Chronic Functional Bowel Syndrome Enhances Gut-Brain Axis Dysfunction, Neuroinflammation, Cognitive Impairment, and vulnerability to Dementia

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Abbreviations

Aβ amyloid beta

AD Alzheimer's disease

ALI acute lung injury

APP amyloid precursor protein

BBB blood-brain barrier

BOLD blood oxygen level-dependent signal

CBF cerebral blood flow

CD celiac disease

CFGD chronic functional gastrointestinal disorders

CgA chromogranin A

CRF Corticotropin-releasing factor

CVO Circumventricular

DLPFC dorsolateral prefrontal cortex

ENS enteric nervous system

EPSC excitatory postsynaptic currents

GIT gastrointestinal tract

HC healthy control

HC healthy control

HF heart failure

HLA human leukocyte antigen

IBS irritable bowel syndrome

IFN-γ interferon gamma

IFL airflow limitation

IL interleukin

IL-1ra Interleukin-1 receptor antagonist

LPS lipopolysaccharide

nAChR nicotinic acetylcholine receptor

NAA N-acetyl-aspartate

NANC non-adrenergic, non-cholinergic pathway

NCGS non-celiac gluten sensitivity

NFκB nuclear factor kappa B

NFT neurofibrillary tangles

NSAID non-steroidal anti-inflammatorY drug

NTS nucleus tractus solitarius (nucleus of the solitary tract)

PSQI Pittsburgh Sleep Quality Index

REM Rapid eye movement

SFO subfornical organ

tau a microtubule-associated protein

TNF tumor necrosis factor

VNS vagus nerve stimulation

Abstract

The irritable bowel syndrome (IBS) is a common chronic functional gastrointestinal disorder world wide that lasts for decades. The human gut harbors a diverse population of microbial organisms which is symbiotic and important for well being. However, studies on conventional, germ-free, and obese animals have shown that alteration in normal commensal gut microbiota and an increase in pathogenic microbiota - termed “dysbiosis”, impact gut function, homeostasis, and health. Diarrhea, constipation, visceral hypersensitivity, and abdominal pain arise in IBS from the gut-induced dysfunctional metabolic, immune, and neuro-immune communication. Dysbiosis in IBS is associated with gut inflammation. Gut-related inflammation is pivotal in promoting endotoxemia, systemic inflammation, and neuroinflammation. A significant proportion of IBS patients chronically consume alcohol, non-steroidal anti-inflammatories, and fatty diet; they may also suffer from co-morbid respiratory, neuromuscular, psychological, sleep, and neurological disorders. The above pathophysiological substrate is underpinned by dysbiosis, and dysfunctional bidirectional “Gut-Brain Axis” pathways. Pathogenic gut microbiota-related systemic inflammation (due to increased lipopolysaccharide and pro-inflammatory cytokines, and barrier dysfunction), may trigger neuroinflammation enhancing dysfunctional brain regions including hippocampus and cerebellum. These as well as dysfunctional vago-vagal gut-brain axis may promote cognitive impairment. Indeed, inflammation is characteristic of a broad spectrum of neurodegenerative diseases that manifest demntia. It is argued that an awareness of pathophysiological impact of IBS and implementation of appropriate therapeutic measures may prevent cognitive impairment and minimize vulnerability to dementia.

Key words: Irritable bowel syndrome; dysbiosis; endotoxemia; neuroinflammation; gut-brain axis dysfunction; cognitive impairment; dementia

Running Title: Irritable bowel syndrome, neuroinflammation and gut brain axis dysfunction

1. Introduction

Gut microbiota is a major topic of interest in gastrointestinal biology. Here, the terms microbiota, microbiome, and microflora are used interchangeably. The human gut contains ~1,000 different bacterial species with 99% belonging to about 40 species [1]. The bacterial density increases progressively along the small bowel ranging from ~10^4 in the jejunum to 10^7 colony-forming units per gram of luminal content at the ileal end (with a predominance of gram-negative aerobes and some obligate anaerobes) [2]. In the colon, the bacterial count may reach around 10^{12} colony-forming units per gram (predominant being anaerobes). Estimations show that 60% of the fecal mass is accounted for by bacteria [2]. The gut microbiome and its pathogens change during ontogeny in humans [3] and animals [4, 5]. The proximity of trillions of microbes with the mucosa and gut lymphoid tissue helps explain the importance of a balanced microbiota in preserving mucosal health, whereas an unbalanced composition resulting in dysbiosis may increase various diseases not only of the gut mucosa but also within the entire body. These may include obesity, colon cancer, autoimmune disorders, allergy, and indeed the inflammatory bowel disease (IBD) [6].

Apart from effective digestion and absorption of food, healthy gastrointestinal (GI) tract (GIT) has normal and stable commensal intestinal microbiota, and an effective immune status. The GI barrier adjacent to the microbiota plays an important role in maintaining this health. However, an impairment of this barrier in GIT may enhance the risk of developing infection and inflammation; in addition, it may promote extraintestinal conditions such as immune-mediated and metabolic disorders. Indeed, these have been shown to occur in functional GI diseases. The gut microbiota, therefore, is an important environmental factor that affects host metabolism through several mechanisms - including increased energy harvest from the diet, altered endocrine function, and upregulated inflammation (both within the gut and systemic) [7, 8, 9]. Hence, GI enteric microbiome is dynamic and plays cardinal roles in nutritional, immunological, and physiologic status of the host. Further, microbiota is modulated by various factors including consumption of alcohol, non-steroidal anti-inflammatories (NSAIDs), prebiotics, probiotics, and macronutrients viz. fat and protein [10, 11]. Some recent interesting papers can be consulted on gut pathology and immune homeostasis-related topics [12-15].

Important data from germ-free animals (mice) and humans exposed to pathogenic bacterial infections, and the effect of probiotic bacteria, clearly indicate a role for the gut microbiota in the regulation of mood, anxiety, depression, pain and cognition [9, 16]. Accumulating evidence further reveals that the gut microbiota also communicates with CNS through neural, endocrine and immune pathways [9, 16-23]. Thus, in gut pathologies, gut-brain axis may influence brain function and behavior [24, 25].

The irritable bowel syndrome (IBS) patients carry a significant burden of comorbidity also [26-28]. Further, IBS patients are treated only symptomatically, regarding IBS as just a functional condition. This paper has analyzed the complex and dynamic role of intestinal gut microbiome and gut epithelial reactions in innate immune signaling, and the neurological dysfunctions in IBS. Consequently, the current approach has underlined insights and provides a comprehensive understanding of the role of gut dyshomeostasis, gut-brain axis dysfunction, and neuroinflammation in triggering cognitive decline – thus enhancing vulnerability to dementia. The root cause(s) of dementia remains elusive, and at present, there is no cure. Thus, identifying risk factors and strategies for preventing or delaying the onset and progression of cognitive decline/dementia is of utmost importance. Indeed, gut inflammation-related pathological impact may provide an important piece of the puzzle related to impairment of cognition.

One theme that continues to emerge is that dementia (be it Alzheimer's disease (AD) or other type) is a multi-factorial-multisystem condition, and inflammation plays a central role [29-40]. Recently, there has been a significant focus on the role of diverse modulatory mechanisms including systemic and neuroinflammation that underpin cognitive decline/dementia [41-49]. Emphasis has been placed on the matrix of upstream interaction; these disparate key mechanisms/factors may have the "synergistic-additive impact", and promote an array of pathophysiological effects including memory dysfunction [46-49]. The focus of this paper, however, is to present a hitherto unappreciated, yet ubiquitous, neuro-modulatory pathophysiological mechanism that originates from the inflamed dysfunctional gut, and may be extremely important in triggering cognitive decline and triggering dementia. The current rationalization of the gut-related prolonged neurotoxic insult underscores the neurophysiological and metabolic dyshomeostasis of yet another important body system that may be a precursor to cognitive dysfunction and dementia. The hope here is that therapeutic strategies to ameliorate gut inflammation and dysfunctional "Gut-Brain axis" may attenuate memory-breaking processes, and foster memory-making mechanisms. Fortunately, such strategies may be fairly simple, straightforward, and easily exploitable. The approach underscored here, therefore, may offer a new option and an addition to our armamentarium for preventing/ameliorating, and possibly treating dementia.

