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Brain Neuropeptides, Neuroinflammation, and Irritable Bowel Syndrome

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Abstract
Background: Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by chronic abdominal symptoms, but its pathogenesis is not fully understood. ***Summary:*** We have recently shown in rats that neuropeptides such as orexin, ghrelin, and oxytocin act in the brain to improve the intestinal barrier dysfunction, which is a major pathophysiology of IBS. We have additionally shown that the neuropeptides injected intracisternally induced a visceral antinociceptive action against colonic distension. Since it has been known that intestinal barrier dysfunction causes visceral hypersensitivity, the other main pathophysiology of IBS, the neuropeptides act centrally to reduce leaky gut, followed by improvement of visceral sensation, leading to therapeutic action on IBS. It has been recently reported that there is a bidirectional relationship between neuroinflammation in the brain and the pathophysiology of IBS. For example, activation of microglia in the brain causes visceral hypersensitivity. Accumulating evidence has suggested that orexin, ghrelin, or oxytocin could improve neuroinflammation in the CNS. All these results suggest that neuropeptides such as orexin, ghrelin, and oxytocin act in the brain to improve intestinal barrier function and visceral sensation and also induce a protective action against neuroinflammation in the brain. ***Key Messages:*** We therefore speculated that orexin, ghrelin, or oxytocin in the brain possess dual actions, improvement of visceral sensation/leaky gut in the gut, and reduction of neuroinflammation in the brain, thereby inducing a therapeutic effect on IBS in a convergent manner.

Introduction

Irritable bowel syndrome (IBS) is a functional bowel disorder characterized by chronic abdominal symptoms. Previous studies have revealed that visceral hypersensitivity and intestinal barrier dysfunction are the main pathophysiology of IBS. Since brain-gut axis is considered to be an important factor in IBS, we have examined roles of the brain in the regulation of visceral sensation and intestinal barrier function and have shown that the central nervous system (CNS) regulates visceral sensation in response to colonic distension and intestinal barrier function [1–4]. Based on the findings, we have speculated that impairment of central regulation of visceral sensation and intestinal barrier function may lead to visceral hypersensitivity and leaky gut, which are the main causes of IBS.

Leaky gut, intestinal barrier dysfunction, plays a critical role in the onset of IBS because Creekmore et al. [5] have shown that leaky gut induced visceral hypersensitivity.

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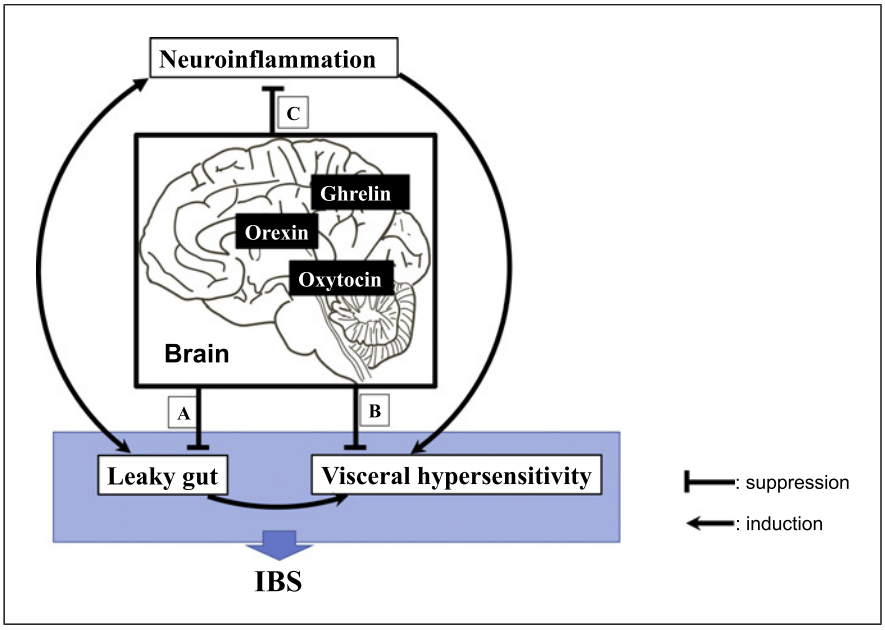

Fig. 1. Schematic illustration on the involvement of neuropeptides in neuroinflammation and pathophysiology (leaky gut and visceral hypersensitivity) of IBS.

