

OSOVINA CREVA–JETRA–NERVNI SISTEM U NEUROREGENERACIJI I NEURODEGENERACIJI: MEHANISTIČKI PUTEVI, TERAPIJSKI POTENCIJAL I TRANSLACIONI ZNAČAJ

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SAŽETAK

Crevna mikrobiota sve više se prepoznaje kao značajan regulator sistemskog metabolizma, imunskog odgovora i funkcije nervnog sistema. Interakcije između creva, jetre, imunskog i nervnog sistema mogu stoga predstavljati međusobno povezanu biološku mrežu od značaja za neurodegeneraciju, neuroregeneraciju i druga hronična oboljenja. Cilj rada bio je da se prikažu dostupni dokazi o osovini creva–jetra–nervni sistem i da se proceni njen potencijalni značaj za neuroinflamaciju, neurodegeneraciju, regeneraciju perifernih nerava, degeneraciju intervertebralnog diska, metabolička oboljenja jetre i razvoj novih terapijskih pristupa. Sproveden je narativni pregled literature korišćenjem baza PubMed/MEDLINE, Scopus, Web of Science i Google Scholar. Pretraga je obuhvatila publikacije dostupne do maja 2026. godine, koje su se bavile osovino creva–jetra–nervni sistem, crevnom mikrobiotom, mikrobnim metabolitima, signalizacijom žučnih kiselina, disfunkcijom crevne barijere, neuroinflamacijom, neurodegeneracijom, regeneracijom perifernih nerava, degeneracijom intervertebralnog diska i metaboličkim oboljenjima jetre. U pregled su uključene 35 publikacije relevantne za predmet istraživanja. Dostupni dokazi ukazuju na ulogu mikrobnih metabolita, uključujući kratkolančane masne kiseline, metabolite triptofana i derivate žučnih kiselina, u imunskoj, metaboličkoj i neuralnom signalizaciji. Disbioza i narušena funkcija crevne barijere mogu doprineti sistemskoj inflamaciji i poremećaju komunikacije između creva i jetre. Postoje dokazi o povezanosti promena crevne mikrobiote sa degeneracijom intervertebralnog diska. Prebiotici, probiotici, sinbiotici, transplantacija fekalne mikrobiote, postbiotici, mikrobn metaboliti i pristupi usmereni na signalizaciju žučnih kiselina predstavljaju potencijalne terapijske strategije. Ipak, većina dokaza o neurološkim i neuroregenerativnim efektima potiče iz eksperimentalnih istraživanja, dok su direktni klinički dokazi ograničeni. Osovina creva–jetra–nerv predstavlja obećavajući biološki i potencijalno terapijski okvir, ali su direktni klinički dokazi o neuroregenerativnoj efikasnosti i dalje ograničeni. Dalja mehanistička i kontrolisana translaciona istraživanja neophodna su za potvrdu uzročnosti i terapijske primenljivosti.

Ključne reči: osovina creva–jetra–nervni sistem, crevna mikrobiota, neurodegeneracija, regeneracija perifernih nerava, TGR5

Uvod

Tradicionalno su neurološki poremećaji proučavani prvenstveno u kontekstu centralnog ili perifernog nervnog sistema. Međutim, sve veći broj dokaza ukazuje na to da je funkcija i homeostaza nervnog sistema značajno uslovljena njegovim interakcijama sa perifernim organima, naročito gastrointestinalnim traktom i jetrom. Ova saznanja dovela su do razvoja koncepta osovine creva–jetra–nervni sistem, kao teorijskog okvira za razumevanje dvosmerne komunikacije između crevne mikrobiote, metaboličkih i imunoloških procesa i nervnog sistema (1).