2. Irritable Bowel Syndrome (IBS): A Chronic Functional Gastrointestinal Disorder

IBS is one of the most common chronic functional gastrointestinal disorders (CFGD) World wide and is reported to occur in 10–20% of the general population [50]. In some Scandinavian communities, it can be as high as 25-28% [51]. IBS currently lacks an adequate treatment. The current thinking is that the cause of IBS is multifactorial, involving host, gut microbiota and the environment - these interact to induce mucosal inflammation [52, 53]. Inflammation can commence via several sources including infection, stress, food allergy and dysbiotic changes in gut microbiota. Post-infective IBS is heralded by low-grade mucosal inflammation that occurs in the terminal ileum and throughout the colon (for many months) after an attack of acute gastroenteritis. There is prolonged gut permeability in the small as well as large bowel in both post-infective IBS and diarrhea-predominant IBS. The IBS pathophysiology is therefore complex.

Several factors, including central, peripheral, and psychosocial, as well as abnormal visceral hypersensitivity, GI motility, and secretion are considered to contribute to the symptom-complex of IBS. GI motor function may differ in different IBS patients; hence based on their bowel pattern, IBS patients may be grouped into constipation- predominant, diarrhea- predominant, or mixed.

In comparison with normal controls, IBS patients showed a significant increase (72%) in mucosal immune cells [54]. IBS patients show increased numbers of CD3+, CD4+, and CD8+ T cells and mast cells (compared with controls). Interestingly, compared to male IBS patients, female IBS patients possess greater numbers of mast cells. Further, mucosal infiltration of mast cell/immunocytes in IBS patients was significantly correlated with abdominal bloating and dysmotility-related dyspepsia symptoms [54].

The IBS patients harbor altered proportions of commensal bacteria in the gut. The postinfectious IBS category is considered to be initiated following enteric infection by the enteropathogen [55]. Compared with fecal flora of healthy persons, the IBS patients undergo definable alterations with significant variations [56-58]. High counts of *Veillonella* and *Lactobacillus* are found in patients with IBS; they are correlated with higher levels of fatty acids, and implicated in clinical symptoms of IBS [59]. Further, upregulated cytokine levels and TLR activity contribute to inflammation in IBS patients [60]. Their gut flora influences not only immune system, but sensory and motor dysfunctions also that interact with higher brain centers. Indeed, this neurophysiological interaction is the so-called "gut–brain axis" [61] (also see below).

IBS is a functional multifactorial disease characterized by diarrhea, abdominal pain, erratic bowel habit, bloating, and several metabolic alterations [62]. Sugar malabsorption in the bowel leads to bloating, cramps, diarrhea and other symptoms of IBS including malabsorption of other nutrients. The gas produced by bacteria anywhere in the gut in IBS [63] can cause gas-related symptoms such as bloating and abdominal distension. About 35 % of the IBS patients have chronic pelvic pain [64]. ~ 44% of these patients have small intestinal bacterial overgrowth with microscopic colitis (SIBOM). However, diarrhea happens to be the main symptom in these patients with SIBOM, although the presence of abdominal pain, bloating and flatulence are quite prominent as well [65, 66]. In IBS, various comorbid symptoms may include headache, dizziness, palpitations, sleep disturbances, musculoskeletal, urinary, and gastro-esophageal reflux [51, 69], as well as myositis, arthritis [67], and Ménière disease– to name a few [68]. Further, a high proportion of IBS patients report psychological problems including stress, depression, agitation, low coping ability, and obsessive-compulsive disorder [17, 18, 51, 69, 70]. Valid, precise, and reliable measurement of psychological factors has shown that indeed ~50% of IBS patients may have demonstrable psychiatric illness [70].

The IBS is said to arise due to primary alterations in the periphery (i.e. bottom up), or primary alterations in the CNS (i.e. top down), or by a combination thereof. The physiological effects of physical

and psychological stressors on gut function and gut-brain interactions are mediated by the enhanced responsiveness of central stress/emotion circuits resulting in outputs of the autonomic, neuroendocrine, attention, and pain modulatory responses. Consequently, IBS patients show correspondingly enhanced responsiveness manifesting altered modulation of gastrointestinal motility, secretion, immune function and alterated perceptual and emotional response to visceral events [17, 18, 71]. Chromogranin A (CgA) is a common marker for endocrine cells. Recent studies have shown that CgA cell density in the ileum of IBS patients was reduced (63.2 ±4.4 in controls Vs 28.6 ±2.1 in IBS) [72, 73]. The GI tract hormones play an important role in regulating gastrointestinal motility; however, disturbances in GI motility are universally present in IBS patients. This may in part be related to a reduction in the total amount of endocrine cells [72, 73].

Among IBS patients, 35% were reported to be human leukocyte antigen (HLA)-DQ2-positive, 23% had increased intraepithelial lymphocytes (IEL) counts, and 30% had increased celiac disease (CD)-associated antibodies such as HLA-DQ2 in duodenal aspirate. However, when the HLA-DQ2-positive and intestinal CD antibody-positive IBS patients complied with a gluten-free diet, their stool frequency and intestinal IgA decreased significantly [74]. The probability of non-celiac gluten sensitivity (NCGS) in IBS patients may be 10 times higher than the prevalence of CD in the general population [75]. Indeed, prevalence of biopsy-proven CD in IBS has been shown to be 4-fold more than that in controls without IBS [76]. A collaborative study conducted at 4 different sites, from 2003 to 2008, studied 492 patients with IBS and 458 asymptomatic individuals. It was found that 7% of patients with IBS had CD-associated antibodies, indicating that gluten sensitivity might also mediate their IBS symptoms [75].

IBS is a complex multidimensional disorder encompassing inflammation pathophysiology, pain, hypersensitivity, impaired central processing of afferent sensory information, psychological distress, somatization, stress, and sleep perturbations [77]. It is considered to be associated with brain-gut axis dysregulation, involving dysfunctional enteric, autonomic and central nervous systems. Visceral hypersensitivity is an important pathophysiological factor in IBS. Various internal and external factors can modulate visceral sensitivity and GI motility, e.g. through enhanced responsiveness of the gut to stress and ingested nutrients. Visceral pain processing is abnormal in IBS. Noxious distension of the GIT activates regions associated with unpleasant sensation/pain via autonomic mechanism. 35% of IBS patients possess chronic pelvic pain [64]. The IBS patients with hypersensitivity and pain conduct greater activation of insula and reduced deactivation in the anterior cingulate cortex during noxious rectal/GIT distensions, in comparison with controls [78].

Autonomic activity (heart rate variability) was analyzed in IBS patients who underwent polysomnography. A substantial vagal withdrawal during REM sleep occurs in IBS patients [79]. IBS patients with depressive symptoms (IBS+DS) were compared to IBS patients without depressive symptoms (IBS-DS). IBS+DS patients had increased severity of gastrointestinal symptom, increased sleep complaints, and alterations in sleep architecture, compared to IBS-DS or healthy controls [80]. The

diarrhea-predominant IBS patients had significant vagal withdrawal compared to other IBS patients (those with predominantly constipation) during REM and non-REM sleep. Further, these diarrhea-predominant patients had significantly greater sympathetic dominance during non-REM, than the other IBS group of patients [81]. The above observations have been confirmed recently. Compared to constipation-predominant patients, the diarrhea-predominant IBS subjects demonstrated, across sequential NREM periods and REM cycles, significantly increased parasympathetic modulation and lower sympathetic/parasympathetic nervous system balance [82-84].