Furthermore, leaky gut is involved in the pathogenesis of not only gastrointestinal diseases such as IBS but also neurodegenerative disease such as Alzheimer's disease, Parkinson's disease (PD), and autism [6]. It has been reported that leaky gut was considered to induce endotoxemia, systemic inflammation, and neuroinflammation [7]. For instance, in a rat model, neuroinflammation in the CNS also induced visceral hypersensitivity [8]. These findings suggest that neuroinflammation in the CNS may mediate the development of IBS in the state of leaky gut. Thus, neuroinflammation may be involved in the pathophysiology of IBS. In this review, we discuss on the involvement of neuropeptides in neuroinflammation and pathophysiology of IBS.

Leaky Gut and Visceral Sensation Regulated by Brain Neuropeptides

A disturbed intestinal barrier function, leaky gut, has been considered to be involved in the pathophysiology in many human diseases such as IBS, inflammatory bowel disease, dementia, and autism disorders [6]. Although evidence has suggested that intestinal permeability is controlled by a lot of peripheral mechanisms such as mucus secretion, tight junction proteins, neuroimmune modulators, and microbiota [6, 9], the central regulatory mechanisms of intestinal barrier function still remain to be clarified.

We have performed a couple of studies to examine a central role of orexin, ghrelin, or oxytocin in regulation of intestinal barrier function in rats. Orexin-A, ghrelin, or oxytocin but not orexin-B or des-acyl ghrelin injected intracsiternally improved intestinal hyperpermeability in response to LPS. These results suggest that orexin, ghrelin, and oxytocin act centrally in the brain to improve leaky gut (Fig. 1A). The results also suggest that the brain indeed plays a vital role in regulation of intestinal barrier function [1, 2, 4]. The improvement of leaky gut by neuropeptides such as orexin, ghrelin, or oxytocin was prevented by atropine or surgical vagotomy, suggesting that the vagal cholinergic pathway mediates the action. Ghrelin-induced improvement of leaky gut was blocked by orexin antagonist and orexin-induced action was prevented by oxytocin antagonist, suggesting a functional communication among orexin, ghrelin, and oxytocin in the brain. In any event, the vagal efferent pathway is essential for the central regulatory mechanism of intestinal barrier function.

We have done a series of experiments to clarify central mechanisms of regulation of visceral sensation with special reference to neuropeptides in the CNS. Visceral sensation was evaluated by colonic distension-induced abdominal withdrawal reflex in conscious rats. Orexin in the brain is capable of inducing visceral antinociception. Intracisternal but not intraperitoneal injection of orexin-A, ghrelin, or oxytocin increased the threshold volume of abdominal withdrawal reflex, suggesting that orexin, ghrelin, or oxytocin act centrally to induce visceral antinociception (Fig. 1B). In contrast, intracisternal orexin-B or des-acyl ghrelin failed to alter the threshold volume. Intracisternal SB334867 [10], an OX1R antagonist, injected centrally completely blocked the morphine-induced antinociceptive

action, furthermore supporting the involvement of OX1R in central orexin-induced visceral hyposensitivity and that endogenous orexin indeed mediates the antinociceptive effect of morphine on visceral sensation through the OX1R. The brain orexin signaling to induce visceral antinociception against colonic distension mediates visceral hyposensitivity by not only morphine but levodopa [11] or central ghrelin [12] because intracisternal OX1R antagonist significantly blocked visceral antinociception induced by levodopa or centrally injected ghrelin, suggesting that brain orexin signaling plays a vital role in providing a visceral antinociceptive action.

Creekmore et al. [5] have recently demonstrated that the level of stress-associated visceral hyperalgesia directly correlates with the magnitude of altered colon epithelial permeability, suggesting a tight correlation between visceral sensation and intestinal permeability. We have showed that orexin, ghrelin, or oxytocin induced a visceral hyposensitivity in rats [3] and that each neuropeptide also improved the intestinal permeability. These findings suggest that the improvement of intestinal barrier function by the neuropeptides would be deeply associated with the changed visceral sensation. In other words, orexin, ghrelin, or oxytocin may act centrally to improve intestinal permeability, followed by inducing a visceral antinociception.

