International Journal of
Molecular Sciences

MDPI

Review

Central Regulation of the Liver–Gut–Spleen Axis: A Systematic Review Without Meta-Analysis

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Abstract

Chronic metabolic and inflammatory disorders are characterized by interconnected neuroendocrine, metabolic, immune, intestinal, and microbial alterations. This systematic review qualitatively synthesizes current evidence regarding the role of central–peripheral signaling pathways in regulating the liver–gut–spleen axis and influencing host–microbiota interactions. A PRISMA-guided literature search identified studies examining hypothalamic–pituitary–adrenal axis activity, autonomic signaling, bile-acid metabolism, splenic neuroimmune responses, intestinal epithelial function, and microbial ecology. Findings from human and experimental studies were synthesized narratively. The reviewed literature consistently indicates that activation of central stress pathways, including hypothalamic–pituitary–adrenal axis signaling, glucocorticoid release, and sympathetic nervous system activity, is associated with changes in hepatic metabolism, bile-acid homeostasis, and splenic immune regulation. These host-derived processes influence intestinal barrier function, epithelial homeostasis, inflammatory signaling, and the luminal environment, thereby shaping microbial community structure and activity. Evidence also supports extensive bidirectional communication among the brain, liver, spleen, gut, and microbiota through neural, endocrine, metabolic, and immune pathways. Collectively, the literature supports a conceptual framework in which the brain functions as a major regulatory hub, while the liver and spleen serve as key metabolic and immune intermediaries within an integrated neuroendocrine–immunometabolic network. However, the available evidence remains heterogeneous and is derived from both observational human studies and experimental models. Further longitudinal and interventional investigations are required to clarify causal relationships and determine the therapeutic relevance of targeting the brain–liver–gut–spleen axis in metabolic and inflammatory diseases.

Keywords: brain-liver-gut-spleen axis; hypothalamic-pituitary-adrenal axis; bile acids; farnesoid X receptor; Takeda G protein-coupled receptor 5; splenic neuroimmune regulation; intestinal epithelium; gut microbiota; neuroendocrine-immunometabolic regulation; metabolic dysfunction-associated steatotic liver disease; growth hormone; insulin-like growth factor-I; prolactin

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Academic Editor: Tomasz Brzozowski

Received: 2 October 2026
Revised: 4 November 2026
Accepted: 9 November 2026
Published: 27 November 2026

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1. Introduction

Metabolic dysfunction-associated steatotic liver disease (MASLD), metabolic syndrome, and other chronic inflammatory disorders are increasingly recognized as systemic conditions involving coordinated interactions among neuroendocrine, metabolic, immune,

intestinal, and microbial networks [1–6]. Traditional explanatory models have frequently focused on either individual organs or the gut microbiota as primary drivers of disease [7–9]. Although these frameworks have generated important insights, they do not fully explain the coordinated alterations in stress responses, hepatic metabolism, immune activation, intestinal function, and microbial ecology observed across experimental and clinical studies [10–13]. Emerging evidence supports extensive bidirectional communication among the brain, liver, spleen, gut, and microbiota through interconnected neural, endocrine, metabolic, and immune pathways [14–18]. Central regulation by the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system influences peripheral organ function through glucocorticoids, catecholamines, and neuroimmune reflexes [19–22]. These signals contribute to the maintenance of metabolic homeostasis and the modulation of inflammatory responses across multiple tissues [23–26]. The liver occupies a central position within systemic homeostasis because it integrates metabolic, endocrine, immunological, and nutritional functions. Its specialised immune environment supports tolerance, inflammatory regulation, and host defence, reinforcing the concept of the liver as a metabolic–immunological interface. Through reciprocal communication with the gut—via bile acids, metabolites, inflammatory mediators, and microbial products, and with the spleen, via immune-cell trafficking, cytokine signalling, and neuroimmune pathways—the liver contributes to coordinated liver–gut and liver–spleen axes nested within a broader brain–liver–gut–spleen network. Endocrine pathways involving growth hormone (GH), insulin-like growth factor-I, and prolactin further modulate hepatic metabolic and immune programs, supporting an integrated neuroendocrine–hepatic framework relevant to MASLD pathobiology [27,28]. Through the coordinated activity of farnesoid X receptor (FXR), Takeda G protein-coupled receptor 5 (TGR5), cholesterol 7α-hydroxylase (CYP7A1), Kupffer cells, and hepatic stellate cells, the liver translatesneurohormonal signals into metabolic and inflammatory responses [29–36]. In addition, bile acids act as signaling molecules capable of influencing both intestinal physiology and central nervous system activity, suggesting the existence of feedback loops linking hepatic and neurohormonal function [37–40]. The spleen represents a complementary neuroimmune interface connecting autonomic regulation with systemic inflammation [41–43]. Experimental studies have demonstrated that splenic sympathetic innervation influences inflammasome activation, cytokine production, monocyte mobilization, and adaptive immune responses. Although human evidence remains comparatively limited, these observations suggest that splenic neuroimmune mechanisms may contribute to the amplification and maintenance of chronic inflammatory states [41–43]. The intestinal tract constitutes a major site where hepatic and immune signals converge. Bile-acid composition, cytokine gradients, epithelial turnover, oxidative balance, and barrier integrity collectively shape the intestinal environment and influence microbial community structure and function [44–49]. Conversely, microbial metabolites, including short-chain fatty acids, indoles, phenylpropanoids, and bile-acid derivatives, can modulate host metabolism, immune signalling, and central–peripheral signaling pathways, highlighting the reciprocal nature of host–microbiota interactions [50–55]. Despite growing recognition of these interconnected pathways, the relative contribution of neuroendocrine regulation and microbial dysbiosis to disease initiation remains incompletely understood. In MASLD and related disorders, alterations in stress signalling, hepatic metabolism, immune activation, epithelial function, and microbial composition frequently coexist, making it difficult to distinguish primary drivers from secondary adaptations [56–60]. Rather than operating as isolated mechanisms, central central–peripheral signaling pathways and host–microbiota interactions likely form an integrated network characterized by both hierarchical organization and bidirectional feedback regulation. Accordingly, the aim of this systematic review was to synthesize current evidence regarding the role of central central–peripheral signaling

