Modulation of Functional Gastrointestinal Disorders by Paraventricular Nucleus and The Effect of Acupuncture

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Abstract. Functional gastrointestinal disorders (FGIDs) refer to gastrointestinal motility disorders and irritable bowel syndrome (IBS). Its characteristics are abdominal pain, diarrhea and constipation. These multifactorial conditions often have limited treatment efficacy, prompting ~50% of patients to seek alternatives like acupuncture, which has shown promising therapeutic effects recently. The paraventricular nucleus (PVN) is a multifunctional neuroendocrine nucleus located in the medial thalamus. It contains large cell neurons that synthesize oxytocin (OXT) and vasopressin (VP), and small cell neurons, including corticotropin-releasing hormone (CRH) neurons. The PVN regulates cardiovascular and electrolyte homeostasis and is crucial in FGIDs' pathogenesis. It affects gastrointestinal diseases via mechanisms like visceral pain, motility disorders, nausea, vomiting, and gastric mucosal damage. Neural circuits such as BNST-PVN, PVN-LSV, and PVN-DMV are also involved in this regulationAcupuncture, a traditional Chinese medical treatment, shows promise for FGIDs by modulating visceral pain and gastrointestinal motility via effects on CRH receptors in the PVN. This provides a novel treatment approach. Future studies should focus on clarifying the exact mechanism of acupuncture in the PVN and exploring the effects of different acupoints on the PVN., stimulation frequencies, and intensities affect the PVN.In summary, the PVN is a key brain center whose dysfunction or changes in hormone/receptor expression are linked to FGIDs. Acupuncture's regulation of the PVN offers a potential therapy. This review highlights the PVN's role in FGIDs, acupuncture's effects, and future research directions.

Keywords: Paraventricular nucleus of hypothalamus, acupuncture and moxibustion, gastrointestinal tract, corticotropin releasing hormone, neurocircuit.

1. Introduction

Gastrointestinal diseases cause symptoms like diarrhea, abdominal pain, nausea, vomiting, fullness, constipation and bloating. When no structural abnormalities are present, these are known as functional gastrointestinal disorders (FGIDs), such as irritable bowel syndrome (IBS) and gastric motility disorder. Recent studies show that the PVN is involved in regulating gastrointestinal diseases [1-2]. Because of the complicated, multifactorial nature of FGIDs, present treatments are often not satisfactory, leading nearly 50% of FGID patients to seek complementary and alternative medicine. Acupuncture, a traditional Chinese medicine therapy, has shown significant efficacy in treating FGIDs by alleviating symptoms like abdominal pain, regulating intestinal function, and reducing nausea and vomiting, possibly via effects on the hypothalamic PVN [3].This review summarizes the PVN's role and mechanisms in regulating FGIDs over the past five years, discusses the role of electroacupuncture, and proposes future research directions to explore the PVN's regulatory potential and acupuncture's therapeutic effects in FGIDs.

2. Structure and function of PVN

The PVN, located dorsocaudal to the supraoptic nucleus in the medial thalamus, is composed of different neuronal groups and lies within the upper boundary of the third ventricle [4]. The PVN is a multifunctional neuroendocrine nucleus located dorsocaudal to the supraoptic nucleus in the medial thalamus [4]. It consists of large and small cell neurons. Large cell neurons synthesize oxytocin (OXT) and vasopressin (VP), which are released into the posterior pituitary and systemic circulation [5]. Small cell neurons are more complex, including CRH, TRH, and somatostatin neurons, whose axons project to the median eminence to regulate the HPA axis via the anterior pituitary [6]. Some small cell neurons also project to brainstem and spinal cord autonomic centers, regulating cardiovascular and electrolyte homeostasis. PVN receives input from the hypothalamus and periventricular areas, the vagus nerve afferent, and the solitary tract nucleus. Thus, PVN is a key regulator of autonomic activity and can influence FGIDs through this pathway.

