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Metabolism and Target Organ Damage

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Navigating gut-liver metabolic homeostasis: the role of the autonomic nervous system

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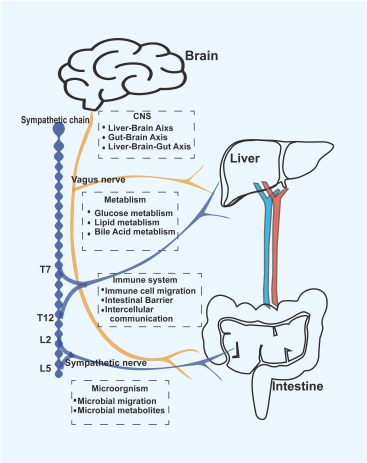

Abstract

The frequent clinical co-occurrence of intestinal and hepatic disorders points to underlying bidirectional communication along the gut-liver axis. Existing research has primarily focused on metabolic and humoral interactions, including bile acid circulation and portal venous signaling, whereas the autonomic nervous system (ANS) has received comparatively limited attention as an integrative regulatory pathway. This review reframes the axis through a neural perspective, arguing that the ANS functions as a master coordinator of metabolic homeostasis, linking immune regulation, metabolic function, and gut microbiota activity into a unified neuro-immune-endocrine network. The sympathetic and parasympathetic branches, along with the enteric nervous system, modulate barrier integrity, immune cell trafficking, hepatic glucose and lipid metabolism, and microbial

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composition via neurotransmitter-mediated and receptor-dependent signaling pathways. Dysregulation of this autonomic circuitry disrupts metabolic balance and is implicated in the shared pathophysiology of conditions such as inflammatory bowel disease (IBD) and metabolic dysfunction-associated steatotic liver disease (MASLD). Conversely, neuromodulation strategies, particularly noninvasive vagus nerve stimulation, have demonstrated therapeutic potential in reducing inflammation and restoring metabolic balance. By positioning the ANS as one of the central regulators of gut-liver metabolic cross-talk, this review advances current mechanistic understanding of gut-liver comorbidities and highlights bioelectronic medicine as a promising therapeutic strategy for metabolic disorders. This perspective bridges neuroscience, gastroenterology, and hepatology, offering novel insights for the management of complex, multi-organ metabolic diseases.

INTRODUCTION

Intestinal and hepatic diseases represent a growing global health burden due to their rising incidence and substantial clinical impact[1,2]. For instance, the worldwide prevalence of inflammatory bowel disease (IBD) increased by 88.3% from 1990 to 2021[3]. Similarly, the epidemiological footprint of metabolic dysfunction-associated steatotic liver disease (MASLD) has escalated dramatically, with recorded cases surging from 78,082 in 2010 to 621,400 in 2021[4]. In parallel, a growing body of literature underscores a robust, bidirectional cross-talk between the intestine and liver[5]. While a high-fat diet predisposes preclinical models to colitis[6,7], patients with IBD exhibit an elevated risk of developing MASLD[8,9]. As the prevalence of these metabolic and inflammatory conditions continues to rise in parallel with industrialization and lifestyle changes, it is imperative to identify key contributing factors in modern high-paced societies.

Dietary imbalance and overnutrition are well-recognized contributors to intestinal and hepatic dysfunction through their effects on lipid accumulation and systemic metabolic dysregulation. More recently, accelerated societal cadences and escalating psychosocial stress have emerged as formidable disruptors of metabolic homeostasis, particularly in the intestine and liver. Psychological stress influences not only endocrine pathways involved in metabolic balance but also the autonomic nervous system (ANS), which coordinates metabolic homeostasis, enteric nervous activity, immune responses, and rapid stress adaptation in these organs[10].

Composed of the sympathetic, parasympathetic, and enteric divisions, the ANS orchestrates metabolic homeostasis, immune regulation, and stress adaptation through neurotransmitter release and neural circuits[11-13]. Growing evidence indicates that ANS dysfunction is closely associated with a high incidence of gastrointestinal and hepatic diseases, particularly those involving metabolic components[14]. Notably, intestinal and hepatic disorders frequently co-occur with psychological disturbances such as anxiety and depression, and emotional states are known to influence disease progression in conditions like irritable bowel syndrome and MASLD. Anatomically, the ANS establishes a direct signaling pathway between the gut and liver. The vagus nerve originates from the medulla oblongata and extensively innervates both organs, while shared brainstem nuclei integrate hepatic and intestinal neural inputs. Together, these neural connections provide a structural basis for inter-organ communication and metabolic coordination[3,15-18]. Collectively, these observations suggest that ANS dysregulation may play a critical role in the pathogenesis of gut-liver metabolic comorbidities[19]. Nevertheless, the granular neural circuitries whereby the ANS orchestrates this inter-organ metabolic dialogue remain largely enigmatic, thereby warranting a systematic synthesis.

In this review, we summarize current clinical and preclinical evidence regarding the regulatory roles of the ANS in intestinal and hepatic physiology and pathology, with particular emphasis on metabolic regulation. We further discuss emerging bioelectronic neuromodulation strategies and their effects on the gut

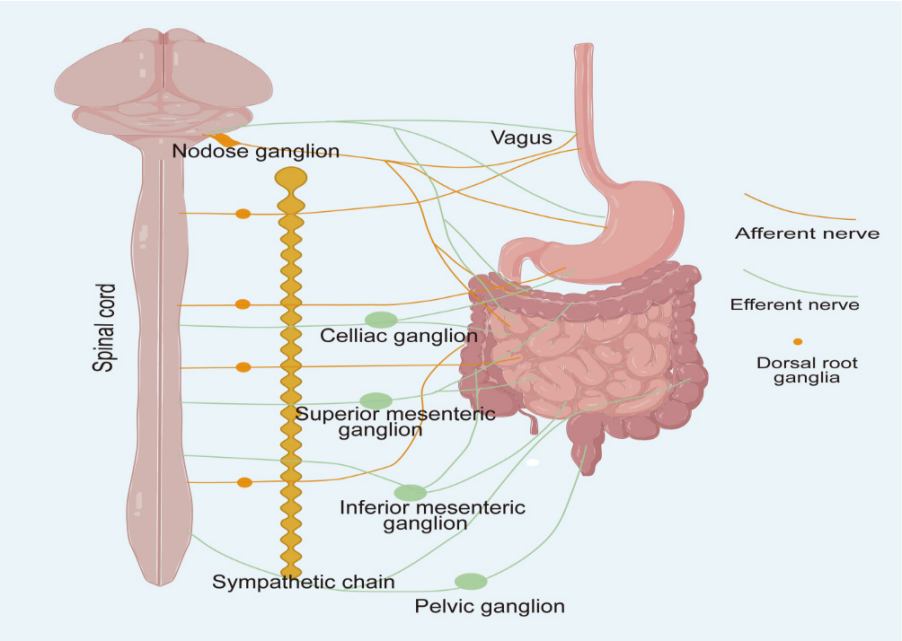

Figure 1. Sympathetic input to the gastrointestinal tract is conveyed by postganglionic efferent neurons that arise from the celiac, superior mesenteric, and inferior mesenteric ganglia. Sympathetic fibers projecting to the stomach, duodenum, and small intestine originate from spinal segments T6-T9, whereas those innervating the colon derive from segments L2-L5. Parasympathetic innervation is provided by the vagus nerve and pelvic splanchnic nerves. The cell bodies of vagal sensory neurons are located in the nodose ganglion. In contrast, general visceral afferent fibers, including those associated with sympathetic and pelvic splanchnic pathways, travel alongside their corresponding efferent nerves, and their neuronal cell bodies are found in the dorsal root ganglia. Image created with Adobe Illustrator.

microbiome and hepatic metabolism, providing a translational framework that links basic neuroscience with clinical gastroenterology and hepatology.