pathways in coordinating communication along the liver–gut–spleen axis. Particular attention was given to interactions involving HPA-axis activity, autonomic regulation, hepatic bile-acid metabolism, splenic neuroimmune responses, intestinal epithelial biology, and gut microbial ecology. By integrating findings from human and animal studies, this review evaluates evidence supporting a hierarchical organization of these systems while acknowledging the bidirectional feedback mechanisms that contribute to physiological homeostasis and disease progression.

2. Materials and Methods

2.1. Study Design and Registration

This study was conducted as a qualitative systematic review in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The review aimed to synthesize and critically interpret the available evidence regarding the role of central–peripheral signaling pathways in regulating interactions among the brain, liver, spleen, gut, and microbiota. The objective was to synthesize the available evidence on neuroendocrine regulation of the liver–gut–spleen axis, with particular emphasis on interactions among central stress pathways, hepatic metabolism, splenic immune responses, intestinal physiology, and gut microbial ecology. This registration is waiting for approval from its contributors. Once approved, the registration will remain private until the embargo ends. The study identification, screening, eligibility assessment, and inclusion processes are summarized in the PRISMA flow diagram (Figure 1).

2.2. Literature Search Strategy

A comprehensive literature search was conducted in PubMed/MEDLINE, Embase, Web of Science, Scopus, and Google Scholar to identify relevant publications published between January 1990 and July 2026. The search strategy combined terms related to neuroendocrine regulation, hepatic metabolism, splenic immunity, intestinal physiology, bile acid signaling, and microbial ecology. Representative search terms included "hypothalamic–pituitary–adrenal axis," "HPA axis," "glucocorticoids," "sympathetic nervous system," "stress signaling," "farnesoid X receptor," "FXR," "Takeda G protein-coupled receptor 5," "TGR5," "cholesterol 7α-hydroxylase," "CYP7A1," "Kupffer cells," "splenic sympathetic innervation," "NLRP3 inflammasome," "interleukin-6," "interleukin-23," "tumor necrosis factor-alpha," "intestinal epithelial barrier," "tight junctions," "bile acid metabolism," "gut microbiota," "microbiome," "short-chain fatty acids," "indoles," and "host–microbiota interactions." The reference lists of relevant articles and review papers were also manually screened to identify additional potentially eligible studies.

2.3. Eligibility Criteria

Studies were considered eligible for inclusion if they met the following criteria: (1) they investigated neuroendocrine, metabolic, immune, epithelial, or microbiota-related mechanisms relevant to the liver–gut–spleen axis; (2) they employed human clinical, observational, interventional, or translational study designs, or mechanistic animal experiments; (3) they evaluated at least one component of HPA axis activity, autonomic regulation, bile acid metabolism, splenic immune function, intestinal epithelial biology, or microbial ecology; and (4) they were published in peer-reviewed journals and available in English. Studies were excluded if they were (1) conference abstracts lacking sufficient methodological information; (2) commentaries, editorials, or opinion articles that did not provide primary data or substantial mechanistic evidence relevant to the review objectives; or (3) studies that did not address interactions involving neuroendocrine regulation, the liver, the spleen, the intestine, or the gut microbiota.