Crevna mikrobiota prepoznata je kao značajan regulator fiziologije domaćina zahvaljujući produkciji bioaktivnih metabolita, modulaciji imunoloških odgovora i održavanju integriteta epitelne barijere. Promene u sastavu mikrobiote povezane su sa neurodegenerativnim bolestima, kognitivnim padom i hroničnom neuroinflamacijom, što ukazuje na mogućnost da disbioza doprinosi ne samo nastanku, već i progresiji bolesti (2,3). Osovina mikrobiota–crevo–nervni sistem danas se smatra važnim putem kojim periferni signali mogu uticati na funkciju nervnog sistema i ponašanje (1,4).

THE GUT–LIVER–NERVOUS SYSTEM AXIS IN NEUROREGENERATION AND NEURODEGENERATION: MECHANISTIC PATHWAYS, THERAPEUTICAL MODULATION, AND TRANSLATIONAL RELEVANCE

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ABSTRACT

The gut microbiota is increasingly recognized as an important regulator of systemic metabolism, immune activity, and nervous system function. Interactions among the intestine, liver, immune system, and nervous system may therefore represent a biologically interconnected network with relevance to neurodegeneration, neuroregeneration, and other chronic disorders. The aim of this review was to summarize current evidence supporting the gut–liver–nerve axis and to evaluate its potential relevance to neuroinflammation, neurodegeneration, peripheral nerve regeneration, intervertebral disc degeneration, metabolic liver disease, and emerging therapeutic strategies. A narrative literature review was conducted using PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar, covering publications available up to May 2026. Studies addressing the gut–liver–nervous system axis, gut microbiota, microbial metabolites, bile acid signaling, intestinal barrier dysfunction, neuroinflammation, neurodegeneration, peripheral nerve regeneration, intervertebral disc degeneration, and metabolic liver disease were identified and qualitatively synthesized. A total of 35 publications were included in the final qualitative synthesis. Available evidence indicates that microbial metabolites, including short-chain fatty acids, tryptophan-derived metabolites, and bile acid derivatives, participate in immune, metabolic, and neural signaling. Dysbiosis and impaired intestinal barrier function may contribute to systemic inflammation and altered gut–liver communication. Emerging evidence also supports an association between gut microbiota and intervertebral disc degeneration. Prebiotics, probiotics, synbiotics, fecal microbiota transplantation, postbiotics, microbial metabolites, and bile acid-directed approaches represent potential therapeutic strategies, although neurological applications remain predominantly investigational. The gut–liver–nervous system axis represents a promising biological and therapeutic framework, but definitive clinical evidence for neuroregenerative efficacy remains limited. Further mechanistic and controlled translational studies are required to establish causality and therapeutic applicability.

Keywords: gut–liver–nervous system axis, gut microbiota, neurodegeneration, peripheral nerve regeneration, TGR5

Introduction

Traditionally, neurological disorders have been studied primarily within the context of the central or peripheral nervous system. However, growing evidence indicates that neural health is profoundly influenced by interactions with peripheral organs, particularly the gastrointestinal tract and the liver. These findings have led to the emergence of the gut–liver–nervous system axis as a conceptual framework describing the bidirectional communication among microbial, metabolic, immune, and neural systems (1).

