgesia (Zhou Q. et al., 2009, Price D. D. et al., 2009). A subgroup of somatic hypersensitivity was observed in an IBS patient, possibly due to temporal summation generated by rigorous NMDA receptor activation. Increased central sensitization could be responsible for chronic pain in the IBS patients indicated above (Zhou Q. et al., 2010). Much animal research in irritable bowel syndrome patients provides knowledge about hypersensitivity mechanisms from the spinal cord. According to Zhou Q. et al. (2008), 24 percent of rats treated with intra-colonic trinitrobenzene sulfonic acid (TNBS) developed hypersensitivity to both nociceptive colonic distension and heat stimuli in the TNBS- induced colitis model. Al Chaer E. D. et al., 2000 employed neonatal rats as an animal model and administered mustard oil injections, which induced delayed somatic and visceral

hypersensitivity similar to TNBS therapy results. Dorsal horn neurons that received somatic and colonic feedback showed increased impulse and spontaneous activity in response to somatic stimulation and colonic distension. This finding suggests that dorsal horn neurons and primary colonic afferent neurons in IBS patients dynamically retain both somatic and visceral hypersensitivity with which they synapse. The role of the central nervous system in regulating VHS has grown dramatically over the last decade. Increased levels of c-Fos have been found to activate the CNS in animal models of visceral hypersensitivity. Myers B. et al., 2010 found that in rat models of bowel illness, levels of a corticotrophin-releasing factor, a key regulator of the stress response, increased in several brain tissues. Consequently, targeting central nervous system processes with cognitive behavioral therapy or other core therapies may lead to crucial therapeutic techniques for inflammatory bowel syndrome, such as amitriptyline (Thoua N. M. et al., 2009).

Factors Affecting the Permeability of Intestine:

Gut Microbiome:

Good gut function necessitates communication between the gut and the brain. The brain-gut axis connects the central nervous system (CNS), the enteric nervous system (ENS), immune cells, and the microbiota. By controlling secretory factors and motility, the autonomic nervous system exerts direct extrinsic control over the gut, sustaining its physiological functionality (Isabelle A. M. et al., 2020). The gut is essential in maintaining general homeostasis, food digestion, and absorption. The gastrointestinal system aids nutrition absorption while simultaneously functioning as a barrier for toxic compounds, microbes, and macromolecules (Bjarnason I. et al., 1995; Macdonald, T. T. et al., 2005). With over a thousand organisms residing in GIT, the total number of bacterial cells in the human body is estimated to be ten times that of human cells (Orel R. and T. K. Trop 2014). The gut microbiota significantly impacts energy metabolism, nutrition, immune system development, and host defense (T. J. Borody et al., 2013). The development of both systemic and gastrointestinal disorders has been related to changes in the microbiota (D. Festi et al., 2014; G. Escobedo et al., 2014).

As a result, the term "mucosal barrier" appears to suitably emphasize the function of the gut in its relationship with bacteria (J. H. Cummings et al., 2004). It is not a static shield but an active system with specialized pieces. According to Bischoff et al. (2014), permeability is a functional property of this barrier. This allows us to coexist with bacterial symbionts while keeping macromolecules and pathogens out of the luminal barrier (Maynard C.L. et al., 2012, Hooper L. V. et al., 2012). Changes in the immunological or mechanical barriers allow pathogenic microorganisms and inflammatory luminal macromolecules to enter the systemic circulation quickly. Antigens and microorganisms can pass through the mucosal gut due to hyperpermeability. As a result of this translocation, patients with IBS may have symptoms such as chronic diarrhea, mucosal immunological reactions, and stomach pain.

Gut Dysfunctioning:

A break in the gut barrier can also result in systemic abnormalities and local gastrointestinal problems. Inflammatory bowel disease, rheumatoid arthritis, celiac disease, allergy disorders, food allergies, and several dermatological diseases have been associated with increased intestinal barrier permeability, according to Bjarnason I. et al. (1995). According to studies by Camilleri M. & Gorman H. (2007), IBS may have increased intestinal permeability. Post-infectious IBS is characterized by persistent subclinical inflammation, increased intestinal permeability, mast cells, pro-inflammatory cytokines, serotonin-containing entero-chromatin cells, and T lymphocytes (Spiller R. C. et al., 2000; Dunlop S. P. et al., 2006). Protease, histamine, prostaglandins, and cytokines are released together with increased mast cell and T-lymphocyte counts in the intestinal mucosa of a subset of IBS patients (Spiller R. C. et al., 2000). These mediators are known to produce intestinal dysfunction through signaling to epithelial, neuronal, and muscular cells.