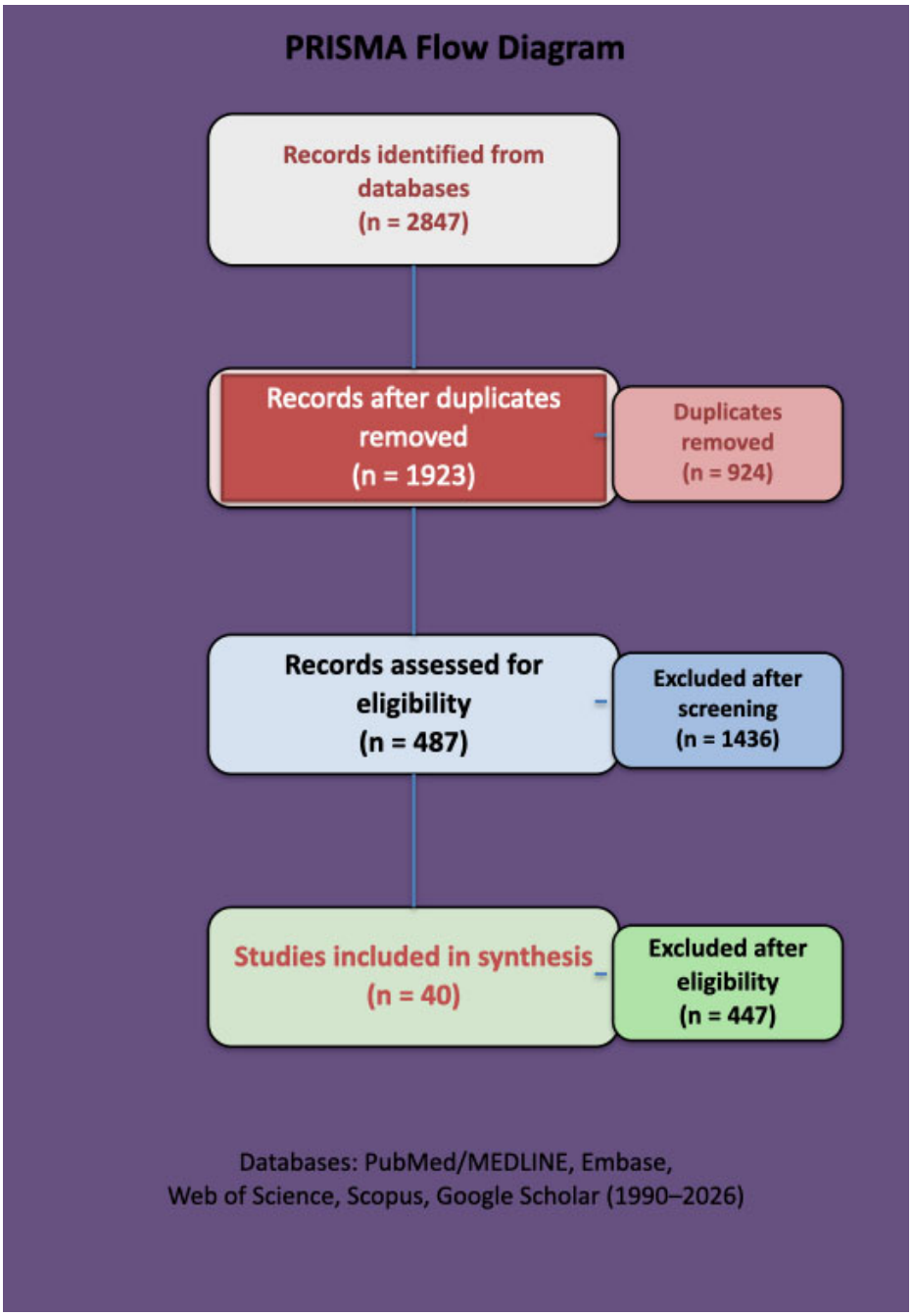


Figure 1. PRISMA flow diagram summarizing the literature search and study selection process across the databases (PubMed/MEDLINE, Embase, Web of Science, Scopus, and Google Scholar) searched for publications from January 1990 to July 2026. A total of 40 studies were included in the final qualitative synthesis.

2.4. Study Selection

Titles and abstracts retrieved from the literature search were screened for relevance. Full texts of potentially eligible articles were subsequently reviewed and assessed according to the predefined inclusion and exclusion criteria. Discrepancies regarding study eligibility were resolved through discussion among the authors until consensus was reached.

2.5. Data Extraction

Data extraction was conducted manually using a standardized data extraction form. Information collected included study characteristics (authors, year, study design, population, and setting) and key qualitative findings relevant to the review objectives. Emphasis was placed on identifying reported interactions among neuroendocrine signaling, hepatic metabolism, splenic immune regulation, intestinal physiology, and gut microbial ecology.

2.6. Data Synthesis

Given the substantial heterogeneity of study designs, experimental methodologies, biological endpoints, and reported outcomes, quantitative meta-analysis was not considered appropriate. Therefore, findings were synthesized qualitatively. Evidence from human studies and animal models was integrated narratively to identify recurring mechanistic patterns and relationships among neuroendocrine signaling, hepatic metabolic regulation, splenic immune activation, intestinal epithelial responses, and microbial ecosystem dynamics. The review specifically examined evidence supporting both hierarchical regulatory organization and bidirectional feedback interactions within the brain–liver–gut–spleen axis.

2.7. Assessment of Evidence

Given the qualitative nature of the review and the heterogeneity of the included studies, no formal risk-of-bias assessment or quantitative quality scoring was performed. Instead, the interpretation of findings was based on methodological transparency, biological plausibility, consistency across studies, and concordance between human and experimental evidence.

3. Results

3.1. Study Characteristics

The included literature comprised observational human studies, interventional clinical investigations, translational research, and mechanistic animal experiments. The included studies investigated multiple components of the brain–liver–gut–spleen axis, including neuroendocrine regulation, hepatic metabolism, splenic immune function, intestinal physiology, and host–microbiota interactions. The distribution of evidence across biological compartments and principal signaling pathways is summarized in Table 1.

Table 1. Representative studies and reviews included in the qualitative synthesis. The table summarizes selected publications contributing to the conceptual framework of the brain–liver–gut–spleen axis, including mechanistic animal studies, human observational investigations, longitudinal multi-omics cohorts, translational research, and narrative reviews. These publications address interactions among central and peripheral signaling pathways, hepatic bile-acid metabolism, splenic immune regulation, intestinal epithelial physiology, and gut microbial ecology. Human investigations primarily provide evidence of associations, whereas several proposed mechanisms, particularly those involving neural regulation of splenic immunity, derive predominantly from preclinical studies. The included publications examine individual components or pairwise interactions and do not necessarily demonstrate an integrated four-organ pathway. For reviews, the species column indicates the evidence discussed rather than a newly recruited study population.