THE ANS IN THE GASTROINTESTINAL METABOLIC REGULATION

Distribution of the ANS in the gastrointestinal tract

The ANS functions as a major neural interface between the central nervous system (CNS) and the gut. The gut nervous system comprises the enteric nervous system (ENS), sympathetic nervous system (SNS), and parasympathetic nervous system (PNS)[20,21]. The ENS, an intrinsic neural network within the gastrointestinal tract, comprises a meshwork of enteric neurons and glial cells embedded within the myenteric and submucosal plexuses. It senses intestinal alterations and maintains normal gastrointestinal function[22]. The SNS and PNS belong to the exogenous nervous system. Preganglionic sympathetic neurons innervating the upper gastrointestinal tract arise from the T6-T9 thoracic spinal segments, while those destined for the colon originate within the L2-L5 lumbar spinal segments [Figure 1][23]. Most postganglionic sympathetic neurons innervating the gastrointestinal tract are located within the prevertebral ganglia, with some originating from paravertebral ganglia[24,25]. The intestinal parasympathetic nerves consist of the vagus nerve and sacral plexus nerves[26]. The vagus nerve, which provides widespread innervation to the stomach, small intestine, and proximal colon, arises from a discrete topographic network within the brainstem, encompassing the dorsal motor nucleus of the vagus, the nucleus tractus solitarius, and the nucleus ambiguus. Sacral plexus nerves in the distal colon originate primarily from preganglionic neurons within the S1-S4 spinal cord[27,28]. Unlike the SNS, the PNS lacks a continuous ganglion chain. Instead, it comprises discrete ganglia juxtaposed to their terminal target organs, featuring elongated preganglionic fibers coupled with shortened postganglionic counterparts[29].

Table 1. The primary functions of key neurotransmitter in the gut-liver axis

	Neurotransmitters	Receptors	Functions
SNS	NE	β2-AR	Increased hepatic glucose output; Inhibition of tight junction protein expression; Involvement in inflammatory responses; Regulation of tumor metabolism; Contraction of intestinal smooth muscle
		β3-AR	Attenuation of cAMP signaling and promotion of lipid synthesis in hepatocytes
		α1-AR	Contraction of intestinal smooth muscle
PNS	ACh	mAChR	Relaxation of intestinal smooth muscle; Promotion of bile acid secretion; Promotion of digestive juice secretion
		nAChR	Anti-inflammatory response
ENS	VIP	VPAC2	Relaxation of intestinal smooth muscle
	VIP	VPAC1	Regulation of intestinal stem cell differentiation and relaxation of intestinal smooth muscle
		VPAC2	Contraction of intestinal smooth muscle
	CCK	CCK1R	Regulation of intestinal peristalsis; Stimulation of gallbladder contraction; Participation in satiety signaling

SNS: Sympathetic nervous system; PNS: parasympathetic nervous system; ENS: enteric nervous system; NE: norepinephrine; Ach: acetylcholine; VIP: vasoactive intestinal peptide; CCK: cholecystokinin; β2-AR: β2-adrenergic receptor.

Autonomic regulation of intestinal metabolic functions

ANS is involved in coordinating and regulating key functions of the gastrointestinal tract via neurotransmitter release and neural circuits [Table 1], including movement, secretion, vasomotor regulation and local reflexes, all of which fundamentally sustain efficient nutrient absorption and metabolic processing. Both the small and large intestines possess considerable autonomous control and can function independently without exogenous neural input[30]. This intrinsic activity is primarily mediated by the ENS through the pacemaker function of interstitial cells of Cajal. The ENS modulates gastrointestinal function through neuropeptides such as vasoactive intestinal peptide and cholecystokinin, contributing to digestive function[31]. The coordinated action of the PNS and SNS, which encompasses motility, vasoconstriction/vasodilation, and glandular secretion, provides finer control over gastrointestinal function than either system alone, and all these processes are critical for optimal nutrient metabolism and energy balance. Overall, maintenance of autonomic homeostasis is essential for normal intestinal physiology and systemic metabolic balance.

ANS regulates gastrointestinal motility

The movement of the gastrointestinal tract is coordinated by the ENS, SNS and PNS to ensure proper nutrient digestion and absorption. As a general paradigm, parasympathetic inputs predominantly exert pro-kinetic, excitatory influences, whereas sympathetic signaling operates as an overarching inhibitory brake. In the upper gastrointestinal tract, the PNS achieves precise regulation of gastrointestinal motility through two different signal inputs. The excitatory cholinergic pathway drives smooth muscle contraction via the activation of muscarinic cholinergic receptors on gastrointestinal musculature, whereas the nonadrenergic, noncholinergic pathway causes smooth muscle relaxation through mainly the release of nitric oxide and/or vasoactive intestinal polypeptide[32]. Regulation of this signaling is achieved by ENS integration and transmission of command signals to the myenteric plexus, rather than direct input to smooth muscle[33]. The inhibitory effect of SNS on gastrointestinal motility is likewise indirect, mediated by the provision of inhibitory presynaptic inputs that constrain enteric neuronal excitation[34]. It has been suggested that sympathetic axons preferentially target cholinergic excitatory neurons rather than nitrergic neurons, reducing the release of excitatory neurotransmitters and suppressing intestinal motility[35]. Selective modulation of specific neural signaling pathways enables precise regulation of intestinal peristalsis and gastrointestinal metabolic function.

ANS regulates the blood flow in the gastrointestinal tract

The regulation of blood flow in the gastrointestinal tract is under bidirectional control by the ANS, with sympathetic nerves primarily mediating vasoconstriction and parasympathetic nerves promoting vasodilation. This mechanism ensures adequate delivery of nutrients and metabolic substrates. Nucleus tractus solitarius (NTS) receives vagal afferent input and provides strong excitatory projections to neurons in the rostral ventrolateral medulla (RVLM) which is a region containing sympathetic premotor neurons[36,37]. These RVLM neurons project directly to sympathetic preganglionic neurons located in the intermediolateral cell column of the spinal cord and modulate visceral blood flow and metabolic substrate distribution. The vagus nerve responds to diverse mechanical, chemical, and osmotic stimuli, including low-intensity gastric distension and bitter substances that activate RVLM neurons[38]. In contrast, systemic administration of cholecystokinin (CCK) suppresses the activity of RVLM neurons. CCK released from enteroendocrine cells (EECs) in response to food intake not only induces gastrointestinal relaxation via the vagus nerve but also regulates postprandial splanchnic blood flow through a vagal-sympathetic vasomotor reflex. These coordinated responses help maintain optimal conditions for postprandial metabolism[39,40].