Several disorders, acute pancreatitis (J. E. Fishman et al., 2014), multiple organ failure (G. M. Swank and E. A. Deitch et al., 1996), major surgery (J. P. M. Derikx et al., 2008), and severe trauma (J. J. de Haan et al., 2009) are among the conditions linked to changes in intestinal permeability that may explain the high incidence of gram-negative sepsis (J. H. Cummings et al., 2004). Irritable bowel syndrome and steatohepatitis (NASH) have both been associated with a disturbance of the complex permeability pathway (M. Camilleri et al., 2012; C. Martnez et al., 2013; Z. Mujagic et al., 2014; and K. Ray, 2015). These inflammatory factors may become active and increase intestinal permeability, especially in a subset of IBS patients with diarrhea as their primary symptom (Zhou Q. et al., 2010). Animal models have demonstrated that increased intestinal permeability can result in hypersensitivity. In a different investigation, abdominal muscle electromyography and acute partial restraint stress were enhanced in response to intestinal distension (Ait-Belgnaoui et al., 2005). Increased intestinal permeability was investigated in the IBS group, where diarrhea predominated (Zhou Q. et al., 2009). Compared to people without intestinal hyperpermeability, those with intestinal hyperpermeability had higher functional bowel problem severity index scores. Thermal and visceral hypersensitivity increased along with increases in the functional bowel disorder severity index (FBDSI) scores. In IBS patients with diarrhea as their predominant symptom, intestinal hyperpermeability may provide a prolonged nociceptive drive from the GIT to the spinal cord, which causes central sensitization. The severity of IBS symptoms, as determined by the FBDSI scale in the report, was also correlated with the presence of somatic and visceral hypersensitivity.

Moreover, IBS sufferers with somatic and visceral sensitivities have more excellent intestinal permeability (Zhou Q. et al., 2009). Bacteria and inflammatory chemicals may pass through the mucosa due to intestinal hyperpermeability, sensitizing the mesenteric plexus and overlapping standard spinal segments. In IBS patients, spinal sensitization can be established and maintained using impulse feedback from the colon to the spinal cord. The FBDSI score was associated with visceral and thermal hypersensitivity and increased intestinal permeability in IBS

patients. Patients with inflammatory bowel syndrome with increased intestinal permeability and a high functional bowel disorder severity index score may exhibit central sensitization, which justifies using different central nervous system therapeutic strategies.

Glutamine Deficiency:

The term "gut-brain axis" refers to the intricate neural pathway that connects the brain and gastrointestinal tract (Rhee S.H. et al., 2009). The brain-gut axis also directly affects the development of the CNS and numerous elements of behavior in both pathological and normal states. The gut-brain axis ensures that the digestive tract is correctly aligned and maintained to retain various physiological processes. In contrast, it is clear that the brain-gut axis can regulate a number of gastrointestinal functions in both healthy and diseased states (Rhee S.H. et al., 2009; Carabotti M. et al., 2015).