Since the main pathologies of IBS are leaky gut and visceral hypersensitivity, the above findings that neuropeptides such as orexin, ghrelin, and oxytocin act in the brain to improve leaky gut and visceral hypersensitivity strongly suggest that each neuropeptide is capable of inducing therapeutic potential for IBS. We therefore speculate that a novel clinical therapy would be developed for IBS patients by targeting for orexin, ghrelin, and oxytocin signals in the brain.

Neuroinflammation and IBS

In recent years, chronic neuroinflammation has attracted attention for its association with neurodegenerative diseases such as Alzheimer's disease and PD as well as psychiatric disorders such as schizophrenia and depression [13]. According to the review by Daulatzai, leaky gut in IBS is capable of inducing neuroinflammation in the brain, thereby leading to dementia [14]. In barrier dysfunction in IBS, LPS released from the gut bacteria promotes pro-inflammatory cytokines, which trigger neuroinflammation to enhance dysfunctional brain regions including hippocampus and cerebellum. The above cascade may promote cognitive impairment leading to dementia. Since IBS is reported to be a risk factor for Alzheimer disease [15], the above pathway may explain the mechanism by which dementia develops in IBS.

In turn, accumulating evidence have suggested that neuroinflammation in the brain could contribute to the pathophysiology in IBS (Fig. 1). Neuroinflammation in the brain is reported to induce visceral hypersensitivity. Zhang and colleague have shown that microglial activation of hippocampal and paraventricular nucleus induced visceral hypersensitivity in rat [16, 17]. Additionally, Yuan. et al. [18] have shown that microglia in the amygdala is involved in chronic stress-induced visceral hypersensitivity in rat. Moreover, neuroinflammation in the brain is reported to be implicated in leaky gut. Neuroinflammation following traumatic brain injury (TBI) induce intestinal barrier dysfunction [19]. In addition, neurodegenerative diseases such as Alzheimer's disease, PD, and multiple sclerosis, in which prolonged neuroinflammation is involved in the pathogenesis, have been reported to be associated with intestinal barrier dysfunction [6]. In this context, neuroinflammation in the brain may cause visceral hypersensitivity and leaky gut, leading to IBS. Thus, neuroinflammation and IBS are related bidirectionally. These findings have suggested that neuroinflammation is a contributor to the pathophysiology in IBS.

Orexin and Neuroinflammation

Orexin, a well-known neuropeptide that regulates feeding and sleep wakefulness, is produced only in the lateral hypothalamus, but orexin nerves send axonal projections throughout the brain [20]. It has been reported that orexins are implicated in a wide variety of functions such as gastrointestinal motility, anxiety/depression, neuroendocrinological response, and energy balance [2, 3]. Orexin has two subtypes, orexin A and orexin B, both derived from a common precursor, prepro-orexin. Orexin A has affinity for orexin 1 receptors (OXR1) and orexin 2 receptors (OXR2), while orexin B has affinity only for OXR2. Several studies have shown that orexin A has neuroprotective properties. Duffy et al. have demonstrated that orexin A improved high-fat diet-induced neuroinflammation. Transgenic mice deficient in orexin A neurons contributed to high-fat diet-induced hippocampal neuroinflammation and cognitive decline [21]. These findings suggest that endogenous orexin A in the brain regulates excessive neuroinflammation in the hippocampus and maintains cognitive function. Becquet et al. examined the effects of orexin A on mice with experimental autoimmune encephalomyelitis (EAE), a widely used model of multiple sclerosis. Orexin A

suppressed the infiltration of CD4+ T lymphocytes by EAE and decreased the expression of chemokines (MCP-1/CCL2 and IP-10/CXCL10) and cytokines (IFN-γ, IL-17, TNF-α, IL-10, and TGFβ) in the CNS. In addition, orexin A administration was neuroprotective, reducing demyelination, astrogliosis, and microglial activation [22]. The above research is due to orexin A but not orexin B, suggesting that OXR1-mediated pathway may ameliorate neurodegenerative disease by suppressing excessive microglial activation. Xiong et al. examined the effects of orexin A on mice treated with the middle cerebral artery occlusion (MCAO)-reperfusion procedure, which is commonly used to create stroke models. Transgenic mice with loss of orexin A-producing neurons had worse infarct volume after MCAO reperfusion treatment. Macrophage/microglial infiltration was higher in loss of orexin A transgenic mice compared with wild-type mice. Pre-MCAO intracerebroventricular injection of orexin A significantly reduced infarct volume and macrophage/microglial infiltration in both genotypes [23]. These findings suggest that orexin acts in the brain to improve brain neuroinflammation (Fig. 1C).