3. Intestinal Microbiota:

The gut is colonized by bacteria from the moment of birth. It supports a diverse bacterial ecosystem; the gut flora has between 500 and 1000 distinct bacterial species. The human gut microbiota is composed of 10^{13} to 10^{14} microorganisms, and contain 100 times as many genes as the human genome [85]. The homeostatic role of the intestinal microbiome involves interaction with the host mucosa as well as with potential pathogens. They, therefore, orchestrate homeostasis by communicating with the epithelium and upregulating innate and adaptive immune mechanisms of the gut. A vast literature is available on various aspects of animal and human gut microbiota [7-15].

4. Dysbiosis: The Silent Assasin

The normal intestinal microflora plays an essential role in host metabolism and provides a natural defence mechanism against invading pathogens. Polyphasic analysis of fecal bacteria showed that significant structural changes occur in the microbiota with aging, and this was especially evident with respect to protective bifidobacteria. Reductions in these organisms in the large bowel may be related to increased disease risk in elderly people [86]. Analysis of the fecal flora samples from 35,292 stool samples of adults showed that the elderly (>60 yo) undergo the most profound changes in terms of bacteria-specific colonic microbiota [87]. Age affects the gut microbiota with a decrease in beneficial organisms such as anaerobes and bifidobacteria and an increase in enterobacteria [88, 89]. Further, one of the most common nosocomial infections viz. *Clostridium difficile* in the elderly causes diarrhea and has a profound effect on morbidity and mortality [90]. Evidence indicates, therefore, that the composition of the human gut microbiota, as well as its homeostasis in terms of host's immune system may be crucial in the host physiology and health status [89, 91]. Thus, decreased intestinal immunity may enhance GI infections. Changes in the gut microbiota during aging may be a function of age-related altered nutrition and polypharmacy. This is expected since age-related physiological changes in the GIT, vis-a-vis modification in lifestyle, nutritional behaviour, excess alcohol intake, general health, and functionality of the subdued immune system, must inevitably affect the gut microbial ecosystem. Alteration in composition of intestinal microbiota has a serious impact and promotes several chronic conditions including obesity and inflammatory diseases (see below).

It is well established that enteric infection may trigger IBS, in at least a subset of patients, evidenced by low grade inflammation and immune activation in the bowel. The microbiome of the GIT influences many host organs including the gut and the brain; it is an important determinant of normal function in these systems. Any disruption of the balance between the host and its normal intestinal microbiota, owing to dysbiosis, may result in altered mucosal immune system, and cause variable gut inflammation in IBS patients [92]. Thus, dysbiosis regardless of cause (infection, gluten, alcohol, or drugs such as antibiotics and NSAIDS) induces chronic gut inflammation and dysfunction in IBS. Ongoing fluctuations in gut physiology destabilize the balance/proportion of commensal and pathogenic bacteria enhancing a vicious cycle of chronic dysbiosis. Evidence obtained from animal models has provided a unifying paradigm in that changes in gut microbiota influence behavior– alterations in gut flora → gut dysfunction → gut inflammation → behavioral changes in IBS (Fig. 1). Thus, according to this dysbiosis hypothesis, infection, dietary sensitivity (e.g. gluten) and/or drugs (e.g. alcohol) may upregulate gut inflammatory and functional changes and contribute to psychiatric co-morbidity [17-19; 93]. Furthermore, despite similar symptoms and underlying gut dysfunction, there is likely to be heterogeneity in the above pathogenesis in disparate subgroups of IBS patients.

IgA found in mucosal secretions of the gut maintains immune homeostasis, promotes tolerance, and defends against pathogens. The intestinal epithelium—which constitutes the interface between the enteric microbiota and host tissues—actively contributes to the maintenance of mucosal homeostasis and defends against pathogenic microbial invasion. The disruption of microbial community viz. dysbiosis predisposes the host to infection, by enteropathogens. The translocation of intestinal bacteria and/or pathogen-associated molecules e.g. LPS, therefore, enhances inflammatory-immune responses. The latter impact adversely inducing neuroplastic changes in the enteric nervous system (ENS), gut-brain axis dysfunction, and causing diverse pathophysiological states in IBS [94].

5. Gut Inflammation

The intestinal epithelium – a mucosal surface can be colonized by large numbers of bacteria. The host controls/modulates bacteria through a state of "controlled minimal inflammation", and bacteria and their products such as LPS, are prevented from breaching the intestinal barrier. This is accomplished via several strategies including tight-junctions (between epithelial cells), mucus covering the epithelium, secretion of IgA, and an array of proteins, enzymes, and peptides that are bactericidal. However, impairment in the above mechanism(s) may contribute to gut inflammation, noted in IBS [22, 63, 95].

The intestinal mucosa of IBS patients contains an increased number of mast cells and activated T lymphocytes as well as an increased release of mediators known to signal to epithelial, neuronal, and muscle cells - leading to intestinal dysfunction [22, 63, 95, 96]. This may promote the activation of mucosal immune responses causing hypermotility and diarrhea. There is evidence of increased intestinal

permeability in diarrhea-predominant IBS. This mucosal barrier defect allows the passage of an increased load of antigens of dietary and LPS of bacterial origin from the lumen. Further, immune factors released by the immunocytes, including proteases, histamine, and prostanoids, enhance the mucosal permeability and contribute to the activation of abnormal neural responses involved in gut motor function, abdominal pain perception, and changes in bowel habits [22, 63, 95].

Several external and internal factors also enhance GIT pathology including stress, nutrients such as excess fat and gluten (in gluten-sensitive persons), NSAIDs, and alcohol; these can exert additive effects and modulate proinflammatory mediators, GI inflammation, visceral hypersensitivity, GI motility, and pain in IBS patients.

6. Lipopolysaccharide and Systemic Inflammation

There is substantial evidence for the involvement of the intestinal microbiota in the functioning of the immune system and homeostasis; they interact with lymphoid follicles of the mucosa, as well as with regulatory and effector T cells. The importance of the intestinal microbiota in immunity became obvious when animals grown in germ-free environments showed delayed onset of cellular and serologic responses and reduced immune impact [96-98]. Further, a lack of intestinal commensal microbiota leads to defective systemic immune system with reduction in $CD4^{+}$T cell numbers and systemic antibody levels [99] - including IgA (the predominant immunoglobulin in the gut) that normally neutralizes toxins and pathogenic microbes [96].

LPS (endotoxin - component of gram-negative bacterial cell walls) can stimulate production of the proinflammatory cytokines TNF-α, IL-1β and IL-6 from monocytes and macrophages [100, 101]. Briefly, LPS triggers the well characterized intracellular inflammatory cascade, which may include stress-activated and mitogen-activated protein kinases, c-Jun N-terminal kinase, and p38 pathway. CD14 lymphocyte antigen 96 and TLR4, which act as co-receptors for LPS, are considered to be the main molecules mediating the inflammatory conditions. Following its binding to receptors, LPS induces production of pro-inflammatory cytokines via activation of the nuclear factor κB (NFκB) [100, 102]. Accordingly, several studies have reported high levels of proinflammatory cytokines, notably TNF-α and IL-1β [103-105] in persons whose guts harbor pathogenic bacteria. Conversely, TNF-α null mice showed improved metabolic homeostasis [106].