ANS regulates the secretion of glands in the gastrointestinal tract

Intestinal gland secretion is regulated by intricate neural mechanisms, wherein the ENS, SNS, and PNS each play important roles in coordinating digestive enzyme and hormone secretion to maintain proper nutrient metabolism. The ENS regulates the proliferation and differentiation of intestinal stem cells through the release of vasoactive intestinal peptide (VIP)[41], dictating both the density and secretory repertoire of specialized mucosal cells, including enterochromaffin populations[42]. The synergistic interaction between the SNS and PNS is evident in the control of various digestive secretions. For instance, in salivary secretion, parasympathetic fibers via the facial and glossopharyngeal nerves directly stimulate salivary secretion to initiate carbohydrate digestion, while sympathetic fibers primarily induce contraction of myoepithelial cells to facilitate saliva expulsion[20]. Similar synergistic mechanisms govern the secretion of gastric juice, pancreatic juice, and bile[20]. The SNS and PNS coordinately regulate digestive gland output in response to physiological demands, supporting efficient nutrient processing and metabolic homeostasis.

THE ANS IN HEPATIC METABOLIC CONTROL

Distribution of the ANS in the liver

Sympathetic nerves to the liver originate from the thoracolumbar spinal cord (T7-T12). Preganglionic fibers travel by means of greater splanchnic nerves to the celiac and superior mesenteric ganglia, where synapses form[43]. Postganglionic fibers, primarily releasing norepinephrine (NE), then innervate the liver[43,44]. Parasympathetic innervation primarily originates fromthe craniosacral region, predominantly cholinergic (acetylcholine, ACh), and mainly via the hepatic branches of the vagus nerve, exerting a stimulatory effect on liver function[43,45,46]. Both sympathetic and parasympathetic fibers enter the liver under the mediation of hepatic portal, forming plexuses around three major vascular structures: the hepatic artery, portal vein, and bile duct[47]. The anterior hepatic plexus primarily distributes along the hepatic artery, while the posterior hepatic plexus distributes along the extrahepatic bile duct and portal vein[44-47] [Figure 2].

Autonomic regulation of hepatic metabolic functions

The ANS is a pivotal contributor to regulating liver metabolism, such as hepatic glucose, lipid, and bile acid metabolism, making the liver a central hub for systemic metabolic control.

Rapid regulation of glucose homeostasis is mediated by hepatic autonomic efferent pathways. Sympathetic nerve terminals release NE, thereby engaging hepatocyte β2-adrenergic receptors (β2-ARs) to augment hepatic glucose output[48,49]. Neuropeptides like galanin released from SNS terminals can also enhance hepatic

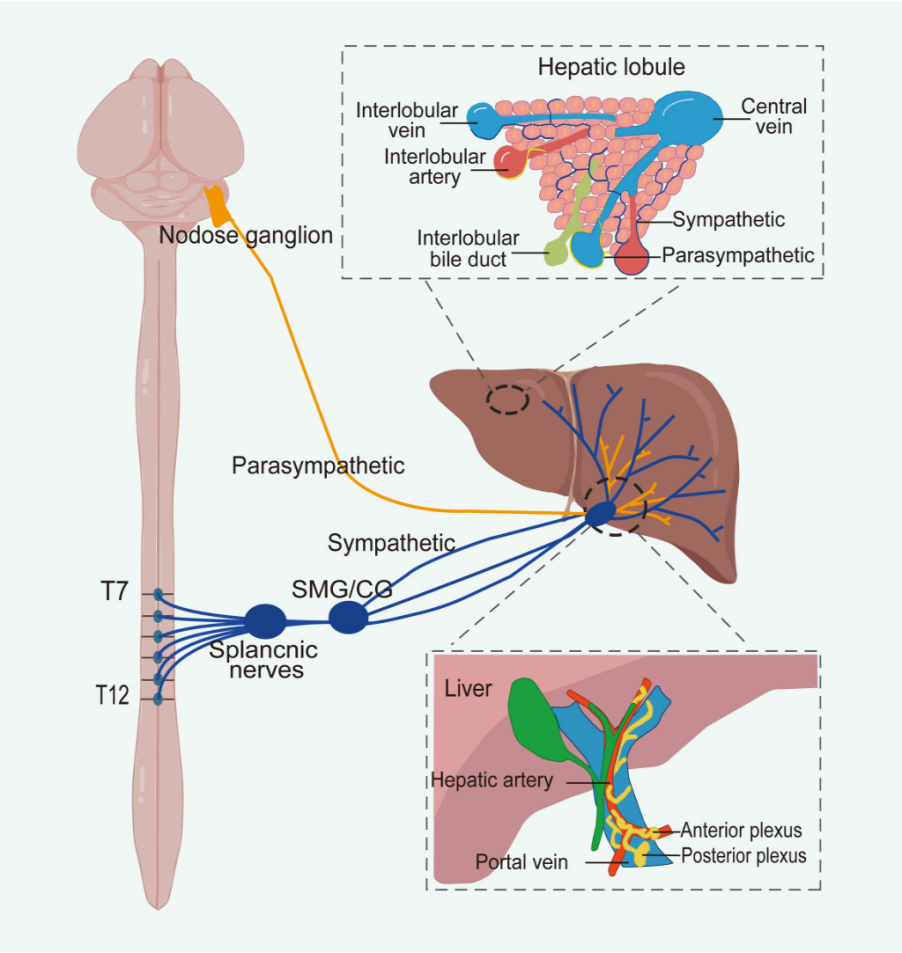

Figure 2. The sympathetic innervation of the liver arises from spinal segments T7 to T12, whereas parasympathetic innervation originates from nodose ganglion within the craniosacral regions. At the hepatic hilum, both sympathetic and parasympathetic fibers contribute to the formation of anterior and posterior autonomic plexuses. The anterior plexus surrounds the common hepatic artery, while the posterior plexus is located along the portal vein. Within the liver parenchyma, autonomic nerves are distributed around the hepatic artery, portal vein, and bile ducts. Notably, sympathetic fibers extend through the connective tissue and penetrate into the hepatic lobules, ultimately reaching the hepatocytes. Image created with Adobe Illustrator. SMG: Superior mesenteric ganglion; CG: celiac ganglion.

glucose metabolism[50-52]. Interestingly, Liu *et al.* delineated a rapid glucoregulatory circuit: paraventricular nucleus (PVN) corticotropin-releasing hormone (CRH) neurons → ventromedial nucleus of the hypothalamus (VMH) → raphe pallidus → sympathetic nerves → liver (the hypothalamic-sympathetic-liver axis), distinct from the classic HPA axis that raises blood sugar comparatively slowly[53]. In adrenalectomized mice, physical stressors induced rapid hyperglycemia and increased activity of key gluconeogenic enzymes in the liver, indicating that HSL axis activation promotes glucose release via hepatic gluconeogenesis[54]. On the other hand, the PNS generally promotes anabolic processes, enhancing glucose storage and insulin sensitivity[55,56]. Acute hepatic vagotomy or central vagal stimulation in rats significantly increased arterial and portal venous insulin levels or inhibited insulin secretion, respectively, suggesting a role for hepatic vagal nerves in insulin secretion regulation[57]. Complete hepatic denervation may abolish net hepatic glucose uptake[58], as observed in liver transplant recipients during hypoglycemia[59].