3. Regulation mechanism of PVN on gastrointestinal diseases

3.1. PVN participates in the regulation of visceral pain

3.1.1 CRH neuron activity in the PVN

The PVN is crucial for visceral pain regulation. PVN CRH neurons, linked to visceral hypersensitivity, are activated in response to pain [7]. In rats with neonatal colorectal dilation, PVN CRH neuron activation was observed, and GABA or GABA A receptor agonists mitigated visceral hyperalgesia [8]. Susceptible mice exhibited higher CRH expression, firing rates, and excitability in the PVN compared to resistant mice [9]. Overall, elevated PVN CRH neuron excitability is a key driver of visceral pain onset and progression.

Early-life stress (ELS) predisposes individuals to chronic visceral ache in adulthood, with mast cells implicated in visceral hypersensitivity. Chen Z et al study reveals that ELS, modeled by newborn maternal separation (MS), visceral hypersensitivity in adult rats was triggered by activation of hypothalamic PVN mast cells. The mast cell stabilizer chromoly mitigated this activation. Wild-type mice exposed to ms, but not mast cell deficient mice, developed chronic hypersensitivity. MS increased proinflammatory mediators, CRH+ cell count, and CRH protein in the PVN, Melatonin prevents these effects. Compound 48/80, a mast degranulator, induced similar effects, which were also cromolyn-sensitive. They conclude that PVN mast cell activation by ELS contributes to adult visceral hypersensitivity by modulating CRH neuronal activity and proinflammatory mediators[10].

3.1.2 OXT neuron activity in the PVN

Neural activation of OXT and CRH in the PVN, the anterior cingulate cortex (ACC) and central amygdala (CeA) during colonic dilation (CRD) are central to the IBS model. Tsushima H et al.hypothesized that OXT neurons in the PVN respond to CRD and influence anxiety and visceral perception. They found that OXT antagonists induced hypersensitivity and anxiety, while OXT neurons were indeed activated by CRD. High-dose antagonists suppressed ACC activity but activated CRH neurons in the CeA. This suggests OXT's dual role in regulating CRH neurons and ACC, warranting further investigation into its interaction with CRH in visceral pain and anxiety [11].

3.1.3 VP V1 receptor

Chronic visceral hypersensitivity (CVH), a mark of irritable bowel syndrome IBS is poorly understood in terms of central regulation. Su Z et al. found that PVN glutamate microinjection dose-dependently reduced CVH, an effect reversed by PVN/NTS ablation or VP V1 receptor antagonist DPVDAV pretreatment. Vagus nerve discharge frequency decreased post-injection. Mucosal oxidative stress, proliferation, and apoptosis were linked to CVH regulation. These results indicate that PVN and NTS participate in CVH, and Visceral hypersensitivity can be mitigated by VP V1, providing new insights and therapeutic targets [12].

3.1.4 Small-conductance Ca2+-Activated K+ Channel (SK)

Visceral hypersensitivity, a hallmark of IBS, is associated with CNS changes, including SK alterations. Ji NN et al. studied SK2 in the PVN of newborn CRD-induced rats, which showed a reduction in hypersensitivity and membrane SK2 and p-PKA. Dynasore or 1-EBIO treatment upregulates SK2 in PVN, alleviating hypersensitivity and normalizing neuronal firing; conversely, SK2 inhibition (apamin) or PKA activation (8-Br-cAMP) exacerbates allergic responses. These researches suggest that SK2 downregulation in the PVN, potentially due to PKA activation, contributes to hypersensitivity, targeting SK2 activation emerges as a promising therapeutic strategy for visceral pain management [1].