Ghrelin and Neuroinflammation

Ghrelin, an endogenous ligand for the growth hormone secretagogue receptor type (GHSR), is mainly produced in stomach, but it is also synthesized in heart, pancreas, small intestine, kidney, and the gonads [24]. In the brain, ghrelin is produced by hypothalamic neurons in the arcuate nucleus, lateral hypothalamus, and paraventricular nucleus and has a wide variety of physiological functions, such as promoting secretion of growth hormone, stimulating appetite, modulating metabolism, or regulating cardiovascular and gastrointestinal functions [1]. In addition, there are also several reports that ghrelin alleviates neuroinflammation in the CNS. Santos et al. [25] examined the effects of ghrelin in a mouse model of Alzheimer's disease by injecting amyloid-β (Aβ 1–40) intracerebroventricularly. They found that administration of Aβ to ghrelin knockout mice significantly impaired recognition memory, spatial orientation, and ability in olfactory discrimination, whereas 7 days of ghrelin treatment prevented these deficits. These findings imply that endogenous ghrelin suppresses Aβ-induced neuroinflammation and maintains recognition memory, spatial orientation, and ability in olfactory discrimination. Wang et al. examined the effects of ghrelin in a mouse model of PD generated by 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine administration and showed that ghrelin protected dopaminergic neurons through enhancement of autophagy, inhibition of endoplasmic reticulum stress, and suppression of α-synuclein accumulation [26]. Using the EAE rat model, Liu et al. [27] found that ghrelin suppressed microglial activation, thereby reducing neuroinflammation and improving demyelination. According to the findings above, ghrelin suppresses neuroinflammation in the CNS (Fig. 1C).

Oxytocin and Neuroinflammmation

Oxytocin is a hypothalamic neuropeptide, classically well known as the uterine contraction hormone during parturition and milk secretion during nursing. However, oxytocinergic neurons project widely in the CNS and improve stress-related social behavior or anxiety. There are also studies regarding oxytocin that it improved neurodegenerative diseases. Jasso. et al. [28] have evaluated the effects of a single oral dose of oxytocin on neuropsychiatric behavior and emotional processing in patients with behavior-altering frontotemporal dementia and found significant improvements in Neuropsychiatric Inventory scores in the oxytocin group compared to controls, particularly in the reduction of anger facial expression recognition by behavior-altering frontotemporal dementia patients. The therapeutic effect on the above neurodegenerative diseases may be attributed to the improvement of neuroinflammation. Yuan et al. have demonstrated that oxytocin suppressed the expression of pro-inflammatory cytokine at the mRNA and proteins levels in LPS-stimulated microglia cells. And also, they showed that oxytocin suppressed LPS-induced neuroinflammation in vivo [29]. Otherwise, Chen et al. have reported that microinjection of oxytocin into the medial prefrontal cortex alleviated epilepsy and cognitive dysfunction induced by TBI through reducing neuroinflammation. In addition, they found that oxytocin improved TBI-induced blood-brain barrier disruption [30]. Therefore, oxytocin may reduce the development of dementia by suppressing neuroinflammation (Fig. 1C).

Conclusion

There is a tight relationship between neuroinflammation in the brain and pathophysiology in IBS. Orexin, ghrelin, or oxytocin act centrally in the brain to improve not only leaky gut and visceral sensation but also neuroinflammation in the brain. These findings suggest that the neuropeptides act in the brain to improve IBS pathophysiology through dual

mechanisms, improving intestinal functions such as intestinal barrier function and visceral antinociceptive action, and reducing neuroinflammation in the brain. All these results suggest that neuropeptides including orexin, ghrelin, and oxytocin in the brain may have a therapeutic potential for IBS.

Conflict of Interest Statement

The authors declare that they have no conflict of interest.

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Author Contributions

Masatomo Ishioh: writing – original draft. Tsukasa Nozu: conceptualization. Toshikatsu Okumura: conceptualization and writing – original draft.

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