In lipid metabolism, the SNS and PNS collectively maintain hepatic lipid homeostasis[60]. The SNS primarily promotes hepatic lipid accumulation. Elevated hepatic sympathetic tonus drives steatosis by simultaneously accelerating free fatty acid uptake and intrahepatic de novo lipogenesis[61]. Consistent with this, sympathetic denervation has been shown to reverse established hepatic steatosis in obese mice[61] and to reduce VLDL-TG

secretion in dyslipidemic rats[62]. Together, these findings indicate that chronic sympathetic overactivity is a central pathogenic factor in the development of MASLD[63-65]. In contrast, the PNS mediates anti-steatotic signals from the brain. Adipose tissue-derived leptin translocates across the blood-brain barrier to exert central actions on the dorsal vagal complex, subsequently enhancing triglyceride export and suppress hepatic de novo lipogenesis through vagal efferent signaling[66]. These centrally mediated leptin effects depend on intact hepatic vagal innervation and are absent in liver-transplanted recipients lacking neural input to the graft[67]. Vagal sensory neurons innervating the liver are required for the development of diet-induced hepatic steatosis[68].

The ANS precisely regulates bile acid synthesis and secretion through bidirectional actions of sympathetic and parasympathetic nerves, serving as a crucial component in maintaining bile acid pool stability. The PNS enhances cholecystokinin-induced Cl^-/HCO_3^- exchange in cholangiocytes by releasing acetylcholine, synergizing with secretin to promote bile secretion[69]. The SNS primarily acts on cholangiocyte α_1-adrenergic receptors by virtue of norepinephrine, reducing bile secretion[70]. This dual innervation ensures bile secretion adapts to varying physiological demands. Animal studies in Wistar rats demonstrate that vagus nerve transection significantly elevates levels of bile acids such as TMDCA, GHDCA, ω-MCA, α-MCA, CA, isoCDCA, CDCA, DCA, 7-oxo-HDCA, and 12-oxo-CA. This mechanism involves the vagus nerve activating the intestinal FXR-Fgf15 signaling pathway while simultaneously suppressing hepatic expression of the bile acid synthase Cyp7a1[71]. Recent studies further confirm that parasympathetic nerve terminals in the human hepatic biliary system release vesicular acetylcholine transporter (VAChT, a parasympathetic marker)[72], providing direct evidence for cholinergic nerves directly regulating bile secretion.

Although the ENS is anatomically localized within the gastrointestinal tract, it exerts indirect regulatory effects on liver function via a complex, multi-component gut-liver axis. Central to this regulation are EECs, which act as specialized chemosensory epithelial cells capable of detecting luminal chemical and microbial stimuli. Upon activation, EECs secrete neuroactive hormones, including serotonin, glucagon-like peptide-1 (GLP-1), and CCK, that signal to the central nervous system primarily by means of vagal afferent fibers[68]. Subsequent central integration modulates autonomic outflow to the liver and affects hepatic metabolic, synthetic, and detoxification functions[73]. Concurrently, the gut microbiota contributes to this regulatory network by producing bioactive metabolites that modulate EEC activity, maintain intestinal barrier integrity, and shape both local and systemic immune responses, collectively impacting hepatic physiology and pathophysiology[74,75]. Collectively, current evidence indicates that ENS-mediated regulation of liver function involves bidirectional crosstalk among neural, endocrine, microbial, and immune components. However, the precise molecular and neural circuit mechanisms underlying this inter-organ communication remain incompletely understood.

ANS IN THE GUT-LIVER METABOLIC AXIS

Extensive clinical studies indicate that 60%-80% of patients with PSC have IBD, while 2%-14% of IBD patients are diagnosed with PSC[76]. Whether IBD is an extraintestinal manifestation of PSC or a closely related comorbidity remains controversial. However, evidence strongly supports that gut-liver communication is involved in shared metabolic and inflammatory pathways, though the precise underlying mechanisms are still unclear[77,78]. This article summarizes how ANS enables interorgan dialogue among the intestine, liver and brain through immunity, metabolism and intestinal microbes, with particular focus on metabolic regulation [Figure 3].

Autonomic regulation of gut-liver axis immunometabolic homeostasis

Sympathetic and parasympathetic nerves jointly constitute a refined neuro-immune dialogue network within the gut-liver axis by regulating barrier function, immune cell migration, and intercellular communication, all of which have secondary effects on tissue metabolic function.