Reference	Study Type	Species	Main Biological System	Principal Findings Relevant to the Liver–Gut–Spleen Axis
Chrousos, 2009 Nat. Rev. Endocrinol. [1]	Review	Human-focused; includes animal evidence	Neuroendocrine–immune system	Reviewed how dysregulation of the stress system, including the hypothalamic–pituitary–adrenal (HPA) axis, contributes to metabolic and inflammatory disorders.

Table 1. *Cont.*

Reference	Study Type	Species	Main Biological System	Principal Findings Relevant to the Liver–Gut–Spleen Axis
Bhatt and Franco, 2025. [4]	Review	Human-focused; includes comparative animal evidence	Glucocorticoid–immune signaling	Reviewed the context-dependent permissive and suppressive effects of endogenous glucocorticoids on immunity, distinguishing physiological actions from the effects of pharmacological glucocorticoids.
Kelly et al., 2022 [6]	Review	Human/animal evidence	Neuro immune regulation	Reviewed therapeutic approaches targeting the inflammatory reflex to modulate inflammatory responses.
Zhou et al., 2019 [2]	Longitudinal observational multi-omics study	Human	Host–microbiome interactions	Characterized longitudinal host and microbial changes in individuals with prediabetes, providing a framework for studying coordinated metabolic, immune, and microbial responses.
Lloyd-Price et al., 2019 [3]	Longitudinal multi-omics cohort study	Human	Gut microbiome–host inflammatory interactions	Characterized changes in microbial community composition, microbial activity, and host molecular profiles associated with inflammatory bowel disease activity.
Li et al., 2026 [10]	Review	Human/animal and in vitro evidence	Hepatic and intestinal FXR signaling	Reviewed FXR functions in bile-acid homeostasis, inflammation, fibrosis, and lipid and glucose metabolism, together with advances in FXR-targeted drug development.
Chaudhari et al., 2021 [11]	Experimental translational study	Human and mouse; in vitro models	Gut bile acids–TGR5–metabolic signaling	Identified cholic acid-7-sulfate as a gut-restricted TGR5 agonist increased after sleeve gastrectomy; demonstrated stimulation of GLP-1 secretion and improved glucose tolerance in insulin-resistant mice.
Katafuchi and Makishima, 2022 [16]	Review	Human/animal evidence	Entero-hepatic FXR–FGF15/19 signaling	Reviewed how intestinal FXR activation induces FGF15/19 signaling to hepatic FGFR4–β-klotho, regulating bile-acid synthesis and other aspects of hepatic metabolism.
Mota and Madden, 2022 *Am*. J. Physiol. Regul. Integr. Comp. Physiol. [12]	Review	Predominantly animal evidence, with clinical implications	Brain–spleen neuro-immune communication	Reviewed autonomic regulation of splenic immune activity and the potential therapeutic use of neural pathways controlling inflammatory responses.
Yu et al., 2022 Neuron [34]	Experimental mechanistic study with human genetic and patient analyses	Primarily rat; additional mouse, *Drosophila*, and human evidence	Sympathetic neurons–splenic immune cells	Demonstrated that neuron-derived neuropeptide Y modulates splenic lymphocyte activation and proliferation and attenuates inflammatory responses, supporting neural control of splenic immunity. pubmed.ncbi.nlm.nih

Table 1. *Cont.*

Reference	Study Type	Species	Main Biological System	Principal Findings Relevant to the Liver–Gut–Spleen Axis
Coll and Schroder, 2025 Nat. Rev. Immunol [13]	Review	Human/animal evidence	Inflammasomes and innate immunity	Reviewed inflammasome components as therapeutic targets in inflammatory disease, providing mechanistic context for innate immune signaling.
Turner, 2009 Nat.Rev. Immunol [14]	Review	Human/animal evidence	Intestinal epithelial barrier	Reviewed mechanisms controlling intestinal mucosal barrier function and the contribution of barrier dysfunction to disease.
Song et al., 2025 [35]	Review	Human/animal and in vitro evidence	Bile acids–intestinal FXR/TGR5–barrier function	Reviewed how bile-acid metabolism and signaling through FXR and TGR5 influence intestinal epithelial integrity, mucosal immunity, and barrier homeostasis.
Lamas et al., 2017 Nat. Med. [17]	Experimental mechanistic study with human translational analyses	Mouse and human	Gut microbiota–tryptophan metabolism–mucosal immunity	Linked CARD9-associated alterations in microbial tryptophan metabolism to reduced aryl hydrocarbon receptor ligand availability and impaired mucosal immune protection.
Pedersen et al., 2016 Nature [20]	Human observational study with experimental validation	Human and mouse	Gut microbiota–circulating metabolites–insulin sensitivity	Linked microbial amino-acid biosynthetic potential and circulating branched-chain amino acids with insulin resistance, with experimental evidence supporting a contribution of selected gut bacteria to metabolic dysfunction.
Chen et al., 2023 Front. Endocrinol [32]	Review	Human/animal evidence	Bile-acid signaling–gut–brain link	Reviewed proposed links between bile-acid signaling and anxiety, providing a conceptual connection between enterohepatic metabolism and neurobehavioral regulation.