Gut bacteria play important metabolic functions in both health and disease. For example, evidence suggests a role for the gut microbiota in both the etiology of nonalcoholic fatty liver disease (NFLD) and its progression to steatohepatitis (NASH). Both NFLD and NASH are strongly linked to obesity, the metabolic syndrome, and inflammation [107, 108]. Furthermore, intestinal overgrowth of Gram-negative bacteria could promote insulin resistance, endogenous ethanol production and choline deficiency. Among

the potential mediators of this association is LPS. Endogenous LPS is continuously produced by the death of intestinal Gram-negative bacteria (Fig. 1); it then migrates into intestinal capillaries [109].

LPS infusion in mice resulted in increased fasting levels of glucose and insulin, as well as weight gain; the effects of this treatment on total body fat, steatosis and adipose tissue were similar to those induced by a high-fat diet [110]. Concomitant with these changes, macrophage numbers in the adipose tissue and levels of inflammatory markers increase both systemically and in the brain. Furthermore, insulin sensitivity was dysfunctional in LPS-infused mice. Interestingly, increased deposition of fat was similar in visceral and subcutaneous regions in both the high-fat diet and LPS-infused groups of animals [111].

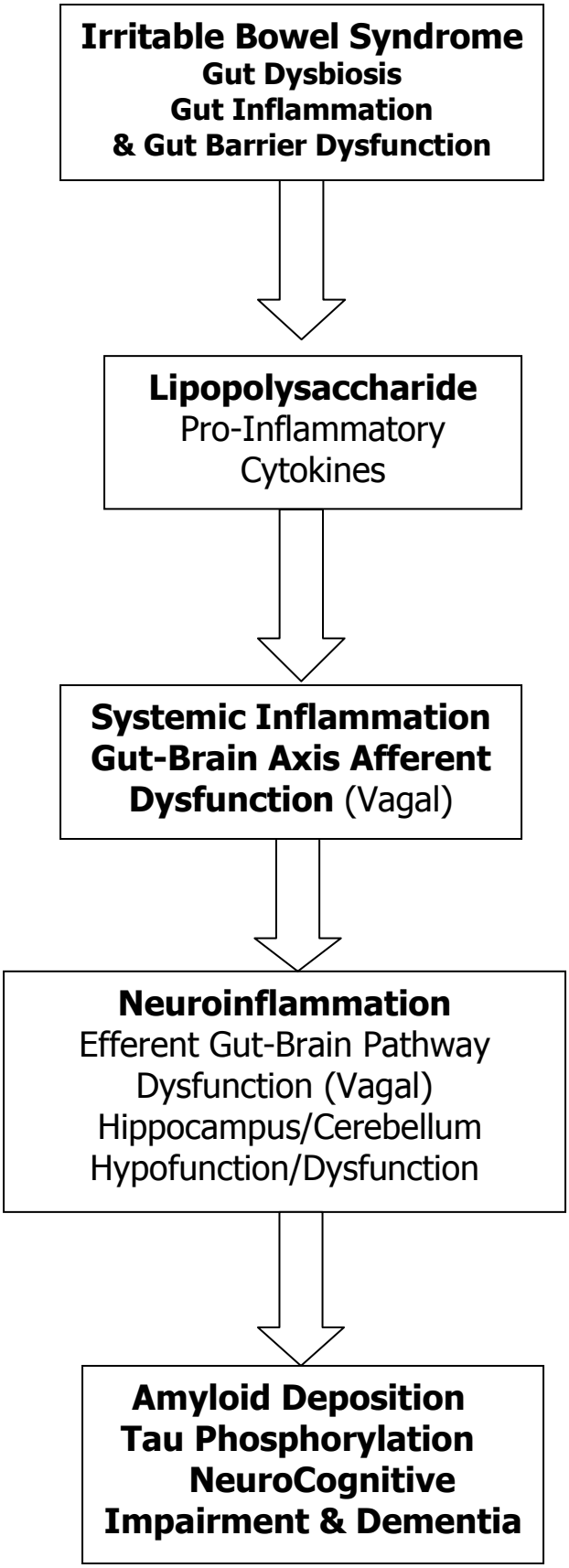
Irritable Bowel Syndrome
Gut Dysbiosis
Gut Inflammation
& Gut Barrier Dysfunction
Lipopolysaccharide
Pro-Inflammatory
Cytokines
Systemic Inflammation
Gut-Brain Axis Afferent
Dysfunction (Vagal)
Neuroinflammation
Efferent Gut-Brain Pathway
Dysfunction (Vagal)
Hippocampus/Cerebellum
Hypofunction/Dysfunction
Amyloid Deposition
Tau Phosphorylation
NeuroCognitive
Impairment & Dementia

Fig. 1. Schematic representation showing dysbiosis, gut inflammation, and barrier dysfunction in IBS. LPS released from the pathogenic gut bacteria promotes pro-inflammatory cytokines. They induce systemic inflammation/endotoxemia; the latter triggers neuroinflammation in several key brain regions. There is an ongoing dysfunction of gut-brain bidirectional pathway. The above cascade may promote cognitive impairment and lead to dementia.

7. Gut-Brain Axis

GIT is endowed with immunologic and non-immunologic mechanisms that neutralize and eliminate deleterious factors such as pathogenic microbes, other pathogens, and food antigens. GIT has the most extensive immune system/ integrated neuro-immune network encompassing immune cells, lymphoid aggregates and intraepithelial lymphocytes. Hence, there is extensive/abundant mucosal immunity in the GIT, and indeed the intestinal mucosa of an adult contains about 80% of the body's activated B cells - terminally differentiated to plasma cells (PCs). Most mucosal PCs produce IgA. Further, the secretion of mucus, gastric acid, water and electrolyte as well as peristalsis are regulated by "intrinsic – i.e. ENS" and "extrinsic – i.e. CNS" counterparts.

Almost every function of GIT is under the regulatory influence of the nervous system, including the vagal afferents, spinal afferents, sympathetic and parasympathetic efferents, and enteric nervous system (ENS). The ENS is considered to be the Gut's brain and governs the GIT activity/homeostasis. Inputs from the CNS modify gut function(s) while inputs from the gut to the brain mediate symptoms [24, 25, 112]. Several GIT diseases including the IBS and non celiac gluten sensitivity (NCGS) are impacted by dysfunctional GI innervation.

Several studies indicate that abnormal processing of afferent signals occurs in IBS patients. Autonomic dysfunction/imbalance may include low vagal tone and increased sympathetic activity, and this may alter visceral perception in IBS patients [113]. It is generally accepted now that there is dysfunctional bidirectional pathway between the GIT and the CNS in IBS; this "brain-gut axis" perturbation may underpin symptomatology of this functional syndrome [9, 93, 114-119]. This renders the IBS patients susceptible to the altered transport of intestinal gas, bowel distention, bloating, enhanced perception of gut stimuli, hence abdominal discomfort and pain, as well as psychosocial factors [120]. The symbiotic relationship between the commensal gut microbiota and its host (animals/humans) protects from the effects of infection and inflammation, as well as modulates the normal behavioral responses [24]. Consistent robust evidence indicates that gut bacteria influence the ENS, an effect that may contribute to afferent signaling of LPS, proinflammatory cytokines, and inflammation to the brain. Thus, various regions in the brain may then synthesize their own pro-inflammatory cytokines [121]. Further, changes in the composition of the gut microbiota, I.e. dysbiosis, may impact normal physiology promoting diseases ranging from inflammation to obesity, via endocrine, immune, and neural pathways. The vagus nerve

occupies an important route for communicating signals from GIT and gut bacteria to the CNS [9, 118, 119]. Moreover, various physiological and neurological abnormalities (discussed above) in IBS trigger not only gut inflammation and immunocytic increase, but an increase in intestinal permeability. Consequently, disturbances of the ANS occurring in IBS may correlate with brain-gut axis dysfunction (Fig. 1) [17-23].