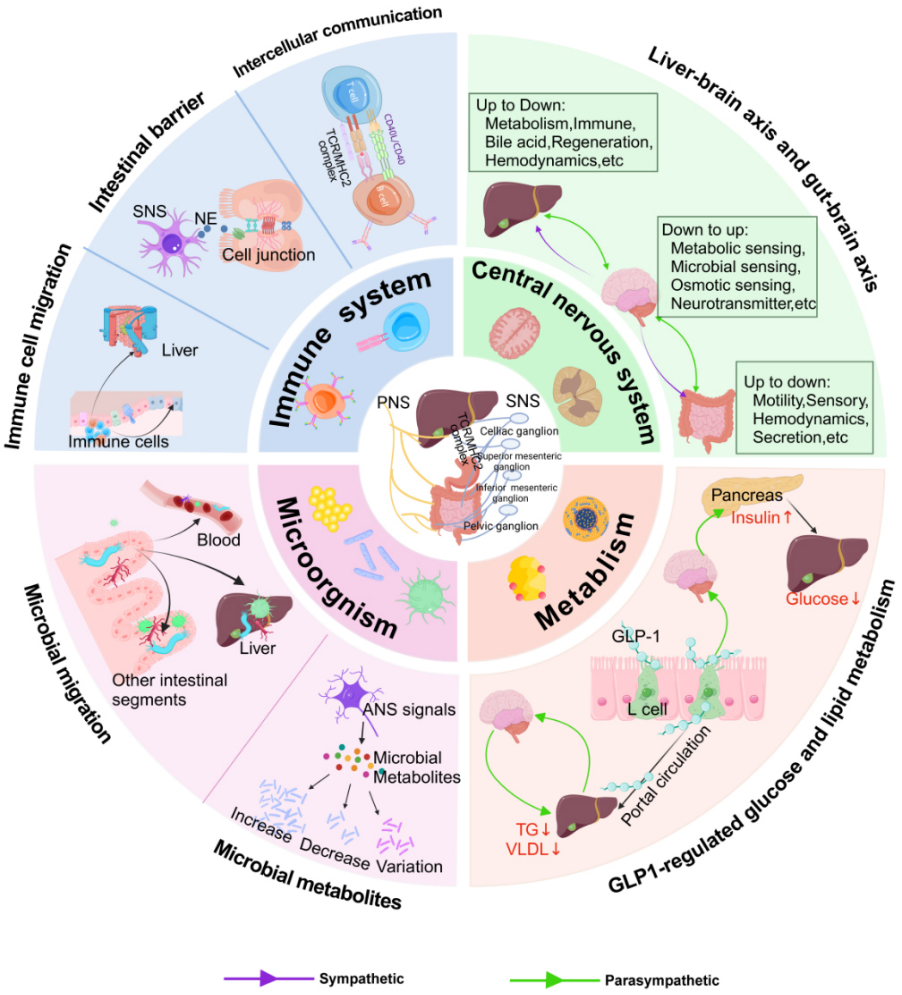

Figure 3. The ANS orchestrates gut-liver metabolic homeostasis through integrated neuro-metabolic pathways. The ANS modulates gut-liver metabolic communication via four interconnected routes: glucose and lipid metabolism, immunometabolism, microbial metabolism, and CNS metabolic integration. In metabolic regulation, the ANS controls hepatic and intestinal glucose/lipid metabolism via GLP-1 signaling and direct neural inputs, regulating gluconeogenesis, lipogenesis, and energy balance. In immunometabolism, the ANS shapes the metabolic microenvironment of gut and liver by modulating immune cell trafficking and barrier integrity, influencing insulin sensitivity and nutrient processing. Regarding microbial metabolism, autonomic innervation affects microbial metabolite production (SCFAs, bile acids), which subsequently regulate host metabolism, insulin secretion, and energy expenditure. Parasympathetic pathways convey ascending signals to the central nervous system, which integrates this information and coordinates sympathetic and parasympathetic efferent outputs to target organs. These neural circuits collectively regulate gut-liver metabolic homeostasis. Image created with cnsknowall.com. SNS: Sympathetic nervous system; ANS: autonomic nervous system; NE: norepinephrine; TG: triglyceride; VLDL: very low density lipoprotein; GLP-1: glucagon-like peptide-1; TCR: T cell receptor; MHC II: major histocompatibility complex class II.

Maintaining intestinal barrier integrity relies on stable expression of epithelial tight junction proteins[79]. Sympathetic-derived norepinephrine engages β2-ARs on intestinal epithelial and immune cells populations, subsequently driving the downregulation of tight junction proteins, compromising epithelial barrier integrity, and facilitates the translocation of microbial products into the circulation[80]. At the cellular level, sympathetic-derived NE targets dendritic cell populations via β-AR pathways, a signaling axis that critically patterns subsequent T cell activation and dictates the localized immunometabolic microenvironment[81]. Sympathetic signaling additionally regulates immune cell migration by altering portal vein blood flow and metabolic substrate delivery. Sympathetic activation induces intestinal vasoconstriction, reduces immune cell infiltration into the gut and suppresses local immune responses[82]. Clinical studies have identified memory T cells of common origin in intestinal and hepatic samples from PSC-IBD patients, suggesting bidirectional migration of immune cells between the gut and liver that jointly shapes the immune and metabolic microenvironments of both organs[83].

In contrast to the PNS, the vagus nerve exerts protective effects in the gut-liver axis by the "cholinergic anti-inflammatory pathway." Within the intestine, the vagus nerve can sense antigens through high-affinity Immunoglobulin E receptors and release glutamate to modulate dendritic cell function, suppressing Th2-skewed inflammation[84]. Following injury, enteric glial cells are critical for transmitting vagal anti-inflammatory signals, enhancing barrier repair and limiting immune cell recruitment[85]. Concurrently, gut-derived microbial metabolites and luminal inflammatory signals are monitored by hepatic vagal sensory afferents. Through the liver-brain-gut neural arc, these signals are transmitted to the solitary nucleus in the brainstem. Subsequently, through the vagus nerve's parasympathetic efferent pathway, the vagus nerve modulates the abundance of gut immune cells, forming an indirect pathway influencing the hepatic immune and metabolic environment[86].

Autonomic regulation of gut-liver axis metabolic homeostasis

Traditionally, the liver was regarded as a passive metabolic executor, and the gut was viewed primarily as an absorptive organ. Recent paradigms have illuminated the liver not merely as a passive metabolic sink, but as an active sensory organ participating in neuroendocrine feedback loops, operating in concert with extensive gut-CNS conduits via EECs, the ENS, and the microbiota[87-90]. This gut-liver-brain triad forms the physiological basis for metabolic homeostasis, whose disruption precipitates various metabolic disorders such as MASLD[91,92].

A key mediator in this circuit is the gut hormone GLP-1, whose actions illustrate the integrated neural control of metabolism across organs. Upon intraluminal nutrient engagement, mucosal L-cells liberate GLP-1, which subsequently docks with cognate receptors localized on vagal afferent terminals within the intestinal wall and portal vein, initiating a neural signal to the brainstem[93]. The metabolic actions of GLP-1 receptor agonists, including the inhibition of gastric emptying and stimulation of insulin secretion, are mediated through the vagus nerve[94]. Evidence shows that knockdown of GLP-1 receptors in vagal afferent neurons blunts these effects, while vagal nerve stimulation can mimic them by enhancing vagal activity and increasing GLP-1 release[95-97]. The same neural circuit directly controls liver lipid metabolism[98]. In another key experiment, researchers injected GLP-1 into the portal vein and observed a significant reduction in blood triglycerides and hepatic VLDL secretion in both hamsters and mice. When the vagal afferent pathway was interrupted either surgically or pharmacologically, this lipid-lowering effect disappeared[98]. Moreover, the anti-lipemic effect of portal GLP-1 requires not only intact vagal signaling but also efferent changes in sympathetic tone[98]. This indicates that the brain's processing of vagal GLP-1 input includes adjustments to SNS outflow. Regarding bile acid metabolism, activation of intestinal FXR transmits signals to the liver by virtue of vagus nerve and regulates cholesterol 7α-hydroxylase expression, forming a neural component of the enterohepatic feedback loop[99]. Recently, single-cell technologies have advanced the field. Newly identified vagal $CART^+$ neuron subsets regulate insulin and hepatic gluconeogenesis, a mechanism linked to commensal microbiota dysbiosis or depletion, representing a breakthrough in understanding the microbiota-gut-liver axis[100].

Taken together, these paradigms establish the ANS as a critical rheostat that fine-tunes gut-liver metabolic homeostasis utilizing an integrated neuroendocrine framework.