3.2. Neuroendocrine Regulation as an Upstream Modulator of Peripheral Organ Function

Across the reviewed literature, activation of central central–peripheral signaling pathways was consistently associated with metabolic and immunological alterations in peripheral organs. Human and experimental studies demonstrated that HPA-axis activation, glucocorticoid signaling, and sympathetic nervous system activity influence inflammatory responses, metabolic homeostasis, and tissue remodeling. The available evidence supports a role for central stress-related pathways in regulating hepatic metabolism, splenic immune activity, and intestinal physiology. However, the strength of evidence varies across biological compartments, and definitive causal relationships remain incompletely established, particularly in humans.

3.3. Evidence Linking Neuroendocrine Signaling and Hepatic Regulation

Several studies identified the liver as a major target of neuroendocrine regulation. Evidence demonstrated interactions between stress-related pathways and hepatic bile-acid metabolism, including modulation of FXR, TGR5, and CYP7A1 signaling. Additional studies reported associations between neuroendocrine activity and hepatic immune responses involving Kupffer cells, stellate-cell activation, and inflammatory signaling pathways. Collectively, these findings support the concept that neuroendocrine signals can influence both metabolic and immunological functions of the liver.

3.4. Evidence Supporting a Splenic Neuroimmune Interface

The reviewed literature highlighted the spleen as an important interface between neural regulation and immune activity. Experimental studies demonstrated that sympathetic innervation of the spleen can modulate inflammasome activation, cytokine production, monocyte mobilization, and adaptive immune responses. Evidence supporting these mechanisms is strongest in animal models, whereas corresponding human data remain comparatively limited. Nevertheless, available studies suggest that splenic neuroimmune pathways may contribute to systemic inflammatory amplification in chronic metabolic and inflammatory disorders.

3.5. Interactions with Intestinal Physiology

Studies examining intestinal biology reported associations between host-derived metabolic and immune signals and alterations in epithelial function. Changes in bile-acid composition, inflammatory mediators, epithelial turnover, oxidative balance, and barrier integrity were repeatedly linked to modifications of the intestinal environment. FXR-FGF19 signaling, TGR5-mediated pathways, and cytokine-dependent regulation of epithelial homeostasis emerged as recurring mechanisms through which hepatic and immune signals may influence intestinal physiology.

3.6. Host–Microbiota Interactions

The reviewed evidence demonstrated extensive bidirectional communication between host physiology and gut microbial communities. Microbial metabolites, including short-chain fatty acids, indoles, phenylpropanoids, and bile-acid derivatives, were reported to influence metabolic, immune, and neuroendocrine processes. At the same time, multiple studies showed that alterations in bile-acid composition, epithelial barrier function, inflammatory signaling, and nutrient availability can reshape microbial community structure and function. Collectively, these observations suggest that microbial ecology is closely linked to host neurohormonal and immunometabolic status, although the directionality of these interactions remains incompletely resolved.

3.7. Integration of Evidence Across the Liver–Gut–Spleen Axis

Taken together, the reviewed literature supports the existence of extensive communication among the brain, liver, spleen, gut, and microbiota through interconnected neural, endocrine, metabolic, and immune mechanisms. The distribution of evidence across biological compartments and the principal signaling pathways represented in the included studies are summarized in Table 2. Many studies suggest that neuroendocrine and host-derived metabolic alterations may contribute to downstream changes in intestinal physiology and microbial composition. However, substantial evidence also supports reciprocal feedback interactions whereby microbial metabolites, immune mediators, bile acids, and peripheral organ signals influence central and peripheral regulatory pathways. Therefore, the available evidence is most consistent with an integrated and dynamic network characterized by both hierarchical organization and bidirectional communication rather than a strictly linear cascade.

Table 2. Evidence coverage and principal pathways relevant to the proposed brain–liver–gut–spleen axis. The matrix summarizes the human and animal evidence represented in selected original investigations and reviews, together with the biological systems addressed. In the biological-system columns, "Yes" indicates a directly investigated system in an original study or a central topic in a review; "Indirect" indicates a contextual or downstream relationship rather than a primary focus; and "No" indicates that the system is not a principal focus of the publication, not that a biological interaction is absent. For reviews, the human and animal columns describe the evidence discussed rather than newly recruited participants or experimental animals. Coverage does not imply direct demonstration of an integrated four-organ pathway.