As reiterated above, consistent robust evidence indicates that gut dysbiosis influences the ENS, an effect that may contribute to afferent signaling of LPS, proinflammatory cytokines, and inflammation to the brain. Various regions in the brain may then synthesize their own pro-inflammatory cytokines also [121]. Further, dysbiosis may impact normal physiology promoting diseases ranging from inflammation to obesity, via endocrine, immune, and neural pathways. Hence, the vagus nerve occupies an important route for communicating signals from GIT and gut bacteria to the CNS [9, 118, 119]. However, disturbances of the vagus/ANS occurring in IBS may upregulate brain-gut axis dysfunction [19, 20, 23, 122].

7A. Dysfunctional Gut-Brain Axis – Cuts Both Ways

The vagal afferent fibers carry information about physiological status of the gut directly to brainstem circuits. The afferent sensory pathway involves the nodose ganglion neurons. The latter are bipolar and connect the gut directly with NTS neurons in the brainstem [123-127]. The NTS integrate this sensory information and regulates autonomic and homeostasis-related functions of the gut. Dysfunction in this 2-way organization of gut-vagal/brainstem-vagal circuit may be a factor underlying the pathophysiological changes and motility dysfunction observed in IBS [128]. ACh is the main neurotransmitter released from vagal efferent terminals to excite enteric neurons. In the gut, two distinct set of pathways exist: 1) excitatory cholinergic pathway (that increases gastric tone, motility and secretion), and 2) inhibitory non-adrenergic, non-cholinergic (NANC) pathway that inhibits gastric functions [129]. Thus, GI dysfunction may happen either by activation of the NANC pathway and/or by inhibition of the tonic cholinergic pathway. Given the importance of the gut-vagal reflex in the integration and control of visceral functions, any malfunction in vagal reflex may result in GI pathologies, including those of functional disorders such as IBS.

The bi-directional interactions between the nervous and immune systems promote homeostasis of the body [130-134]. The vagus nerve has a counter-inflammatory role [135]. The role of the vagal-efferent parasympathetic system in immunoregulation via α7-nAChR is well documented [136-140]. This anti-inflammatory effect of vagal input is mediated through the activation of nicotinic receptors on macrophages [141, 142], and down-regulation of T cell function [143]. The above observation is strengthened by sub-diaphragmatic vagotomy (in mice) resulting in proliferation of $CD4^+$ T cells and stimulation of pro-inflammatory cytokines, including TNF-α and IFN-γ [143]. Further, direct electrical stimulation of the vagus nerve in rats during endotoxemia inhibited TNF-α synthesis [134]. Similarly, an α7-nAChR-agonist attenuated systemic inflammation causing decreased TNF production [144, 145].

Owing to abundant vagal sensors, the gut continuously sends information to the brain [123]. Signals from the gut are crucial for the control of appetite, regulation of energy balance, glucose homeostasis, and inflammation. In inflammatory reflex, an interaction between the vagus nerve and peripheral macrophages results in attenuation of proinflammatory cytokine release, in response to systemic exposure to bacterial endotoxin. Disease activity index (DAI), macroscopic and histologic scores, myeloperoxidase activity, levels of serum amyloid-A, and colonic tissue levels of IL-1β, and TNF-α increased significantly in vagotomized mice 5 days post-colitis (induced by dextran sodium sulfate or hapten) [135]. Pretreatment with nicotine, however, significantly decreased the above inflammatory markers in these vagotomized mice with colitis [135]. This reiterated that the vagus nerve plays a counter-inflammatory role in acute colitis via nicotinic receptors [135]. This is in keeping with the fact that the efferent vagus nerve inhibits pro-inflammatory cytokine release and protects against inflammation [138]. Hence, this vagal function is aptly termed "the cholinergic anti-inflammatory pathway", reflecting a functional brain-to-immune connection, and that both inflammation and innate immune responses are regulated in part by vagal neural mechanisms [138, 146, 147]. This paradigm has been exploited clinically; electrical vagus nerve stimulation (VNS) is now utilized in the treatment of resistant epilepsy and depression (see VNS below). By the same token, molecular mechanisms of cholinergic anti-inflammatory signaling, mediated by selective α7-nAChR agonists and centrally acting cholinergic enhancers, can also be efficacious in the control of inflammation [148].

Endotoxin generated in GI is a local as well as systemic immunological stressor [61]. Activation of afferent vagus nerve fibres by endotoxin (LPS e.g.) and/or cytokines (released by activated cells) stimulate hypothalamic-pituitary-adrenal anti-inflammatory axis also [149-151]. Thus, inflammation potentiates responses involving both sympathetic and parasympathetic (i.e. gut-brainstem/vagal modulation) [134, 137, 152-155]. When inflammatory state is persistent as in IBS, there is sympathetic hyperactivity and parasympathetic insufficiency in the dual autonomic control. Hence the dysfunctional gut-brain axis may shift the homeostatic balance in favor of sympathetic. This in conjunction with obesity [156-158], chronic alcohol consumption, and hypoxia [159] may cause hypertension and upregulate other deleterious effects [41-49], contributing to ongoing dysfunction in different brain regions. Indeed, dysregulation of the gut-brain-gut communication via abnormal visceral sensory and dysfunctional/dyshomeostatic vagal efferent input may underlie chronic IBS pathology [77, 160, 161].

8. Neuroinflammatory stimulation and Pathogenesis of cognitive impairment in IBS

Vagus arising from nucleus of the solitary tract (NTS)/dorsal vagal complex innervates several key visceral organs including heart, lungs, and GIT; it regulates their vital physiological functions, through ACh - its principal neurotransmitter [162, 163]. The presence of pathogenic bacterial colonization and inflammation in the gut is detected by the afferent/sensory component of the vagus [164]. The efferent response is then communicated via appropriate vagal anti-inflammatory output [132, 138, 162, 165]. Thus,

essentially the vagus nerve provides a bi-directional communication circuit to overcome inflammation [132, 162].

The systemic injection of LPS - dose-dependently increased IL-β protein levels, in the dorsal vagal complex, as well as in the hypothalamus, hippocampus, cerebellum, neocortex, and pituitary, as early as 2 h after LPS infusion [147]. The inflammatory signal reaching the brain induces other effects also. For example, LPS-induced hypotension is mediated by the afferent vagus nerve which conveys the signal to the NTS, which in turn, stimulates norepinephrine release (anterior hypothalamic area) for triggering hypertension [166, 167]. Furthermore, systemic intraperitoneal injection of IL-β promotes IL-β mRNA in the brain; however, subdiaphragmatic vagotomy blocks this pathological effect, shown in the brainstem and hippocampus [146]. This reiterates that the vagus is involved in transmitting cytokine signals to the brain - thus causing the induction of brain cytokines/neuroinflammation (Fig. 1), as well as, potentiating neurotoxic substances including nitric oxide, oxygen radicals and proteolytic enzymes [146, 147].