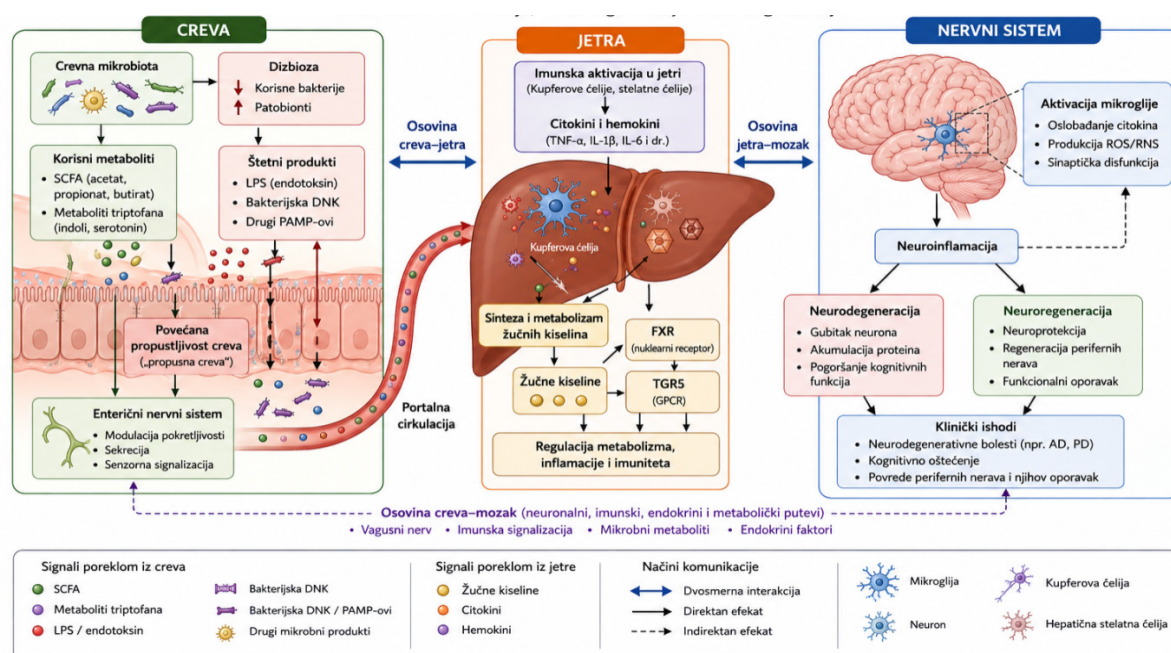
The gut microbiota has been identified as a major regulator of host physiology through the production of bioactive metabolites, modulation of immune responses, and maintenance of epithelial barrier integrity. Alterations in microbial composition have been associated with neurodegenerative diseases, cognitive decline, and chronic neuroinflammation, suggesting that dysbiosis may contribute to both disease initiation and progression (2,3). The microbiota–gut–brain axis is now recognized as a critical pathway through which peripheral signals influence neuronal function and behavior (1,4).

Paralelni napredak u oblasti hepatologije ukazao je na značaj osovine crevo–jetra. Putem portalne cirkulacije, jetra je kontinuirano izložena produktima crevne mikrobiote i metabolitima poreklom iz creva. Poremećaj ove međusobne povezanosti može doprineti razvoju sistemske inflamacije, metaboličke disfunkcije i promena u imunološkoj signalizaciji, sa potencijalno značajnim posledicama po funkciju nervnog sistema (5,6).

Među ključnim medijatorima koji povezuju ove organske sisteme nalaze se žučne kiseline, koje, pored svoje osnovne uloge u varenju i apsorpciji lipida, deluju i kao signalni molekuli sposobni da regulišu metaboličke i inflamatorne puteve. Novija istraživanja pokazala su da su receptori za žučne kiseline

ekspimirani i u centralnom nervnom sistemu, gde mogu učestvovati u regulaciji neuroinflamatornih odgovora i procesa povezanih sa preživljavanjem neurona (7,8).

Nastajući koncept osovine crevo–jetra–nervni sistem polazi od pretpostavke da mikrobni, hepatični, imunološki i nervni putevi funkcionišu kao međusobno povezana biološka mreža, a ne kao izolovani sistemi. Putem dvosmerne komunikacije koja uključuje mikrobne metabolite, signalizaciju posredovanu žučnim kiselinama, inflamatorne medijatore i nervne puteve, promene koje nastaju u crevima mogu uticati kako na neurodegenerativne, tako i na neuroregenerativne procese (slika 1).