3.2. PVN participates in the regulation of gastric motility disorder

3.2.1 The orexin system

The orexin system, comprising orexin-1 receptor (OX1R), orexin-2 receptor (OX2R), and neuropeptides orexin-A/B, is integral to regulating key physiological processes including arousal, wakefulness, and appetite regulation, with orexin-A specifically demonstrating prokinetic effects on gastric motility. In a mechanistic study by Hao et al., electrophysiological recordings of gastric distension (GD)-sensitive neurons in the lateral hypothalamic area (LHA) were combined with real-time gastric motility monitoring to evaluate orexin-A's neuromodulatory effects. Administration of orexin-A in the LHA elicited dose-dependent enhancements in both GD-excited (GD-E) and GD-inhibited (GD-I) neuronal firing rates, paralleled by accelerated gastric contractility. These effects were completely abolished by pretreatment with the selective OX1R antagonist SB334867. Notably, PVN stimulation not only potentiated LHA GD neuronal responsiveness to orexin-A but also amplified gastric motility, with partial reversal observed upon OX1R blockade. These findings delineate two key mechanisms: (1) orexin-A directly activates LHA GD neuronal circuits to drive gastric motility via OX1R signaling; (2) the PVN functionally modulates LHA-mediated gastric motor control, suggesting hierarchical hypothalamic integration in gut-brain axis regulation [13].

3.2.2 OX1R and CRHR

Acute restraint stress (ARS) delayed gastric emptying (GE) by disrupting antro-pyloric coordination and enhancing food intake (FO) and corticosterone (CORT) secretion. The effects of ARS on GE, FO, CORT in plasma and pyloric motility in gastric antrum were weakened by OX1R and CRH receptor antagonists, but fully reversed when both were administered. ARS-triggered orexin (OXA) and CRH release were significantly reduced by SB-334867andα-CRH9,41, respectively. OX1R was found in CRH-positive cells, while the lateral hypothalamic area (LHA) showed dense CRH2 receptor expression without CRH1. ARS significantly increased the OXA immunoreactivity of LHA. SB-334867 and α-CRH9,41 abolished the ARS-induced c-Fos expression in the LHA and PVN. These results indicate that OXA and CRH reciprocally contribute to changes of neuroendocrine response and gastrointestinal motor function caused by stress. The interaction between these systems is crucial for understanding the physiological impact of stress on digestion and hormonal regulation [14].

3.2.3 GABA-OXT interactions

Irritable bowel syndrome IBS is linked to gastrointestinal dysmotility and hyperalgesia, with stress-induced central neural adaptations playing a key role. Li J et al. examines how stress affects rats, mimicking IBS, using long-term water avoidance stress (WAS). They found WAS rats showed increased GABAergic projections in the hypothalamic PVN, reducing OXT expression and gut motility. OXT administration improved these parameters, suggesting that PVN GABA-OXT interactions could be a therapeutic target for IBS [15].

3.2.4 Apelin

Apelin, an Apelin Receptor (APJ) receptor ligand, is upregulated in the PVN under stress and stimulates CRH release, potentially mediating stress-induced gastrointestinal (GI) dysfunction. Bülül

M et al. studied the role of apelin in gastrointestinal motility in rats under stress and non-stress conditions. Before evaluating gastric emptying (GE) and colonic transit (CT) across various stress conditions, APJ antagonist F13A was administered. They found that stress increased apelin and CRH levels, negatively correlating with GE and positively with CT. F13A reversed stress-induced GI changes. Apelin-13 increased corticosterone, Inhibited CT and GE, reduce gastric antrum and colon contraction. Apelin-13 exerts CRH-dependent effects in the gastric antrum, whereas its actions in the colon are CRH-independent. Therefore, central apelin affects gastrointestinal motility through APJ receptor and CRH pathway [16].