8A. Gut Inflammation to Brain Inflammation and Cognitive Dysfunction

Chronically inflamed gut may upregulate barrier breakdown, LPS permeability, generation of proinflammatory cytokines, systemic inflammation, and neuroinflammation. This underscores that IBS syndrome modulates crucial features of inflammation, and may be an important etiopathogenic route in triggering cognitive decline and vulnerability to dementia. A variety of inflammation-related proteins including LPS, complement factors, acute-phase proteins, and pro-inflammatory cytokines increase in AD brains [33]. These components of innate immunity, therefore, promote crucial pathogenic cascade, including systemic and neuroinflammation [31, 32, 36, 168, 169]; these are implicated in the etiopathogenesis of dementia [29, 30, 35-40, 170]. Elevated levels of endotoxin/LPS concentrations occur in plasma from AD patients (compared to healthy controls) [33, 34, 171]. This is consistent with systemic immunologic activation promoting neuroinflammation, and triggering cognitive decline and dementia [29, 30-40, 168, 169, 170].

Inflammatory biomarkers are considered to reflect dementia status [34, 173, 177]. Several studies support that chronic systemic and central inflammatory processes underpin etiopathogenesis of dementia [34, 172-176]. During inflammation activated macrophage- microglia produce proinflammatory cytokines [178]. Assessment of the brains from transgenic APP/PS1 mice revealed proinflammatory cytokine-producing CD4(+) T cells, increased microglial activation, Aβ deposition, and impaired cognitive function [179]. The intra-cerebroventricular administration of CRP increased mRNA levels for amyloid precursor protein (APP), TNF-α, IL-1β, IL-6, and CRP in cerebral cortex and the hippocampus [172]. The overexpression of TNF-α transgenes triggers features of chronic CNS inflammation, ataxia, seizures and paresis, and white matter degeneration [180]. Similarly, peripheral administration of LPS in transgenic APP-Tg mice led to neuroinflammation vulnerability with an increase in IL-6 level [176]. Indeed, IL-1β overexpression results in robust increase in tau phosphorylation in the triple transgenic mouse model of AD

[175]. Various neuropsychiatric symptoms in dementia are linked to the presence of proinflammatory components/cytokines [174, 181].

8B. Inflammation causes Hippocampus Dysfunction and impaired cognitive function

The brain is vulnerable to neuro-inflammatory process through amyloid deposition, and this is implicated in one of the hypotheses of dementia pathogenesis [182, 183]. Several pro-inflammatory cytokines including IL-1β, IL-6, TNF-α, and TGF-β can enhance APP expression [184, 185], upregulate β-secretase mRNA, its protein, and enzymatic activity [186], and thus increase Aβ formation [183, 187] in the hippocampus [188, 189]. Chronic hippocampal inflammation is linked to the onset and progression of a number of neurotoxic factors; they upregulate dementia-related pathologies including Aβ plaques, and neurofibrillary tangles (NFT) [49, 190]. Peripheral inflammation induced through LPS in C57BL/6J mice resulted in significantly higher levels of Aβ1-42 in the hippocampus (compared with saline controls) [191]. Indeed, systemic injection of LPS enhanced APP expression, upregulated β- and γ-secretase activities, and resulted in $A\beta_{1-42}$ accumulation in the hippocampus and the cerebral cortex of mice [183, 194]. Interestingly, even a single injection of LPS has been shown to enhance levels of both Central and peripheral pro-inflammatory cytokines [192]. The Morris water maze and contextual fear conditioning tests have revealed cognitive deficits in LPS-treated mice [191]. Similarly, spatial memory was impaired in the mouse hippocampus following IL-1β expression [193]. A number of studies have confirmed that the systemic inflammation generated by LPS induces memory impairment [183, 195, 196]. The basis of this memory decline may be the relationship between LPS-induced accumulation of Aβ and neuronal cell death; substantial increase of apoptotic cells was revealed in the hippocampus of LPS treated mice (36.2 ± 3.6%) versus the control (2.1 ± 0.8%) [183]. Indeed, numerous data emphasize that pro-inflammatory mediators present in the hippocampus may induce neuro-pathological cascade, enhance cognitive dysfunction, and increase vulnerability for dementia [35-38, 40-49, 190, 197, 198].

8C. Inflammation, Cerebellar Dysfunction, and Dementia

Altered central processing of visceral stimuli in IBS (e.g. chronic pain) modulate visceral sensory signals in both cortical area and the cerebellum [199, 200]. Indeed, cerebellar deficit may contribute to cognitive disability in IBS [200, 201]. Following LPS injection in rats, there is an increase of IL-1β, TNF-α and IL-18 in the cerebellum (albeit at different intervals) [192, 197, 202]. In a mouse model of neuroinflammation, proinflammatory cytokines impaired GABAergic transmission at Purkinje cells. Impairment in the glutamate-aspartate transporter-excitatory amino acid transporter 1 (GLAST-EAAT1) function in cerebellum correlates with prominent astroglial activation. Further, IL-1β released by activated microglia/macrophages and infiltrating lymphocytes are implicated in synaptic alteration. Even a brief incubation of normal mouse cerebellar slices with IL-1β resulted in a rapid GLAST/EAAT1 down-regulation. However, incubation of these slices with spontaneous excitatory postsynaptic currents (EPSCs).

These data highlight the crucial role played by the proinflammatory cytokines in triggering molecular and synaptic dysfunctions involved in neurodegenerative processes of the cerebellum [201].

In addition to its primary role in motor control, cerebellum is considered to contribute to cognitive control also, having a bottom-up influence on cognitive/executive functions [204, 205, 211]. The anatomical and functional connectivity studies support a cerebello-hippocampal interaction [206, 207, 208] e.g. in hippocampal spatial representation map [209], hippocampal place fields, and path integration process [210]. In a model of neuroinflammation, cerebellar culture stimulated with endotoxin LPS and mediated by the pro-inflammatory cytokines, revealed myelin and axonal damage [203]. The quintessential cerebellar functions are linked to cognition. For example, in community-dwelling elderly (60-85 yo), their executive function/attention and processing speed were correlated with absolute gait measures. Indeed, poorer executive function correlates with gait impairments [213]. Further, the "cerebellar cognitive affective syndrome" [212] represents a set of symptoms that are similar to the known symptoms of AD.

Studies have shown that the cerebellum is strongly involved in cholinergic functions. It has a direct influence on the cholinergic function since cerebellar stimulation may affect cortical cholinergic activity [216]. The cerebello-thalamo-cortical pathway is a function of cerebellar theta burst stimulation (TBS), which may modulate central cholinergic functions [214, 215, 216]. Two regions that possess high density of cholinergic receptors are the thalamus and the cerebellum [217, 218, 220]. nAChRs in the mammalian cerebellum regulate synaptic efficacy at two major classes of cerebellar neurons [217-219].

Several pathological changes occur in the cerebellum in AD, including widespread deposits of diffuse amyloid, ubiquitin-immunoreactive dystrophic neurites and increased microglia [221-223]. Molecular layer gliosis and atrophy in the vermis is quite severe in AD [222, 224]. Loss of Purkinje neurons occurs in the vermis, cerebellar hemispheres, and the inferior olivary nucleus [222, 224]. The atrophy of the molecular layer (24%) and the granular layer (22%) correlated with a decrease in Purkinje cells [225]. In AD, cerebellum was replete with microglia in areas of amyloid deposit [226]. Several studies have demonstrated reduced cerebellar volume in the pre-dementia stage as well as throughout AD progression [227, 228]. The posterior cerebellar lobes are significantly smaller in AD patients; indeed cerebellar atrophy is found to be associated with poorer cognitive performance [229, 230] thus reflecting their possible involvement in dementia pathogenesis. Further, the deep cerebellar dentate nucleus undergoes pathology in AD [231]. A significant reduction of cerebral blood flow (CBF) occurs also in the cerebellum in AD [232]. Changes in blood oxygen level-dependent (BOLD) signal in the cerebellum correlated with changes in psychometric measures of episodic memory retrieval [233]. An extensive literature indicates that cerebellar pathology may evolve chronically, in association with global cognitive changes throughout the clinical course of dementia [225, 226, 234-238].