Study	Human	Animal	Brain/Neuroendocrine	Liver	Spleen	Gut	Microbiota	Main Pathway
Chrousos, 2009 pmc.ncbi.nlm.nih [1];	Yes	Yes	Yes	Indirect	No	Indirect	No	HPA-axis activation and stress-system regulation
Bhatt and Franco, 2025 pmc.ncbi.nlm.nih [4];	Yes	Yes	Yes	Indirect	Indirect	Indirect	No	Context-dependent glucocorticoid regulation of immune responses
Kelly et al., 2022 pubmed.ncbi.nlm.nih [6];	Yes	Yes	Yes	No	Yes	Indirect	No	Inflammatory reflex and neural regulation of inflammation
Zhou et al., 2019 pmc.ncbi.nlm.nih [2];	Yes	No	No	Indirect	No	Yes	Yes	Longitudinal host–microbiome and metabolic interactions
Lloyd-Price et al., 2019 pmc.ncbi.nlm.nih [3];	Yes	No	No	No	No	Yes	Yes	Intestinal inflammation and microbial ecosystem remodeling
Li et al., 2026 pmc.ncbi.nlm.nih [10];	Yes	Yes	No	Yes	No	Yes	Indirect	FXR-targeted regulation of bile-acid homeostasis and metabolism
Chaudhari et al., 2021; https://doi.org/10.1016/j.chom.2020.12.004 [11]	Yes	Yes	No	Indirect	No	Yes	No	Gut-restricted TGR5 activation and GLP-1-dependent metabolic regulation
Katafuchi and Makishima, 2022 IJMS [16];	Yes	Yes	No	Yes	No	Yes	Indirect	FXR–FGF15/19 enterohepatic feedback signaling
Mota and Madden, 2022 Am. J. Physiol. Regul. Integr. Comp. Physiol. [12];	Yes	Yes	Yes	No	Yes	No	No	Autonomic regulation of splenic immune responses
Yu et al., 2022 Neuron [34];	Yes	Yes	Yes	No	Yes	No	No	Neuron-derived neuropeptide Y regulation of splenic immunity
Coll and Schroder, 2025 Nat. Rev. Immunol [13];	Yes	Yes	No	Indirect	Indirect	Indirect	—	Inflammasome components as targets for inflammatory disease
Turner, 2009 Am. J. Physiol. Regul. Integr. Comp. Physiol. [14];	Yes	Yes	No	No	No	Yes	Indirect	Intestinal epithelial barrier regulation
Song et al., 2025 pubmed.ncbi.nlm.nih [35];	Yes	Yes	No	Indirect	No	Yes	Yes	Bile-acid–FXR/TGR5 regulation of intestinal barrier function
Lamas et al., 2016 Nat. Med. [17];	Yes	Yes	No	No	No	Yes	Yes	CARD9–microbial tryptophan metabolism–AhR–mucosal immunity
Pedersen et al., 2016 Nature [20];	Yes	Yes	No	Indirect	No	Yes	Yes	Microbial branched-chain amino-acid metabolism and insulin resistance
Chen et al., 2023 Front. Endocrinol [32];	Yes	Yes	Yes	Indirect	No	Yes	Yes	Bile-acid signaling and microbiota–gut–brain communication in anxiety
McMillin et al., 2015 pubmed.ncbi.nlm.nih [33];	No	Yes	Yes	Yes	No	No	No	Hypothalamic bile-acid signaling and suppression of the HPA axis

Table 2. *Cont.*

Study	Human	Animal	Brain/Neuroendocrine	Liver	Spleen	Gut	Microbiota	Main Pathway
Pathak et al., 2018 Hepatology [41];	No	Yes	No	Yes	No	Yes	Yes	Intestinal FXR–microbiota–TGR5/GLP-1 metabolic signaling
Yao et al., 2018 eLife [39]	No	Yes	No	Yes	No	Yes	Yes	Microbial bile salt hydrolase activity, bile-acid composition, and host metabolism

4. Discussion

The evidence reviewed in this systematic review supports a conceptual model in which central–peripheral signaling pathways play an important role in coordinating metabolic, immune, and intestinal responses across multiple organs. Collectively, the literature suggests that the brain functions as a major regulatory hub, while the liver and spleen act as key metabolic and immune intermediaries linking neurohormonal activity to intestinal physiology and microbial ecology [1–20]. A recurring observation across both experimental and clinical studies is that activation of the HPA axis and the sympathetic nervous system is associated with alterations in hepatic metabolism, bile-acid homeostasis, immune regulation, and intestinal function [1–6]. Through FXR- and TGR5-dependent pathways, neurohormonal and metabolic signals may influence bile-acid composition, epithelial integrity, and inflammatory responses, thereby contributing to the intestinal environment in which microbial communities reside [10,11,15,16,25,39].

The liver emerges as a central integrative organ within this framework. Consequently, communication occurs not only along the brain–liver–gut axis but also through reciprocal liver–spleen and liver–gut pathways, while gut-derived signals and microbial metabolites exert feedback effects on both hepatic and central regulatory mechanisms. These multidirectional interactions support a network model rather than a hierarchical linear cascade. Beyond its established metabolic functions, the liver participates in immune regulation through interactions involving Kupffer cells, stellate cells, bile acids, and cytokine networks. Growing evidence also indicates the existence of bidirectional communication between the liver and the central nervous system, including feedback mechanisms mediated by bile acids and related signaling molecules [28–31]. These observations support the view that hepatic responses are both influenced by and capable of influencing neurohormonal activity. The spleen represents another important component of the axis. Experimental studies have demonstrated that sympathetic innervation can modulate inflammasome activation, cytokine production, monocyte mobilization, and T-cell polarization [12,13,32,40]. However, it should be acknowledged that much of the mechanistic evidence supporting splenic neuroimmune regulation derives from animal models, whereas direct confirmation in human metabolic diseases remains comparatively limited. Consequently, the spleen should be viewed as a biologically plausible and increasingly supported component of the axis, although further translational validation is required.

The reviewed literature also highlights extensive communication between host physiology and the gut microbiota. Microbial metabolites, including short-chain fatty acids, indoles, phenylpropanoids, and bile-acid derivatives, have been shown to influence immune function, metabolism, and neurohormonal signaling [17–22,35–39]. Conversely, host-derived factors such as bile-acid composition, epithelial turnover, nutrient availability, and inflammatory mediators have profound effects on microbial community structure and function. Together, these findings support a dynamic process of reciprocal adaptation between host and microbiota.