Autonomic regulation of the gut-liver axis via microbial metabolism

As a core component of the gut-liver axis, the gut microbiota function as a critical determinant in the dynamic balance between the intestine and liver[88,101]. The ANS, in turn, reshapes the microbiota-gut-liver network via direct neural modulation, metabolite intervention, and regulation of microbial translocation, emerging as a novel therapeutic target for metabolic diseases.

Microbial metabolites

Gut metabolites (e.g., SCFAs, secondary bile acids, tryptophan derivatives, neurotransmitters) are small molecules produced by the microbiota that serve as key metabolic mediators[102]. Although of microbial origin, these metabolites reciprocally shape microbial ecology by the means of microenvironmental modifications, gene expression modulation, quorum sensing disruption, and metabolic reprogramming. The ANS can influence these microbial metabolites, regulate microbial composition and function, and affect host metabolism. For example, the ANS can modulate microbial bile acid metabolism by activating receptors like FXR and TGR5. Employing PNS signaling, *Lactiplantibacillus plantarum* increases tauroursodeoxycholic acid (TUDCA) levels and reduces lithocholic acid (LCA) levels, modulating microbial metabolic pathways and promoting beneficial bacteria (e.g., *lactobacilli*) growth[103]. SNS-derived NE, via the Adra2a signaling axis, lowers cAMP to inhibit calcium flux, suppressing GLP-1 release and raising blood glucose[104]. Knockout of Adra2a or treatment with the GLP-1R agonist exendin-4 lowers blood glucose in mice, affecting microbial carbon sources[104]. The vagus nerve promotes primary bile acid secretion by activating hepatic FFAR3. These bile acids stimulate microbial conversion to secondary bile acids in the gut, forming a feedback loop regulating hepatic lipid metabolism[105]. The ANS can shape the gut microbial ecosystem by influencing the production and profile of key metabolites.

Microbial translocation

The ANS critically governs the gut-liver axis by modulating microbial translocation and its attendant metabolic sequelae, a process sustained by the tripartite regulation of epithelial barrier integrity, immune microenvironment dynamics, and microbial ecology. Long-term chronic stress disrupts the intestinal barrier via hyperactivation of SNS signaling, thereby precipitating the translocation of bacterial endotoxins and opportunistic pathogens[106]. However, SNS signaling also participates in maintaining intestinal mucosal immune homeostasis, preserving epithelial barrier integrity, and supporting antimicrobial defense. This functional duality is highly context-dependent, tailored by the precise nature of the physiological or pathological stimulus (e.g., acute or chronic, the magnitude and duration of stimulation). Pharmacological depletion of sympathetic innervation in the lamina propria and mucosa increased inflammatory cell infiltration (CD68 + CD86 macrophages, $Ly6C^+$ monocytes) and promoted the expression of pro-inflammatory cytokines (IL-1β, TNF-α, IFN-γ) in the gut. The translocation of intestinal bacteria into the liver via a compromised epithelial barrier represents a seminal and pervasive event in the pathogenesis of MASLD[107]. Studies in MASLD mouse models demonstrated that *Escherichia coli* (*E. coli*) activates the TLR5/MYD88/TWIST1 pathway in liver sinusoidal endothelial cells through flagellin signaling[107]. These changes promote steatosis, inflammation, and fibrosis in MASLD, highlighting the link between microbial translocation and metabolic dysfunction[107]. Clinical studies have shown that reduced vagus nerve tone in patients with cirrhosis is significantly associated with intestinal flora imbalance and increased risk of hepatic encephalopathy, while vagus nerve stimulation (VNS) can improve liver injury by restoring the intestinal barrier and preserving metabolic homeostasis[108-111]. These findings reveal the potential therapeutic value of ANS in gut-liver axis disease by rebalancing microbial translocation homeostasis and protecting metabolic function.

Autonomic regulation of the gut-liver axis via the CNS

The gut-brain axis is a complex bidirectional network that links brain regions involved in emotion and cognition with peripheral gut function and coordinates metabolic homeostasis[5,112]. The gut signals up to the brain through spinal and vagal visceral afferents and receives "top-down" signals under the mediation of sympathetic and parasympathetic efferents, forming a circuit for metabolic regulation[113]. Vagal afferents from the gut smooth muscle transmit information regarding nutrient status to the CNS[114,115]. Clinically, vagotomy performed for peptic ulcer disease has been associated with an increased incidence of mental

health disorders. In animal studies, transection of subdiaphragmatic vagal afferents induces anxiety- and fear-related behaviors[116,117], suggesting that disruption of gut-derived vagal signaling can trigger psychiatric symptoms. Diverging from the bidirectional modality of the vagus nerve, the SNS operates predominantly as an obligate efferent axis, dictating gastrointestinal motility and glandular output via norepinephrine release during stress states.

Similarly, within the liver-brain axis, hepatic vagal afferents indirectly sense the hepatic microenvironment and relay this information to the NTS, which subsequently modulates hepatic parasympathetic outflow[5,116,118]. Exogenous vagal reflex activity can connect hepatic vagal afferents, the brainstem, vagal efferents, and enteric neurons[118]. Hepatic ischemia-reperfusion (HIR) injury often induces systemic inflammation, depression-like behavior, and reduced prefrontal synaptic protein levels in mice[102]. Notably, subdiaphragmatic vagotomy attenuates these symptoms[119], implicating the vagal signaling in this pathological process. As in the gut-brain axis, parasympathetic pathways mediate bidirectional communication in the liver-brain axis, while sympathetic signaling predominantly provides efferent output[120]. Chronic stress further drives CRH^+ CeM → PVN projections, sustaining hepatic sympathetic outflow. This process compromises intrahepatic sympathetic fibers, elevated circulating norepinephrine levels, β3-adrenergic receptor downregulation, and impaired cAMP signaling in hepatocytes, ultimately contributing to hepatic catecholamine resistance and MASLD progression[10].

Interactions among the brain, liver, and gut involve highly complex regulatory mechanisms[102]. Currently, the liver-brain-gut neural reflex arc proposed by Teratani *et al.* has gained wide recognition[102]. Specifically, hepatic vagal afferents sense the gut microenvironment and signal to the NTS[102]. Central integration within the NTS subsequently modulates peripheral vagal and enteric outputs, culminating in the induction and phenotypic preservation of intestinal pTregs[86]. This reflex arc provides a representative example of how CNS-processed autonomic signaling coordinately regulates immune homeostasis along the gut-liver axis.

TARGETING THE ANS FOR INTERVENTION OF GASTROINTESTINAL DISEASE

Emerging ANS-targeted therapies primarily involve VNS, which can be categorized into invasive and noninvasive approaches. Invasive VNS requires surgical implantation of electrodes around the cervical vagus nerve, whereas noninvasive approaches, especially transcutaneous auricular VNS (taVNS), have attracted increasing research interest because of their safety and convenience. Other noninvasive techniques include transcutaneous cervical VNS and percutaneous electrical nerve field stimulation[121].