8D. Inflammation, Delirium and Dementia

Delirium - a neuropsychiatric condition is characterized by a global impairment in consciousness, attention, and cognition. Delirium is usually characterized by inflammatory mediators into the bloodstream and activation of the inflammatory cascade. The pathophysiology may include perivascular oedema, leukocyte adhesion to vessel lining, endothelial swelling, and decrease in capillary diameters and density. Further, in ageing and neurodegenerative disorders, microglial responses are enhanced following peripheral inflammation [239, 240]. Delirium is a frequent occurrence in dementia patients who suffer from systemic inflammatory stimulation. Therefore, an inter-relationship between aging, systemic inflammation/infection, delirium and dementia, is emphasized [240-242].

9. Multiple Routes to Neuroinflammation

This paper has discussed the dysfunctional crosstalk along the 'brain-gut axis' existing in IBS. The axis dysregulation and neuroinflammation, due in part to the passage of proinflammatory cytokines along the vagus, has been emphasized. However, there are other routes through which the cytokines can reach brain. These are the circumventricular organs (CVOs) and the blood-brain barrier (BBB). CVOs are structures that border the brain ventricular spaces. The fenestrated capillaries of the CVOs lack the typical tight junctions between adjacent endothelial cells [268]. In addition to the lack of the normal BBB and the dense vascular supply, the sensory CVOs (viz. subfornical organ (SFO), organum vasculosum of the lamina terminalis, and the area postrema) are replete with a variety of different receptors for peripheral signals, including regulatory peptides and cytokines (e.g. 1L-β) [269, 270, 271]. CVOs also send efferents to the nucleus of the solitary tract (among many other brain nuclei) [272]. Interestingly, the expression of most of the receptors is upregulated under conditions of systemic inflammation [270]. CVOs are the only regions in the brain in which neurons are exposed to the chemical environment of the systemic circulation. One of the CVOs, the area postrema, has a close relationship with the NTS and dorsal motor nucleus of the vagus nerve [273]. Consequently, there may be more than one entry pathways for the cytokines to interact with neurons of the brainstem, and to upregulate dyshomeostatic processes. Furthermore, there is evidence that blood-borne cytokines TNF-α, IL-1 β, IL-1 receptor antagonist (IL-1ra), and IL-6 cross the BBB to enter CSF and interstitial fluid spaces of the brain [274]. Thus, passage of cytokines across the BBB provides yet another route for systemic cytokines to potentially induce neuroinflammation [274, 275], increase Aβ1-42 in the brain (e.g. hippocampus), and enhance cognitive deficits [40, 46-49, 191, 198, 276, 277]. Cytokines can also induce production of cytokines and chemokines from cells of the BBB, which may then secrete these neurotoxic substances into the brain parenchyma [278, 279, 280]; they can be carried across the BBB by infiltrating leukocytes that extravasate through the BBB and enter neural tissue [281]. Indeed, the BBB has been shown to become more permeable during peripherally evoked inflammation, suggesting the increased vulnerability for neuroinflammation during pathogenesis of dementia [176, 282].

10. IBS, Pathological milieu, and Correlates of Cognitive Dysfunction

IBS patients are victim of a number of pathologies described here. They suffer from chronic stress, pain, gut infection and gut inflammation [112, 249-251]. Prominent sleep disorders commonly occur in patients with IBS. Patients with IBS have impaired sleep quality, reduced slow-wave sleep activity, and significant sleep fragmentation [283], but increased proportion of REM sleep [284]. The overall insomnia rate in IBS patients was found to be about 26.0% compared with the control mean score of total Pittsburgh Sleep Quality Index (PSQI) of 5.83 [285]. Standard clinical polysomnogram, pneumotachograph and supraglottic pressure catheter studies suggest a prevalence pattern of airflow limitation (IFL) and pharyngeal collapse during sleep among IBS patients (compared with healthy control (HC)) [286]. Intermittent hypoxia is known to be a significant pathology that may affect CNS functions and enhance cognitive impairment [44-49].

The IBS patients showed higher fractional anisotropy (FA) in the fornix and external capsule adjacent to the right posterior insula; however chronic pain severity in IBS correlated with FA of the insula and lateral thalamus [161]. Alterations in gray matter (GM) density/volume and cortical thickness (CT) have been studied in IBS patients and the HC group controlling for total brain volume, and global as well as regional properties of large-scale structural brain networks [287]. Relative to HC, the IBS group had lower volumes in the bilateral superior frontal gyrus, bilateral insula, bilateral amygdala, bilateral hippocampus, bilateral middle orbital frontal gyrus, left cingulate, left gyrus rectus, left gyrus rectus, left putamen, and brainstem [287]. Further, regions that involve endogenous pain modulation and central sensory amplification were identified as network hubs in IBS [287, 288]. In addition data underscore that persons with IBS possess latent impairments in cognitive flexibility owing to altered activity of the dorsolateral prefrontal cortex (DLPFC), insula, and the hippocampus, and impaired connectivity between the DLPFC and other areas [289]. Furthermore, there is evidence for the presence of abnormal hypofunction of hippocampal glutamatergic neurotransmission in IBS patients. The hippocampus - a key brain region that provides inhibitory feedback to the HPA axis, exhibits reduced excitatory glutamatergic neurotransmission and reduced N-acetyl-aspartate (NAA; a marker of neuronal integrity) levels in IBS patients [290]. The above data as well as dysfunctional odor identification and odor threshold are consistent with a central etiology of IBS [291] - supporting IBS as a disorder of brain-gut interaction [284]. Each of the factors addressed above could significantly impinge on related CNS functions. Specifically, changes in density of GM among regions involved in cognitive/evaluative functions support an ongoing attenuation of cognitive function in IBS [292] that may lead to dementia.

11.0 Perspective

11A. Corticotropin-releasing factor – A Therapeutic Target

IBS patients have recurrent abdominal pain or discomfort in the absence of any detectable organic abnormalities. Corticotropin-releasing factor (CRF) is an essential coordinator of the stress response orchestrating a host of autonomic, neurochemical, and behavioral responses to stress [243, 244]. Perturbations to this system in humans have been shown in anxiety disorders [245] and IBS [246-248]. Indeed, alterations in central CRF signaling pathways have been confirmed recently also in the pathophysiology of IBS [249]. Moreover, exaggerated brain responses to a pain threat in IBS patients are attenuated by acute administration of a CRF receptor 1 (CRF-R1) antagonist [250].

IBS is characterized by chronic increase in anxiety and stress symptoms [251, 252]; however, there is clinical evidence of increased engagement of the CRF/CRF receptor 1 (CRF-R1) signaling system [253]. Expectation of abdominal pain engages several cortical and limbic brain regions, in accordance with anticipatory signalling of somatic pain [254-256]. Orally administered CRF-R1 (relative to placebo) produced significant blood oxygen level-dependent (BOLD) signal reductions in the amygdala, hippocampus, insula, anterior cingulate, and orbitomedial prefrontal cortices in IBS patients [250]. Such treatment may therefore engage normalization of effective connectivity between key nodes of the emotional-arousal circuit. Furthermore, pretreatment with CRF-R1 antagonist blocked colorectal distention-induced anxiety in rats, thus supporting the concept that peripheral CRH-CRH-R1 system plays an important role in brain-gut sensitization [246, 253, 257].