Slika 1. Osovina creva–jetra–nervni sistem: integrirani mehanistički okvir

Šematski prikaz dvosmerne komunikacije između crevne mikrobiote, jetre i nervnog sistema. Disbioza crevne mikrobiote i povećana propustljivost crevne barijere podstiču translokaciju mikrobih produkata, uključujući lipopolisaharide (LPS), bakterijsku DNK i molekularne obrasce povezane sa patogenima (engl. *Pathogen-Associated Molecular Pattern* – PAMP), u portnu cirkulaciju. Ovi signali aktiviraju hepatičke puteve i utiču na metabolizam žučnih kiselina. Jetra, sa druge strane, oslobađa citokine, hemokine i signalne molekule izvedene iz žučnih kiselina, koje utiču na funkciju centralnog i perifernog nervnog sistema. Neurološki ishodi posredovani su imunskom aktivacijom, odgovorima mikroglije, metaboličkom regulacijom i neuroinflamatornim putevima, što u konačnom ishodu utiče na neurodegeneraciju, neuroregeneraciju, kognitivne funkcije i regeneraciju perifernih nerava. Komunikacija se odvija putem neuralnih, imunskih, endokrinih i metaboličkih puteva, uključujući vagalnu signalizaciju i sistemska cirkulaciju.

Zajedno posmatrano, navedena zapažanja podržavaju integrirani model u kojem su aktivnost crevne mikrobiote, funkcija jetre i homeostaza nervnog sistema tesno međusobno povezani. Osnovne komponente predložene osovine crevo–jetra–nervni sistem i njihov značaj za neurologiju prikazani su u tabeli 1. Prema našim saznanjima, mali broj preglednih radova pokušao je da objedini mikrob-

ne, hepatične i nervne mehanizme u jedinstveni koncept osovine crevo–jetra–nervni sistem, istovremeno obuhvatajući procese neurodegeneracije i neuroregeneracije. Cilj ovog preglednog rada jeste analiza mehanističkih puteva koji čine osnovu ove osovine i razmatranje njihovog značaja za neurodegeneraciju, neuroregeneraciju i razvoj translacionih terapijskih pristupa.

Parallel advances in hepatology have highlighted the importance of the gut–liver axis. Through the portal circulation, the liver is continuously exposed to microbial products and metabolites derived from the intestine. Dysregulation of this relationship may promote systemic inflammation, metabolic dysfunction, and altered immune signaling, all of which have potential consequences for the nervous system (5,6).

Among the key mediators connecting these organ systems are bile acids, which function not only as digestive molecules but also as signaling mediators capable of regulating metabolic and inflammatory pathways. Recent studies have demonstrated that

bile acid receptors are expressed within the central nervous system and may influence neuroinflammatory responses and neuronal survival (7,8).

The emerging concept of the gut–liver–nerve axis proposes that microbial, hepatic, immune, and neural pathways operate as an interconnected biological network rather than as isolated systems. Through bidirectional communication involving microbial metabolites, bile acid signaling, inflammatory mediators, and neural pathways, alterations originating in the gut may influence both neurodegenerative and neuroregenerative processes (Figure 1).