In IBD, taVNS demonstrates clear anti-inflammatory effects. In rodent colitis models, it reduces disease activity index, improves colonic injury, and lowers pro-inflammatory cytokine levels[122,123]. Small clinical studies show that taVNS can induce clinical remission in some patients with mild-to-moderate Crohn's disease (CD) or ulcerative colitis (UC), accompanied by decreased fecal calprotectin[124]. Part of the vagus nerve's anti-inflammatory action is mediated by the "splenic-vagal pathway," as electrical stimulation of the splenic nerve bundle also ameliorates colitis in mice[125]. In gastrointestinal motility disorders, taVNS shows significant prokinetic effects that enhance nutrient processing and metabolism. In functional dyspepsia (FD) patients, it increases gastric volume and restores gastric slow-wave rhythm[126]. In constipation-predominant irritable bowel syndrome (IBS-C), it increases bowel movement frequency, alleviates abdominal pain, and improves anorectal sensation and mood[127]. These benefits are attributed to enhanced vagal tone and restored parasympathetic regulation of gastrointestinal motility after taVNS. Experimental central vagal activation can prevent postoperative gastroparesis[128] [Table 2]. In liver diseases, noninvasive VNS improves metabolic markers in patients with metabolic syndrome and has demonstrated potential efficacy in reducing hepatic steatosis, inflammation, and fibrosis [Table 3][129,130].

Table 2. ANS interventions in gut diseases

Author	Intervention	Disease	Study design	Participants	Location	Major results
Zhu *et al.*[126]	taVNS	FD	double-blind, randomized, sham-controlled, small pilot RCT	18:18	bilateral auricular cymba concha areas	Engagement of vagal pathways was associated with improved gastric accommodation and stabilization of gastric pacemaker activity, supporting therapeutic utility in nonservice FD
Shi *et al.*[138]	taVNS	FD	randomized, sham-controlled, RCT	10-Hz tins group:25-Hz tens group: sham group = 101:99:100	tragus of the left ear	A higher proportion of responders and adequate symptom relief was observed in active stimulation groups relative to sham after 4 weeks
Shi *et al.*[127]	taVNS	IBS-C	randomized, sham-controlled, small pilot RCT	21:19	bilateral auricular cymba concha areas	Concurrent improvement in bowel function and abdominal pain, consistent with modulation of gut-brain signaling
Kovacic *et al.*[139]	PENFS	Abdominal pain-related functional gastrointestinal disorders in adolescents	double-blind, randomized, sham-controlled, RCT	51:47	dorsal and ventral aspects of the ear within 1-1·5 mm of the vascular branches, but not on main arterial branches	Sustained reduction in abdominal pain-related symptom burden in adolescents with functional gastrointestinal disorders
Krasaelap *et al.*[140]	PENFS	IBS in adolescents	double-blind, randomized, sham-controlled, small pilot RCT	27:23	vascular branches of the outer ears	Reduction in pain severity accompanied by improved patient-reported well-being in adolescent IBS
Sahn *et al.*[124]	taVNS	IBD (children)	single-blind, randomized, sham-controlled, small pilot RCT	11:11 (CD:UC=10:12)	cymba conchae of the external left ear	Favorable safety profile with concurrent symptom improvement and decreased fecal calprotectin, indicating reduced intestinal inflammatory activity
Huang *et al.*[141]	TEA	IBS-C	single-blind, randomized, sham-controlled, small pilot RCT	26:26	bilateral PC6 and ST36	Acceleration of colonic transit and attenuation of rectal hypersensitivity, consistent with autonomic regulatory involvement
Zhou *et al.*[142]	TEA	CC	single-blind, randomized, sham-controlled, small pilot RCT	22:22	ST36	Sustained alleviation of constipation linked to enhanced vagal tone and normalization of rectal sensory function

Liu *et al.*[143]	EA	CSFC	single-blind, randomized, parallel, sham-controlled, RCT	536:539	bilateral acupoints of ST25, SP14, andST37	Increased frequency of complete spontaneous bowel movements with a favorable safety profile following 8-week EA
Liu *et al.*[144]	EA	SCC	multicenter, randomized, controlled, noninferiority, RCT	280:280	bilateral ST25, SP14 and ST37	Clinical efficacy comparable to prucalopride with prolonged post-treatment benefit and good tolerability
Iqbal *et al.*[145]	tSNS	CFC	open-label, exploratory research	16	the entire sacrum	No meaningful short-term improvement in chronic constipation
Iqbal *et al.*[146]	tSNS	CFC	open-label, exploratory research	18	behind the medial malleolus where the tibial nerve is most superficial (bilateral)	Clinical benefit observed in a subset of patients, particularly those with less severe disease phenotypes
Gokce *et al.*[147]	tTNS	CFC (geriatric patients)	open-label, exploratory research	44	TENS electrodes were placed below the medial malleolus at approximately 15-cm above the medial malleolus (bilateral)	Significant improvements in defecatory dysfunction, colonic inertia, and pain, with sustained analgesic effects
Chase *et al.*[148]	IFT	chronic treatment-resistant constipation and soiling (children)	open-label, exploratory research	8	Abdominal/paraspinal(T9 and L2)	Marked reduction in soiling and increased spontaneous bowel activity, with partial durability of response
Clarke *et al.*[149]	IFT	STC	randomized, sham-controlled, small pilot RCT	22:8	Abdominal/paraspinal(T9 and L2)	Enhanced colonic transit in pediatric slow transit constipation.
Clarke *et al.*[150]	IFT	STC	double-blind, randomized, sham-controlled, small pilot RCT	16:17	Abdominal/paraspinal(T9 and L2)	Improvements in child-reported quality of life and functional scores restricted to active treatment
Ismail *et al.*[151]	TES	STC (children)	open label, exploratory research	11	Abdominal/paraspinal(T9 and L2)	Home-based TES associated with improved bowel function in treatment-resistant cases
Yik *et al.*[152]	TES	STC (children)	open-label, exploratory research	29	Abdominal/paraspinal(T9 and L2)	Increased defecation frequency and reduced soiling, with approximately half of patients responding
Queralto *et al.*[153]	IFT	STC	prospective, exploratory research	11	Abdominal/paraspinal(T9 and L2)	Preliminary evidence supporting IFT as a noninvasive option for STC
Clarke *et al.*[154]	IFC	STC (children)	open-label, exploratory research	8	Abdominal/paraspinal(T9 and L2)	Increased propagated colonic motor activity with effects persisting for months