It is currently known that neuroactive chemicals, including glutamate, serotonin (5-HT), gamma-aminobutyric acid (GABA), dopamine, and noradrenaline, are produced by both eukaryotes and prokaryotes, resulting in an inter-kingdom communication mechanism. The amino acid glutamine plays a variety of roles in taste perception, energy synthesis, and intermediate metabolism in the gut. Food additives often contain free glutamine, predominantly sourced from dietary proteins. Additionally, some of the free glutamine in the lumen is produced by bacteria (Mazzoli R. et al., 2016). In the ENS (enteric nervous system), where neurons and glial cells generate glutamate, and in the peripheral and central nervous systems, glutamate also performs the function of an excitatory neurotransmitter (Miladinovic T. et al., 2015; Filpa V. et al., 2016). N methyl D aspartate (NMDA) and a-amino 3 hydroxy 5-methyl 4 isoxazolepropionic acid are two examples of glutamate binding receptors (AMPA). The central nervous system stimulatory neurotransmitter receptors alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (AMPA) and N-methyl-d-aspartate receptors (NMDA) are crucial for synaptic plasticity. This excitatory synaptic plasticity affects the pathophysiology of visceral hypersensitivity in functional gastrointestinal diseases (Cheng Fangli et al., 2022). In experimental models of visceral hypersensitivity, the NMDA glutamate receptor's activity in the anterior cingulate cortex increases (Zhou L. et al., 2014).

Similarly, persistent activation of the AMPA receptor, which plays a crucial role in regulating synaptic plasticity and fast excitatory transmission, is associated with hyperalgesia (Wu X. et al., 2008). GluR-1, GluR-2, GluR-3, and GluR-4 are the four component tetramers that make up the receptor AMPA. When mustard oil is administered intra-colonally, it causes visceral hypersensitivity caused by the GluR-2 subunit (Zhou L. et al., 2014). A non-selective (AMPA) glutamate receptor antagonist, 6 cyano 7 nitroquinoxaline 2, 3-dione disodium salt, significantly decreased visceral sensations provided by substance P. (Nakayama T. et al., 2010). The majority of glutamine in the human body is used in the digestive system. The amino acid glutamine, which protects the lining of the GIT and sustains rapidly proliferating intestinal mucosal cells, is an essential source of energy for the digestive tract. According to Filpa V. et al. (2016), glutamate

is a neuro-modulator that controls numerous processes in the gut-brain axis under both diseased and standard settings.

The result of glutamate deficiency-induced epithelium atrophy may be increased intestinal permeability. After the intestinal injury, glutamine administration decreases intestinal permeability and bacterial translocation (Souba W. W. et al., 1990). Patients with advanced esophageal cancer receiving radio-chemotherapy and those with Crohn's disease benefit from glutamine supplementation by having more efficient gastrointestinal systems (Yoshida S. et al., 1998; Sido B.et al., 2006). An enzyme called glutamine synthetase turns ammonia and glutamate into glutamine. This enzyme contributes to ammonia detoxification, interorgan nitrogen flux, cell signaling, and acid-base balance. Congenital glutamine deficiency has been identified in kids with glutamine synthase mutations (Haberle J. et al., 2005). The enzyme synthetase is responsible for converting glutamate and ammonia into glutamine, which is then stored as free glutamine in the mucosal epithelial cells of the gastrointestinal system. Glutamate synthetase inhibited rat intestine cell growth (DeMarco V. et al., 1999). So, when intestinal glutamine synthetase levels are low, as they are in some IBS patients with diarrhea as their primary symptom, low glutamine levels and increased intestinal permeability may result (Zhou Q. et al., 2010). Intestinal permeability modification is an intriguing therapeutic strategy, but further research on its safety and efficacy is needed before it may be used clinically with specific dietary immune modulators.

miRNAs as a marker in patients with gastrointestinal disorders:

Clinical investigations show an increase in microRNA expression in the colon of individuals with IBS. By regulating intestinal pathways such as 5 HT signaling, which induces somatic hypersensitivity and intestinal permeability, these microRNAs have been found to influence epigenetic and genetic processes in patients with irritable bowel syndrome (Kapeller J. et al., 2008). There are naturally occurring noncoding RNAs in the body called miRNAs, and they can control how genes are expressed throughout larval development. It has been established that they are short (Kim J. et al., 2004; Farh K. K. et al., 2005) (21–23 nucleotides). Small interfering RNAs (miRNAs) have 70–100 nucleotide hairpins derived from more significant pre-miRNA precursors. Single-stranded miRNAs attach to the 3' untranslated region of target messenger (m)RNAs by partial sequence homology, either inhibiting translation or, more generally, causing mRNA degradation. Throughout the past decade, miRNAs have emerged as regulators of biological processes like metabolism, cellular development, proliferation, apoptosis, and differentiation, as reported by Garson R.et al., (2010). Several studies have demonstrated that miRNAs can be used as a marker in patients with GIT diseases.