11B. Benefit of Prebiotics, Probiotics, and Synbiotics on Human Commensal Biome

Arguably, the highest density of microorganism resides in the gut in the human body. Several converging studies on gastrointestinal inflammatory conditions suggest that these conditions are probably caused by defects in host immunity and/or alterations in resident GI bacterial populations. The immune mechanisms that are necessary in intestinal homeostasis may become dysfunctional. Given an extremely large numbers of microbes in close contact with the GI tract lining of the host, it is not surprising that dysbiosis might result in an increased risk of bowel inflammation. Bacterial infection [e.g. by diarrheagenic *Escherichia coli* (EC), including enterohemorrhagic (EHEC), enteropathogenic (EPEC), enteroaggregative (EAEC), enteroinvasive (EIEC) and enterotoxigenic (ETEC) strains] can cause substantial morbidity in patients with functional GI disorders (FGID) [258]. Consequently, alterations to the gut flora can lead to pathogenic microbiota in susceptible IBS individuals causing local inflammation, alterations in epithelial function, gut barrier breakdown, and chronicity (see above).

It is quite feasible that immunologically mediated alterations including increased inflammatory mediators, and increased small bowel permeability of LPS can be controlled by several available options. These include Prebiotics, Probiotics, and Synbiotics. Bran is an example of prebiotic; it promotes the growth of commensal bacteria e.g. lactobacilli and bifidobacteria. Probiotics utilize beneficial species such as *Bifidobacteria* and *Lactobacilli*, as exogenous supplementation to intestinal and colonic microbiota. Synbiotics are exogenous supplementation to intestinal and colonic microbiota Synbiotics exploit the synergistic benefit by combining a

prebiotic with probiotic; an example would be *Bifidobacteria* plus fructooligosaccharides (or galactooligosaccharides), or *Lactobacilis rhamnosuss* GG plus inulins.

Chronic treatment with *L. rhamnosus* (JB-1) resulted in reduced stress-induced corticosterone and anxiety- and depression-related behavior, as well as region-dependent alterations in GABA(B1b) receptor mRNA in the brain [12]. These neurochemical and behavioral effects, however, were absent in vagotomized mice, identifying the vagus as a major modulatory communication pathway between the gut microbiota and the brain (see above). This study further underscores the pivotal role of GI bacteria in the bidirectional communication of the gut-brain axis; it highlights that certain bacterial types may induce therapeutic benefits in disorders such as anxiety, depression, and IBS [12].

11C. Vagus Nerve Stimulation

The available current research on VNS shows that the vagus/brain in tandem may modulate immune responses. There have been considerable advances in clinical neurostimulation. VNS is frequently utilized in clinical medicine and is not a novel stimulation modality any longer. VNS has been approved by the FDA as a neurostimulation modality in a subset of patients with treatment-resistant depression [259] and epilepsy [260].

A recent study determined the beneficial effects of VNS and its mechanisms that attenuate LPS-induced (intraperitoneally injected) acute lung injury (ALI). VNS improved lung injury, evidenced by a significant reduction in lung edema, neutrophil infiltration, and pulmonary permeability [261]. Additionally, VNS decreased the expressions of Src-suppressed C kinase substrate and E-selectin proteins in lung tissue and effectively attenuated the levels of proinflammatory cytokines including TNF-α, IL-1β, and IL-6 in bronchoalveolar lavage fluid [261]. The above data document the VNS efficacy in ameliorating LPS-induced ALI.

In canines with heart failure (HF), long-term, low level VNS improved left ventricular (LV) systolic function, prevented progressive LV hypertrophy, and improved biomarkers HF (compared with control animals that did not receive VNS) [262]. Further, other studies in canine model of HF have also shown that Chronic VNS improves cardiac autonomic control and significantly attenuates canine HF [263]. The therapeutic benefit of VNS in dogs included pronounced cardiac and anti-inflammatory benefits, improved heart rate variability and baroreflex sensitivity, and lower plasma norepinephrine, angiotensin II, and C-reactive protein levels [263].

The effect of VNS was recently examined in LPS-challenged (intraperitoneal injection) mice. The endotoxin induced intestinal tight junction injury with increased intestinal permeability, evidenced by increased amount of fluorescein isothiocyanate-dextran (FID) in circulation [264]. VNS (of right cervical vagus nerve) [265] ameliorated the tight junction damage, decreased permeability to fluorescein isothiocyanate-dextran, and reversed the decreased expression of tight junction proteins occludin and zonula occludens 1 [264]. Furthermore, VNS inhibited the enhanced activity of nuclear factor κB. α-bungarotoxin is a specific α7-nAChR

antagonist, its administration prior to VNS significantly abolished the above protective impact of VNS. Since α-bungarotoxin is a specific α7-nAChR antagonist, this interesting study has, therefore, shown that attenuation of tight junction disruption and intestinal epithelial permeability in LPS-induced endotoxemia is mediated by α7-nAChR [264]. A recent simplified transcutaneous auricular VNS technique may be worth pursuing since it is a simpler and least invasive treatment option [266]. Given the above mentioned documented benefits of VNS, particularly its positive effects on many inflammatory diseases of vagus-innervated organs including GIT, there is a strong case for its application in IBS patients.

12. Conclusions

IBS is perhaps the most common gastrointestinal disorder seen in primary care and gastroenterology practice. Recent intense research has revealed how alteration in the composition of the gut microbiome influences animal and human physiology contributing to diseases ranging from inflammation to obesity. The microbiota which has a close relationship forms an integral part of the animal/human organism; it has been confirmed to be an essential inherent factor that impacts human health. An alteration in microbiome, i.e. dysbiosis, can be an immune-diet-mediated mechanism which may be the driving force behind GIT disease development.

The 'gut-brain' or 'brain-gut axis', (depending on whether one considers bottom-up or top-down pathways) is a bi-directional communication system, encompassing ENS and the vagus, as well as sympathetic nerves [25]. The enteric, autonomic and CNS domains are implicated in gut-brain axis dysregulation in IBS. Owing to the abnormal visceral hypersensitivity, chronic abdominal pain is the most distressing symptom in the IBS patients. However, these patients may have cerebella ataxia, myopathy, arthritis, hypotonia, learning disorders, depression, migraine, and headache – to name a few. The altered bacterial communities (in dysbiosis of the gut) enhance gut inflammation, intestinal barrier dysfunction, and systemic to neuroinflammation. Obesity and excess alcohol both exacerbate the above pathological stigmata. Hence gut dysbiosis may serve as significant therapeutic target for the prevention/treatment of IBS-related conditions, including cognitive decline. Important consideration needs to be given to modulate gut inflammation, and paradigms should be considered to develop new therapeutic regimens that seek to abrogate the progression of gut inflammation. Regulation of microflora composition (e.g. by probiotics and prebiotics) offers the possibility to influence the mucosal and systemic immunity dysfunction and restore GI homeostasis. This article addresses the above question of impact of GI functional disorder IBS on health and cognition. The approach presented here lays the foundation for a framework - that addresses key questions in regard to possible therapeutic strategies to abrogate GI inflammation → neuroinflammation, and to ameliorate cognitive impairment. Emphasis has been placed on strong potential that exists for food to manipulate microbiota composition; this may, therefore, provide new therapeutic strategies against the gut diseases, based on dietary intervention [6]. In addition, given the bidirectional communication between the GIT and CNS, an essential question is whether the brain can be exploited to modulate gut-related inflammation in IBS discussed here. The mechanisms underlying

microbiome-gut-brain communication certainly provides us with possibilities of potential therapeutic strategies [9, 119].

VNS may be an important therapeutic modality in this regard to upregulate vagal/parasympathetic function, and ameliorate gut-brain axis dysfunction [267]. It is quite feasible that dysbiosis, immunologically mediated alterations, increased GIT permeability of LPS/pro-inflammatory cytokines and metabolic disorders can be controlled and reversed by several available options. Thse may include therapeutic use of "Prebiotics, Probiotics, and Synbiotics, and VNS".

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