YYang *et al.*[155]	TES	STC (female)	assessor-blinded, randomized, controlled, small pilot RCT	14:14	Abdominal/paraspinal(T9 and L2)	Symptom reduction in female STC patients
Moore[156]	IFT	STC (female)	single-blind, randomized, sham-controlled, small pilot RCT	17:16	NR	Sustained reduction in constipation severity with improved quality of life
Xiao *et al.*[157]	TENS	IBS-D, IBS-C, FC	open-label, exploratory research	IBS-D:IBS-C:FC:HC=24:20:30:30	LI4,ST36, UB57	Clinical efficacy observed in IBS-D.
Xiao *et al.*[158]	TEA	FC	randomized, patient-blinded, sham-controlled, small pilot RCT	27:269:9	ST36	Improved bowel function associated with enhanced rectal sensation and parasympathetic activity
Coban *et al.*[159]	IFC	IBS	double-blind, randomized, sham-controlled, small pilot RCT	29:29	Abdominal/paraspinal(T9 and L2)	Significant improvement in IBS symptoms and quality of life

CC: Chronic constipation; CFC: chronic functional constipation; CSFC: chronic severe functional constipation; EA: electroacupuncture; FC: functional constipation; FD: functional dyspepsia; IBD: inflammatory bowel disease; IBS: irritable bowel syndrome; IBS-C: constipation predominant irritable bowel syndrome; IBS-D: diarrhea-predominant irritable bowel syndrome; IFC: interferential current; IFT: interferential therapy; PENFS: percutaneous electrical nerve field stimulation; SCC: severe chronic constipation; STC: slow transit constipation; taVNS: transcutaneous auricular vagus nerve stimulation; TEA: transcutaneous electrical acustimulation; TENS: transcutaneous electric nerve stimulation; TES: transcutaneous electrical stimulation; tSNS: transcutaneous sacral nerve stimulation; tTNS: transcutaneous tibial nerve stimulation

Table 3. ANS interventions in liver diseases

Author	Intervention	Disease	Study design	Participants	Location	Major results
Adams *et al.*[160]	Liver transplantation	FAP	follow-up study	45	NA	Reduction in circulating mutant transthyretin and slowed axonal degeneration, with limited impact on autonomic dysfunction and persistence of systemic symptoms
Zhao *et al.*[161]	EA	MASLD	randomized, patient-blinded, sham-controlled, RCT	72:72	CV12, CV4, ST25, SP15, LR13, LI4, ST36, SP6, LR3	ChiCTR2200060353
Fu *et al.*[162]	EA	MASLD	randomized, sham-controlled, small pilot RCT	49:49	RN12, RN9, CV4, RN6, ST24, ST25, SP15, GB26, ST40, ST36, SP6	ChiCTR2300075701
Metz *et al.*[67]	Metreleptin	MASLD	randomized, placebo-controlled, small pilot RCT	13:9	NA	Anti-steatotic effects mediated via central-vagal-hepatic signaling, independent of caloric intake
Jakovljevic *et al.*[163]	Resistance exercise	MASLD	randomized, controlled, small pilot RCT	8:9	NA	Improved autonomic balance and hemodynamic responses during submaximal exercise

DHA: Docosahexaenoic; EA: electroacupuncture; EPA: eicosatetraenoic; FAP: familial amyloid polyneuropathy; IR: insulin resistance; MASLD: metabolic dysfunction-associated steatotic liver disease; MR: microvascular reactivity; VPT: vibration perception threshold

Beyond neural stimulation itself, combined microbiota-neural interventions show synergistic potential for metabolic improvement. The gut microbiota, via metabolites like SCFAs, interacts with the immune system and profoundly influences vagal activity, forming a bidirectional "microbiota-gut-brain axis" that regulates host metabolism. For instance, heat-inactivated Pediococcus acidilactici R037 enhances sympathetic activity in white adipose tissue, promoting lipolysis and reducing serum TG, suggesting utility in primary prevention

of coronary artery isease and other metabolic conditions[132]. In alcoholic and non-alcoholic fatty liver diseases, reduced vagal tone correlates with gut dysbiosis, impaired barrier function, and liver inflammation, suggesting that restoring parasympathetic balance could be a novel therapeutic avenue for these metabolic liver diseases[133-135]. Future strategies are shifting towards closed-loop bioelectronic medicine systems that dynamically adjust stimulation parameters based on real-time physiological markers, such as heart rate variability, electrogastrogram, and inflammatory biomarkers, thereby enabling more precise and adaptive neuromodulation.

Challenges and future perspectives

Despite the therapeutic promise, neuromodulation strategies for gut-liver diseases face challenges. A core technical bottleneck is a lack of stimulation specificity. Current studies vary considerably in stimulation frequency, target sites, and treatment duration, highlighting the need for large-scale randomized controlled trials to establish universal protocols[121]. In addition, the metabolic effects of sympathetic activation are highly context dependent. In the tumor microenvironment, SNS-derived NE can promote colorectal cancer progression via a β2-ARs-mediated positive feedback loop that stimulates cancer-associated fibroblasts to secrete nerve growth factor, potentially altering tumor metabolism[136]. These findings emphasize the importance of precise neural targeting and a clearer understanding of the diverse roles of sympathetic signaling in metabolic regulation. This issue is pronounced in the emerging field of "microbiota-neural combination therapy." It remains unclear how neural stimulation precisely affects specific gut microbes and how microbial metabolites feedback onto neural pathways. This knowledge gap hinders the rational design of combined therapies.

Future progress requires integrated multi-organ monitoring systems capable of simultaneously assessing neural activity, gut motility, microbiome, and inflammatory status. In parallel, advances in highly selective neuromodulation technologies are needed to precisely target functional neural subpopulations. Recent studies have shown that distinct sympathetic neuron subsets separately regulate gastrointestinal motility and secretion[137], providing opportunities for more targeted interventions while minimizing off-target effects. Importantly, substantial interspecies differences must also be considered. The distribution of hepatic autonomic innervation differs between rodents and humans, limiting the direct translational applicability of rodent-based findings[44]. Collectively, improving personalized precision medicine approaches is a promising direction in the future. Greater integration of neuroscience, immunology, microbiology, and clinical medicine is essential for developing safe and effective targeted therapies for gut-liver disorders.

CONCLUSION

The ANS functions as a central regulator of the gut-liver axis, integrating metabolic, immune, and microbial homeostasis through its sympathetic, parasympathetic, and enteric branches[5]. Dysregulation of this neural control likely contributes to the shared pathogenesis and frequent co-occurrence of intestinal and hepatic diseases, particularly those involving metabolic dysfunction. Targeting the ANS, especially through vagus nerve modulation such as taVNS, has emerged as a promising therapeutic strategy. However, major challenges exist in stimulation specificity and precise regulation. Further investigation is required to clarify how neural circuits coordinate immune and metabolic signaling across the gut-liver axis. Ultimately, realizing the therapeutic potential of ANS-targeted intervention requires precision medicine approaches targeting the vagus nerve, tailored to complex gut-liver disorders.

DECLARATIONS

Authors' contributions

Writing-original draft, Writing-review & editing: Sun R, He JL, Cheng Y
Writing-review & editing, Project administration: Yu SR, Zhang MN, Yang M, Chen K
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Conflicts of interest

All authors declared that there are no conflicts of interest.

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Consent for publication

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