Patients with IBS have been demonstrated to have altered miRNA expression in colonic tissue, and these miRNAs influence intestinal pathways leading to genetic and epigenetic changes. Serotonin signaling, altered intestinal permeability, and increased visceral and somatic sensitivity may all result from these modifications (Zhou Q. et al., 2010; Kapeller J. et al., 2008; Wu F. et

al., 2008). Expression of specific miRNAs, such as miR 29a, can affect functional activities in the gastrointestinal tract, such as intestinal permeability (Zhou Q. et al., 2010). The gene for glutamine synthetase is anticipated to have a complementary site for the miRNA miR29a in its 3' untranslated region. Due to a complementary location in the GLUL gene, altered miR29a expression decreases glutamine synthetase levels. As glutamine synthetase activity decreases, glutamine levels in the intestines drop, increasing intestinal permeability (Zhou Q. et al., 2010). This finding lends credence to the role of miR29a in regulating intestinal permeability in patients with irritable bowel syndrome who also have diarrhea. This discovery in the pathophysiology of IBS suggests that specific miRNA regulates the stability of the intestinal barrier. Microvesicles in the blood are small, spherical membrane fragments that are shed from the surfaces of most cells and serve as messengers between cells and organs (Valadi H. et al., 2007; Février B. & Raposo G., 2004). Most cells release microvesicles (microparticles) from their plasma membrane or multivesicular endocytic compartments (exosomes). mRNAs, proteins, organelles, miRNAs, and microvesicles can all potentially directly target cells by engaging with receptors or transmitting bioactive substances like membrane receptors. Cell activation follows the release of microvesicles produced from the cell membrane.

The molecular signatures of microvesicles can change along the course of a disease process, and these changes can be utilized to categorize diseases (Valadi H. et al., 2007; Février B. & Raposo G., 2004). Individuals with IBS who suffer from diarrhea more frequently have been discovered to have unique blood micro-vesicles with elevated miRNA expression, specifically miR29a (Zhou Q. et al., 2010). In people with IBS, miRNA expression may be altered in micro-vesicles seen in the blood that originates in the colon. The site of tissue injury is the most likely location for changes in miRNA expression in people with IBS (the colon). The altered microvesicles could potentially reach distant areas and affect subsequent targets. Due to the proximity of different cell types and their frequent contacts inside the GIT, miRNA interactions occurring in a single cell type in the GIT may have the capacity to affect physiology at the cellular and tissue levels. The intricate network of genes responsible for regulating homeostasis in the digestive tract explains the myriad of interactions that control this vital process (Ivy Ka Man Law et al.,2017).

Conclusions:

Most cases of abdominal pain can be traced back to visceral hypersensitivity, which affects a substantial proportion of individuals with IBS. A number of peripheral factors, such as immune system activation, neuronal excitability, and intestine-secreted hormones, have been established as contributors to the development of visceral hypersensitivity in a subgroup of individuals with IBS. However, the underlying mechanisms of this hyper-sensitivity remain unknown. Several factors interact with one another to change the intestinal barrier function and the intestinal microbiota composition. The physiological shock complicates the pathophysiology of inflammatory bowel disease (IBD) in the gut, disrupting the entire enteric nervous system. In addition to increased miRNA expression in colon tissues, other biomarkers are associated with

IBS. Through influencing intestinal pathways like 5 HT signaling, which leads to somatic hypersensitivity and intestinal permeability, these microRNAs have been found to influence epigenetic and genetic processes in IBS patients. In addition to these known mechanisms, there may be others at play. Researchers need to learn more about the interplay between the body's central and peripheral systems and how it can lead to synergy in IBS patients. Hence, the hypersensitive mechanisms in IBS are unclear; nonetheless, physiologic stimuli such as acute gut inflammation or increased intestinal permeability are likely to produce it. Further research is needed to understand the neurobiology underlying specific types of irritable bowel syndrome (IBS). Advanced exploration may help create effective treatments for visceral hypersensitivity in IBS patients, as opposed to the currently used treatments.

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