3.2.5 Epac1 (Exchange Protein Activated by cAMP 1)and SOCS3(Suppressor of cytokine signaling 3)

Huang ST et al. demonstrated in a neonatal colorectal distension (CRD)-induced visceral hypersensitivity model that Epac1 and SOCS3 expression was downregulated in the PVN, concomitant with elevated IL-6 levels. Notably, microinjection of the Epac agonist 8-pCPT into the PVN significantly reduced the firing frequency of CRH neurons, while PVN overexpression of SOCS3 via AAV-SOCS3 mitigated PVN neuronal activation, decreased hypersensitivity, and prevented pain escalation. IL-6 neutralizing antibody intervention reduced hypersensitivity. Conversely, PVN application of the Epac antagonist ESI-09 in naive rats heightened CRH neuronal firing. Knockdown of Epac1 or SOCS3 in PVN enhanced CRH neuron activity, HPA axis function, and visceral nociception sensitivity. Additionally, exogenous IL-6 in PVN replicated visceral hypersensitivity. Their findings show that the Epac1-SOCS3 pathway's inactivation influence on neuroinflammation and CRH neuron sensitization in PVN, causing visceral hypersensitivity and pain in neonatal CRD rats[17].

3.3. PVN regulation of nausea and vomiting

Cisplatin chemotherapy commonly induces nausea and vomiting, yet the hypothalamic mechanisms behind cisplatin-induced nausea are not well understood. Guo et al. investigated orexin-A's role in the ARC on cisplatin-induced nausea/vomiting. They assessed kaolin intake, gastric motility, and performed ARC injections and PVN lesions in cisplatin-treated rats. Fluoro-Gold tracing identified an ARC-PVN pathway. Orexin-A in ARC reduced kaolin intake and improved gastric motility in cisplatin-treated rats, effects blocked by PVN lesions or SB334867. Orexin-A-activated ARC neurons projected to NPY-expressing PVN neurons, with NPY pathway activation mediating orexin-A's anti-emetic effects, revealing a novel ARC-PVN neurocircuit, which can be used as a target for preventing and treating nausea and vomiting caused by cisplatin. [18].

3.4. The regulation of PVN on gastric mucosal injury

3.4.1 Dysregulation of the autophagy-lysosomal pathway in the PVN

Feng A et al. researched the role of autophagy-lysosomal dysfunction of PVN in gastric mucosal injury after gastric ischemia-reperfusion (GI-R) in rats. They established a GI-R rat model by clamping the celiac artery for 30 minutes and reperfusing for 1, 3, or 6 hours. Hematoxylin-eosin staining and gastric mucosal index were used to evaluate gastric injury. Autophagy-lysosomal dysfunction was measured by acid phosphatase activity and LC3 II and Beclin-1 levels. Microglial activation in the PVN was evaluated by immunohistochemical staining, and ROS content and p-GABAB R expression were examined.They found that shorter reperfusion durations correlated with more severe gastric mucosal damage in GI-R rats. Activation of microglia, production of reactive oxygen species, expression of p-GABAB R and gastric injury were increased by autophagy-lysosomal dysfunction of PVN. Activating microglia exacerbated these effects, while inhibiting microglial activation had a protective effect. These findings suggest that GI-R-induced autophagy-lysosome dysfunction of PVN worsens gastric injury by promoting microglial activation, highlighting potential targets for therapeutic intervention [19].

3.4.2 Hypothalamic neuron-astrocyte network

Restraint water-immersion stress (RWIS), a well-established experimental paradigm, represents a compound stress model encompassing both psychological and physiological elements, particularly affecting hypothalamic neuronal activity. Sun H et al. investigated the involvement of astrocyte-neuron interactions in the pathogenesis of restraint water-immersion stress RWIS-mediated gastric mucosal injury. Key findings revealed a bimodal GFAP/c-Fos expression pattern in PVN and SON, peaking at 1h and 5h post-RWIS. Both astrocyte inhibitor L-AA and c-Fos ASO attenuated RWIS-induced gastric injury, suppressing hypothalamic astrocyte and neuronal activation. These results implicate a hypothalamic neuron-astrocyte network in RWIS-mediated gastric damage, suggesting potential therapeutic targets for stress-related ulcers [20].