One of the central themes emerging from this review is that neurohormonal and host-derived metabolic alterations may represent important upstream determinants of intestinal

ecosystem remodeling in chronic disease. Nevertheless, the available evidence does not support a strictly linear model. Rather, the brain, liver, spleen, gut, and microbiota appear to form an integrated biological network characterized by multiple feedback loops operating simultaneously across neural, endocrine, metabolic, and immune domains.

This interpretation is consistent with current concepts of systems biology and physiological homeostasis.

The review also has potential implications for understanding MASLD, metabolic syndrome, and related inflammatory disorders. MASLD and metabolic syndrome are highly heterogeneous conditions whose clinical expression and progression are influenced by age, sex, dietary habits, circadian rhythms, physical activity, sleep quality, psychosocial stress, medication exposure, and disease stage. In addition, endocrine mediators such as GH, insulin-like growth factor-I, and prolactin contribute to the regulation of hepatic metabolism and immune function, further emphasizing the complexity of the neuroendocrine-immunometabolic networks underlying these disorders. These considerations reinforce the need for integrated rather than organ-centred models of disease pathogenesis.

Several studies suggest that therapeutic approaches targeting upstream regulatory pathways, including neurohormonal signaling, autonomic activity, bile-acid metabolism, and immunometabolic regulation, may exert broader systemic effects than interventions directed exclusively at the intestinal microbiota [25–27]. However, the superiority of one therapeutic strategy over another has not been definitively established and remains an important subject for future investigation.

Overall, the available literature supports a framework in which central neuroendocrine regulation, hepatic metabolism, splenic immunity, intestinal physiology, and microbial ecology function as interconnected components of a multidirectional network (Figure 2). Recognizing these interactions may facilitate the development of more integrated approaches to the prevention and treatment of chronic metabolic and inflammatory diseases.

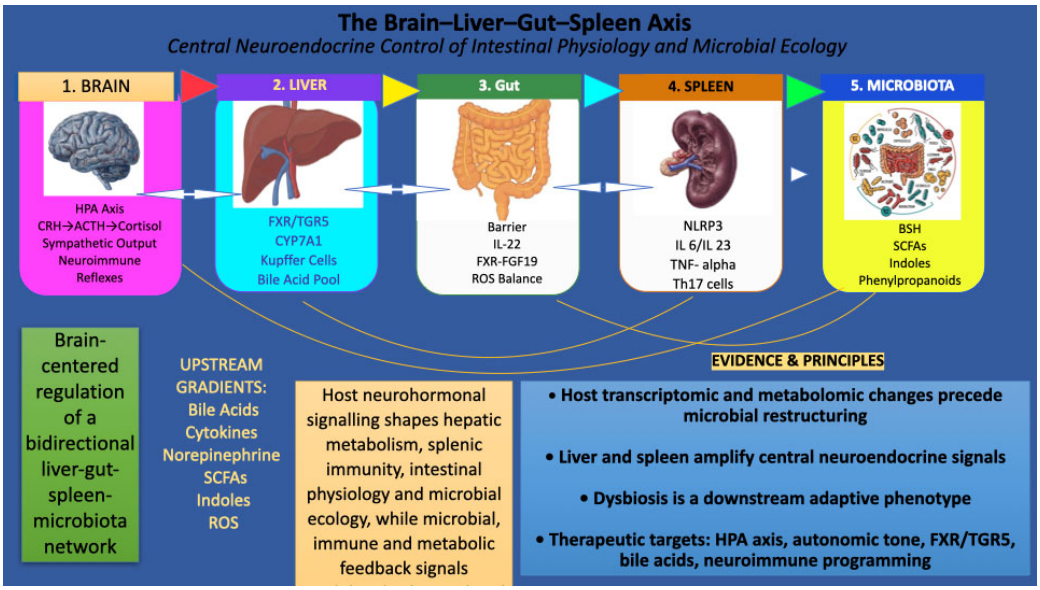


Figure 2. The Brain–Liver–Gut–Spleen Axis: Brain-centered Neuroendocrine Regulation within a Bidirectional Immunometabolic Network. The biological interactions illustrated in this figure were derived from evidence identified through systematic searches of PubMed/MEDLINE, Embase, Scopus, Google Scholar and Web of Science databases and integrated from the literature included in this review.