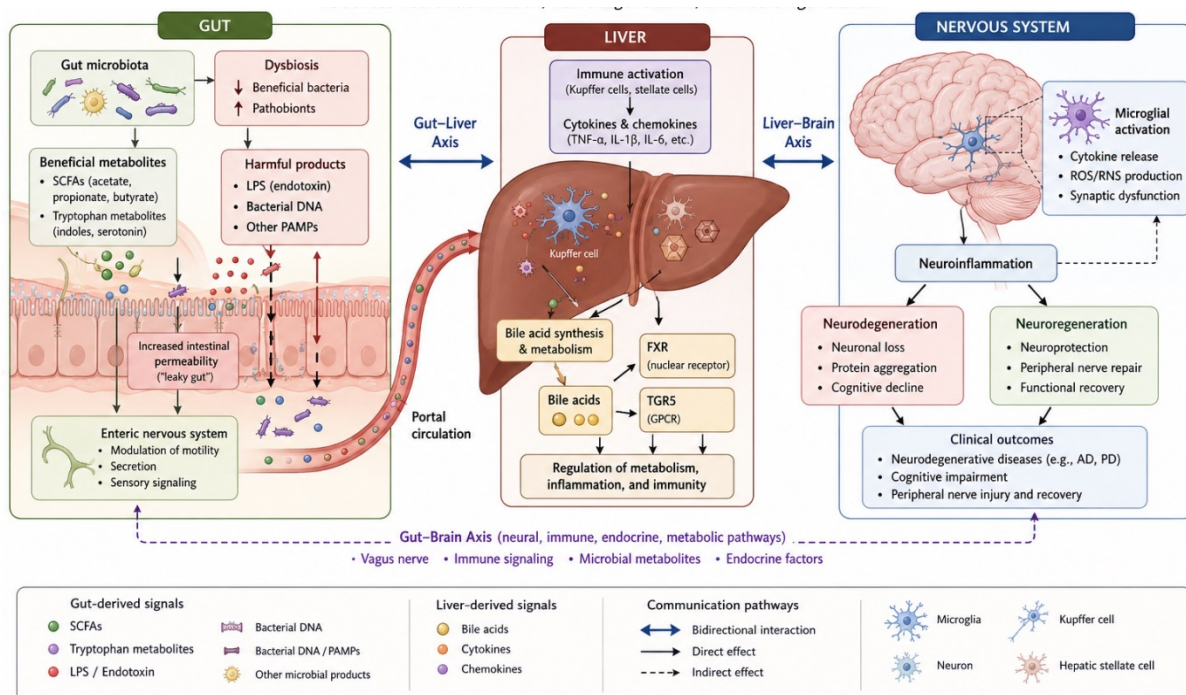


Figure 1. The Gut–Liver–Nervous System Axis: Integrated Mechanistic Framework

Schematic representation of the bidirectional communication among the gut microbiota, liver, and nervous system. Gut microbial dysbiosis and increased intestinal permeability promote the translocation of microbial products, including lipopolysaccharides (LPS), bacterial DNA, and pathogen-associated molecular patterns (PAMPs), into the portal circulation. These signals activate hepatic immune pathways and influence bile acid metabolism. The liver, in turn, releases cytokines, chemokines, and bile acid–derived signaling molecules that affect both central and peripheral nervous system function. Neural outcomes are mediated through immune activation, microglial responses, metabolic regulation, and neuroinflammatory pathways, ultimately influencing neurodegeneration, neuroregeneration, cognitive function, and peripheral nerve repair. Communication occurs through neural, immune, endocrine, and metabolic pathways, including vagal signaling and systemic circulation.

Collectively, these observations support an integrated model in which gut microbial activity, hepatic function, and neural homeostasis are closely interconnected. The principal components of the proposed gut–liver–nerve axis and their neurological relevance are summarized in Table 1. To our knowledge, few reviews have attempted to integrate gut microbial, hepatic, and neural mecha-

nisms into a unified gut–liver–nerve axis framework encompassing both neurodegeneration and neuroregeneration. The aim of this review is to examine the mechanistic pathways underlying the gut–liver–nerve axis and to discuss their relevance to neurodegeneration, neuroregeneration, and translational therapeutic development.