4. PVN regulates the neural circuits of gastrointestinal diseases

4.1. PVN regulates the neural circuits of visceral pain

4.1.1 BNST-PVN neurocircuit

PVN is the "pain classification center" for visceral and somatic pain. Ventral bed nucleus of the stria terminalis（vBNST) glutamatergic and GABAergic neurons project to PVN CRH neurons. During visceral hypersensitivity, GABAergic PVN neurons projecting to anteroventral bed nucleus of the stria terminalis (avBNST) show reduced excitability, and their activation alleviates this response in neonatal colorectal dilation rats, indicating their role in mediating visceral hypersensitivity [8]. In IBS, visceral hypersensitivity often leads to chronic pain. Huang ST et al. used maternal separation (MS) to model this hypersensitivity in mice, showing that hyperactive PVN neurons are involved. GABA injection into the PVN normalized CRH neuron firing, while BNST GABAergic neurons modulated this activity. Casp3 virus-induced apoptosis in these GABA neurons activated PVN CRH neurons, causing hypersensitivity. GABAergic vBNST-PVN circuit activation attenuates hypersensitivity, revealing its role in stress-induced visceral pain and offering new perspectives on chronic pain mechanisms. [9].

GABAergic neurons projecting to avBNST showed reduced excitability during visceral hypersensitivity, and their activation relieved this response in neonatal rats with CRD, indicating their role in mediating visceral hypersensitivity [8]. These experiments show that activating glutamatergic projections and inhibiting GABAergic projections in avBNST-PVN neurons contribute to mice's chronic visceral pain [8].

4.1.2 PVN -LSV neurocircuit

The lateral septum (LS), part of the septum, is crucial for emotional regulation and behavior. It is divided into dorsal, middle, and LSV. Studies in rats show increased cerebral blood flow in the LS during visceral pain, implicating it in visceral hyperalgesia. CRD-exposed mice show increased LSV neuron activity, absent with body surface stimulation. Virus tracing revealed that visceral pain activated CaMKIIα-positive PVN neurons projecting to LSV. Optogenetic modulation of this pathway can alleviate or induce visceral pain, underscoring the PVN's role in regulating visceral pain via its LSV connections [15].

The above research shows that PVN not only receives projections from atrioventricular node, but also projects to LSV of ventrolateral septal nucleus. Liu YJ et al. research shows that purinergic P2X3 receptor is highly expressed in PVN neurons related to visceral pain, and visceral pain is regulated through PVN-LSV loop, so inhibiting PVN-LSV pathway can alleviate chronic visceral pain.

4.2. PVN regulates the neural circuit of gastric motility disorder

4.2.1 PVN-DMV neurocircuit

Gastric dysmotility from GD is linked to activated PVN CRH neurons, which can be mitigated by inhibiting their activity. Wang XY et al. identified a PVN CRH to DMV ChAT neural pathway,

showing that modulating it can alleviate GD-induced gastric motility disorders [21]. Besides CRH, OXT also plays a key role in the PVN-DMV neurocircuitry.

Stress exacerbates functional GI disorders, like delayed gastric emptying and impaired motility. OXT, an anti-stress hormone, modulates gastric functions under stress, but its mechanisms are unclear. Perinatal exposure to high-fat diet (pHFD) alters vagus nerve circuit development in offspring, impacting gastrointestinal motility and stress responses. Carson KE et al. suggested pHFD changes PVN-DMV input, affecting vagal brain-gut stress reactions. Using retrograde tracing, cerebrospinal fluid analysis, gastric recordings, and electrophysiology, they found that pHFD-exposed rats had slower gastric emptying and altered stress responses. pHFD reduces PVN OXT neurons while boosting CRH neurons projecting to DMV. Studies show heightened PVN CRH-DMV projection activity, with CRH1 receptor antagonism restoring proper gastric OXT response. Thus, pHFD disrupts PVN-DMV input, causing vagus nerve brain-gut stress response imbalance [22].