The brain acts as a major regulatory hub through activation of the HPA axis, sympathetic nervous system output, and neuroimmune reflexes. These pathways influence hepatic metabolism, bile-acid homeostasis, and immune regulation through FXR, TGR5, CYP7A1, Kupffer cells, and the hepatic bile-acid pool. The liver communicates bidirectionally with the gut via bile acids, metabolic mediators, immune signals, and the FXR-FGF19 axis, while also interacting with the spleen through inflammatory and immunometabolic pathways. Splenic neuroimmune responses, including NLRP3 inflammasome activation and cytokine production (IL-6, IL-23, TNF-α), contribute to systemic immune regulation. Intestinal physiology is shaped by bile-acid signalling, epithelial barrier integrity, oxidative balance, and immune mediators. Gut microbial communities generate metabolites, including short-chain fatty acids (SCFAs), indoles, phenylpropanoids, and bile-acid derivatives, which influence hepatic, intestinal, immune, and central neuroendocrine functions. Collectively, the brain, liver, spleen, gut, and microbiota form an integrated multidirectional network characterized by continuous neural, endocrine, metabolic, immune, and microbial feedback loops. Although reciprocal communication occurs among all components of the axis, the brain remains a major upstream coordinator of systemic homeostasis. Abbreviations: ACTH, adrenocorticotropic hormone; BSH, bile salt hydrolase; CRH, corticotropin-releasing hormone; CYP7A1, cholesterol 7α-hydroxylase; FXR, farnesoid X receptor; FXR–FGF19, farnesoid X receptor–fibroblast growth factor 19 signaling; HPA axis, hypothalamic–pituitary–adrenal axis; IL-6, interleukin-6; IL-22, interleukin-22; IL-23, interleukin-23; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; TGR5, Takeda G protein-coupled receptor 5; Th17, T helper 17 cells; TNF-α, tumor necrosis factor alpha.

4.1. Limitations

Several limitations should be considered when interpreting the findings of this systematic review. First, the included studies were highly heterogeneous with respect to design, disease populations, biological endpoints, and analytical approaches, which precluded formal quantitative meta-analysis. Consequently, the conclusions rely on qualitative synthesis of the available evidence. Second, many mechanistic pathways discussed within the brain–liver–gut–spleen axis, particularly those involving splenic sympathetic innervation, neuroimmune reflexes, inflammasome activation, and monocyte mobilization, have been characterized predominantly in animal models. Their relevance to human disease therefore requires further validation. Third, most human studies were observational, limiting the ability to establish causal relationships between neuroendocrine activation, hepatic metabolism, immune responses, intestinal physiology, and microbial ecology. The observed associations are likely influenced by complex bidirectional interactions and potential confounding factors. Furthermore, MASLD and metabolic syndrome are biologically heterogeneous disorders influenced by demographic, behavioral, endocrine, environmental, and disease-stage-related factors that were not uniformly assessed across the included studies.

Fourth, publication bias cannot be excluded, as studies reporting significant neuroendocrine, metabolic, or microbiome-related findings may be overrepresented in the literature. Finally, relatively few studies simultaneously examined neuroendocrine, hepatic, splenic, intestinal, and microbial variables within a single integrated framework. Consequently, the proposed brain–liver–gut–spleen axis should be regarded as a biologically plausible and increasingly supported model rather than a definitively established causal hierarchy.

4.2. Future Directions

Future research should prioritize longitudinal and interventional studies capable of clarifying the temporal and causal relationships among neuroendocrine regulation, hepatic metabolism, splenic immune responses, intestinal physiology, and gut microbial ecology. Although existing evidence supports extensive communication across these systems, the sequence of events leading to disease initiation and progression remains incompletely understood. Particular attention should be given to studies evaluating the effects of HPA axis

activation, autonomic nervous system modulation, and neuroimmune reflexes on hepatic bile-acid metabolism and intestinal barrier function. Simultaneous assessment of neuroendocrine biomarkers, bile-acid profiles, immune mediators, and microbial metabolites within the same study populations may help define the relative contribution of individual components of the brain–liver–gut–spleen axis. Additional translational studies are needed to validate in humans several mechanisms currently supported primarily by animal models, including splenic sympathetic regulation of cytokine production, inflammasome activation, monocyte mobilization, and neuroimmune communication pathways. Greater integration of clinical and experimental data will be essential for establishing the relevance of these mechanisms to metabolic syndrome, and related disorders. Furthermore, scientists need to further investigate how liver-derived immunological and nutritional signals influence spleen function and gut microbial ecology, and how these reciprocal pathways contribute to MASLD progression.

5. Conclusions

The brain–liver–gut–spleen axis is best understood as a bidirectional neurohormonal–immunometabolic network, not a linear pathway. Central stress and autonomic signals modulate hepatic bile-acid metabolism and splenic immunity, which in turn reshape intestinal physiology and microbiota; microbial metabolites reciprocally influence the brain and peripheral organs. This framework positions the brain as a regulatory hub and the liver and spleen as metabolic–immune intermediaries in MASLD and related disorders. Human causality remains unproven, so targeting the axis requires longitudinal and interventional validation.

Author Contributions: Conceptualization, G.T.; methodology, G.T. and V.C.; formal analysis, G.T.; investigation, G.T. and V.C.; writing—original draft preparation, G.T.; writing—review and editing, G.T. and V.C.; visualization, G.T.; supervision, G.T. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

Abbreviations

ACTH, adrenocorticotropic hormone; BSH, bile salt hydrolase; CYP7A1, cholesterol 7α-hydroxylase; FXR, farnesoid X receptor; FGF19, fibroblast growth factor 19; GH, growth hormone; HPA axis, hypothalamic–pituitary–adrenal axis; IGF-I, insulin-like growth factor I; IL-6, interleukin-6; IL-22, interleukin-22; IL-23, interleukin-23; MASLD, metabolic dysfunction-associated steatotic liver disease; NLRP3, NOD-, LRR- and pyrin domain-containing protein 3; ROS, reactive oxygen species; SCFAs, short-chain fatty acids; SNS, sympathetic nervous system; TGR5, Takeda G protein-coupled receptor 5; Th17, T helper 17 cells; TNF-α, tumor necrosis factor alpha.

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