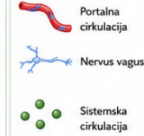
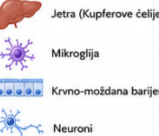
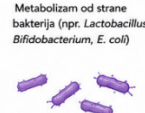
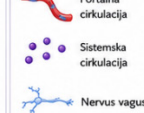
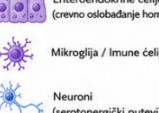
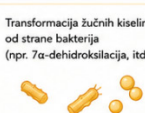
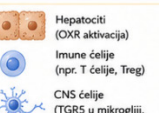
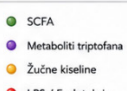
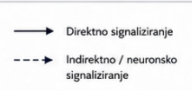
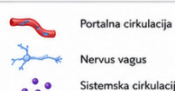
Faktor poreklom iz creva (izvor)	Proizvodnja / metabolizam	Transport / put signalizacije	Glavne mete (jetra / imun sistem / CNS / PNS)	Ključni mehanizmi	Neurološki efekti
Kratkolančane masne kiseline (SCFA) (acetat, propionat, butirat)  Nastaju fermentacijom dijetetskih vlakana	 Fermentacija vlakana od strane bakterija (<i>Clostridia</i> , <i>Bacteroides</i> , <i>Roseburia</i> i dr.)	 Portalna cirkulacija Nervus vagus Sistemska cirkulacija	 Jetra (Kupferove ćelije) Mikroglija Krvno-moždana barijera Neuroni	- Aktivacija GPR41/43 - Inhibicija HDAC - Antiinflamatorni efekti (smanjenje NF-κB, citokina) - Povećanje integriteta BBB - Modulacija mikroglije (M2 polarizacija)	Pretežno neuroprotektivni - Smanjenje neuroinflamacije - Poboljšanje integriteta BBB - Neurogeniza - Poboljšanje kognitivne funkcije - Neurodegeneracija – usporavanje 
Metaboliti triptofana (indoli, kinureneni, serotoniniski prekursori)  Poreklom iz dijetetskog triptofana	 Metabolizam od strane bakterija (npr. <i>Lactobacillus</i> , <i>Bifidobacterium</i> , <i>E. coli</i>)	 Portalna cirkulacija Sistemska cirkulacija Nervus vagus	 Enteroendokrine ćelije (crevno oslobađanje hormona) Mikroglija / Imune ćelije Neuroni (serotonergički putevi)	- Modulacija sinteze serotonina i njegovih signalnih puteva - Aktivacija AhR (AHR) - Imunomodulacija - Regulacija neuroplastičnosti - Održavanje ravnoteže triptofan-kinurenin puta	Dvojak efekti - Zavisno od ravnoteže: - Neuroprotekcija (zaštitno signaliziranje) - Neuroinflamacija (disregulacija puta, prekomerna aktivacija) 
Žučne kiseline (primarne i sekundarne)  Sintetišu se u jetri, modifikuju bakterije	 Transformacija žučnih kiselina od strane bakterija (npr. 7 α -dehidroksilacija, itd.)	 Portalna cirkulacija Sistemska cirkulacija	 Hepatociti (OXR aktivacija) Imune ćelije (npr. T ćelije, Treg) CNS ćelije (TGR5 u mikrogliji, astrocitima, neuronima)	- Regulacija preko FXR i drugih jezičnih puteva - Aktivacija TGR5 - Antiinflamatorna signalizacija (smanjenje AMP-aktivirane proteinkinaze, NF-κB) - Modulacija energetskog metabolizma	Pretežno neuroprotektivni - Smanjenje neuroinflamacije - Poboljšanje kognitivne funkcije - Povećanje preživljavanja neurona - Potencijalne koristi u metaboličkim bolestima 
LPS / Endotoksin (lipopolisaharidi)  Poreklom od Gram-negativnih bakterija	 Oslobađanje usled disbioze i povećane propustljivosti crevnog zida	 Portalna cirkulacija Sistemska cirkulacija	 TLR4 na Kupferovim ćelijama (u jetri) Mikroglija (TLR4 aktivacija) Periferni imune ćelije	- Aktivacija TLR4/NF-κB puta - Proinflamatorni citokini (TNF-α, IL-1β, IL-6) - Oksidativni stres - Poremećaj integriteta BBB	Pretežno neurotoksični - Povećana neuroinflamacija - Oksidativni stres - Disfunkcija sinapsi - Neurodegeneracija 
Skrtačnice: BBB – krvno-moždana barijera FXR – receptor farnesoid X TGR5 – G protein-spregnuti receptor žučnih kiselina 5 AHR (AHR) – aril-hidrokarbonski receptor HDAC – histon deacetilaza NF- κ B – nuklearni faktor κ B AMPK – AMP-aktivirana proteinkinaza TLR4 – Toll-like receptor 4 CNS – centralni nervni sistem PNS – periferni nervni sistem   					