4.2.2 CeA-PVN

Wang H et al. explored how EA modulates gastric function via the GABAergic circuit between CeA and PVN. They found EA activated neurons in CeA and PVN, and a CeA-PVN connection was confirmed. Activating CeA GABAergic neurons raised PVN GABA levels, reducing food intake and gastric emptying. Conversely, EA lowered PVN GABA levels, increasing food intake and gastric emptying. In conclusion, EA at BL21 and CV12 acupoints enhances food and intake gastric emptying in GAD2-Cre mice, likely by inhibiting PVN GABA release through the CeA-PVN GABAergic circuit [23].

4.2.3 Lateral hypothalamic area (LHA)-PVN

Wang C et al. investigated orexin - A's role in the PVN regarding acid secretion and gastric motility. Orexin - A from LHA projects to PVN, activating 63.2% of NPY - excited/GD - E neurons and inhibiting 55.9% of NPY - inhibited/GD - I neurons, dose - dependently increasing acid secretion and gastric motility. Y1 receptor antagonist GR - 231118 partly blocks this effect. LHA electrical stimulation promotes gastric functions through PVN NPY - sensitive/GD neurons, blocked by OX1R antagonist SB - 334867. In conclusion, LHA orexin - A in PVN boosts acid secretion and gastric motility, with Y1 receptor signaling being essential [24].

5. PVN participates in the regulation mechanism of acupuncture on gastrointestinal diseases

5.1. PVN participates in the regulation of visceral pain by acupuncture

Gao F et al. found that EA inhibits colon movement and discharge frequency mediated by PVN neurons, reduces visceral sensitivity in IBS rats, and lowers elevated CRH, corticosterone, and ACTH levels in peripheral serum, thereby alleviating IBS. Additionally, EA inhibits the expression of CRHR1 and CRHR2 in the PVN. By doing so, it blocks the effects of CRH, thus contributing to the treatment of IBS [25].

5.2. PVN participates in the regulation of acupuncture on gastric motility disorder

In GD - induced mouse model, Wang XY et al. showed EA curbed PVN CRH neuron activation. This reduced their inhibition on DMV acetylcholine neurons, increased acetylcholine release, and alleviated gastric motility disorder [21].

This study used a rat IBS model induced by cold-restraint stress, showing elevated CRH, CORT, and ACTH levels, increased visceral sensitivity, and faster intestinal motility. After 3 days of EA treatment, these serum markers, visceral sensitivity, and colonic neuron discharge frequency were reduced. EA also decreased CRH neuron excitability and CRHR1/CRHR2 expression in the PVN and peripheral colon. Thus, EA regulates intestinal function by way of the central CRH system,

revealing its mechanism in IBS and supporting the connection between meridians, viscera, and brain [25].

Neuronal activity and PVN c-fos expression of the dorsal vagal complex (DVC) were significantly increased by EA at RN12 and BL21. It also upregulated motilin (MTL), gastrin (GAS), and the receptors in the gastric antrum. These changes suggest EA enhances gastrointestinal hormone levels and receptors, potentially regulating gastric motility. PVN disruption reduced intragastric pressure, highlighting its role in the effects of EA. The findings suggest that EA performed on RN12 and BL21 affects gastric motility through the PVN - DVC - vagus - gastric route [26].

6. Conclusion

As mentioned above, PVN is a key brain integration center, with its neuronal function and hormone/receptor expression (e.g., OXT, AVP, VP) closely tied to gastrointestinal pathogenesis and regulation. It influences gastrointestinal diseases through mechanisms like visceral pain, motility disorders, nausea, vomiting, and gastric mucosal damage, and through neural circuits like the BNST-PVN, PVN-LSV, and PVN-DMV.Acupuncture, by modulating CRH receptors in the PVN, offers a novel treatment approach for FGIDs. Future research should delve into the precise mechanisms of acupuncture's effects on the PVN in FGIDs, including signal pathway conduction and identifying new neural circuits. Investigating the impact of different acupoint combinations, stimulation frequencies, and intensities on the PVN will strengthen the theoretical basis for acupuncture treatment and guide follow-up research. This will further elucidate the PVN's regulatory role in FGIDs and the potential of acupuncture intervention.

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