Tabela 1. Molekularni medijatori koji povezuju creva i nervni sistem

Pregled glavnih mikrobnih i hepatičkih signalnih molekula uključenih u komunikaciju creva, jetre i mozga. Kratkolančane masne kiseline (SCFA), metaboliti poreklom iz triptofana, žučne kiseline i lipopolisaharidi (LPS) predstavljaju ključne medijatore koji povezuju aktivnost crevne mikrobiote sa funkcijom nervnog sistema. Ovi molekuli dospevaju do ciljnih tkiva putem portnih, sistemskih i nervnih puteva i stupaju u interakciju sa hepatocitima, imunskim ćelijama, mikroglijom, neuronima i krvno-moždanom barijerom. Njihovi biološki efekti uključuju modulaciju neuroinflamacije, imunskog signaliziranja, sinteze neurotransmitera, metaboličke regulacije i preživljavanja neurona. Dok SCFA i žučne kiseline pretežno ostvaruju neuroprotektivne i antiinflamatorne efekte, prekomerna izloženost endotoksinima podstiče neuroinflamaciju i neurodegeneraciju. Efekti metabolita triptofana zavise od konteksta i pod uticajem su ravnoteže mikrobnih i domaćinovih metaboličkih puteva.

Metode

Strategija pretraživanja literature

Sproveden je narativni pregled literature radi analize savremenih dokaza o interakcijama između crevne mikrobiote, jetre, imunološkog sistema i nervnog sistema. Relevantna literatura identifikovana je pretraživanjem baza PubMed/MEDLINE, Scopus, Web of Science i Google Scholar, obuhvatajući publikacije dostupne u periodu do maja 2026. godine.

Strategija pretraživanja zasnivala se na kombinacijama ključnih reči i termina iz Medical Subject Headings (MeSH) povezanih sa osovino crevo–jetra–nervni sistem, uključujući: „gut–brain axis”, „gut–liver axis”, „microbiota”, „neurodegeneration”, „neuroregeneration”, „neuroinflammation”, „bile acids”, „TGR5”, „FXR”, „short-chain fatty acids”, „tryptophan metabolism”, „intestinal permeability”, „endotoxemia”, „peripheral nerve regeneration”, „metabolic dysfunction-associated fatty liver disease”, „cognitive impairment” i „intervertebral disc degeneration”. Za preciziranje pretrage i identifikaciju relevantnih publikacija korišćeni su Bulovi operatori „AND” i „OR”.

Selekcija literature

Prioritet su imali recenzirani originalni naučni radovi, sistematski pregledi, meta-analize i visokokvalitetni narativni pregledi koji su obrađivali mehanističke, translacione ili kliničke aspekte interakcije između crevne mikrobiote, jetre i nervnog sistema. Uključene su eksperimentalne i kliničke studije ukoliko su pružale relevantne dokaze o mikrobnim, hepatičnim, imunološkim ili nervnim signalnim putevima.

Publikacije su odabrane na osnovu njihove naučne relevantnosti u odnosu na ciljeve ovog pregleda. Radovi koji nisu bili direktno povezani sa biološkom komunikacijom između crevne mikrobiote, jetre, imunološkog sistema i nervnog sistema nisu uzimani u obzir. Kongresni apstrakti, uvodnici, komentari i publikacije bez dovoljno metodoloških ili naučnih podataka bili su isključeni. Uključene su isključivo publikacije napisane na engleskom jeziku.

U završnu kvalitativnu sintezu uključeno je ukupno 35 publikacija.

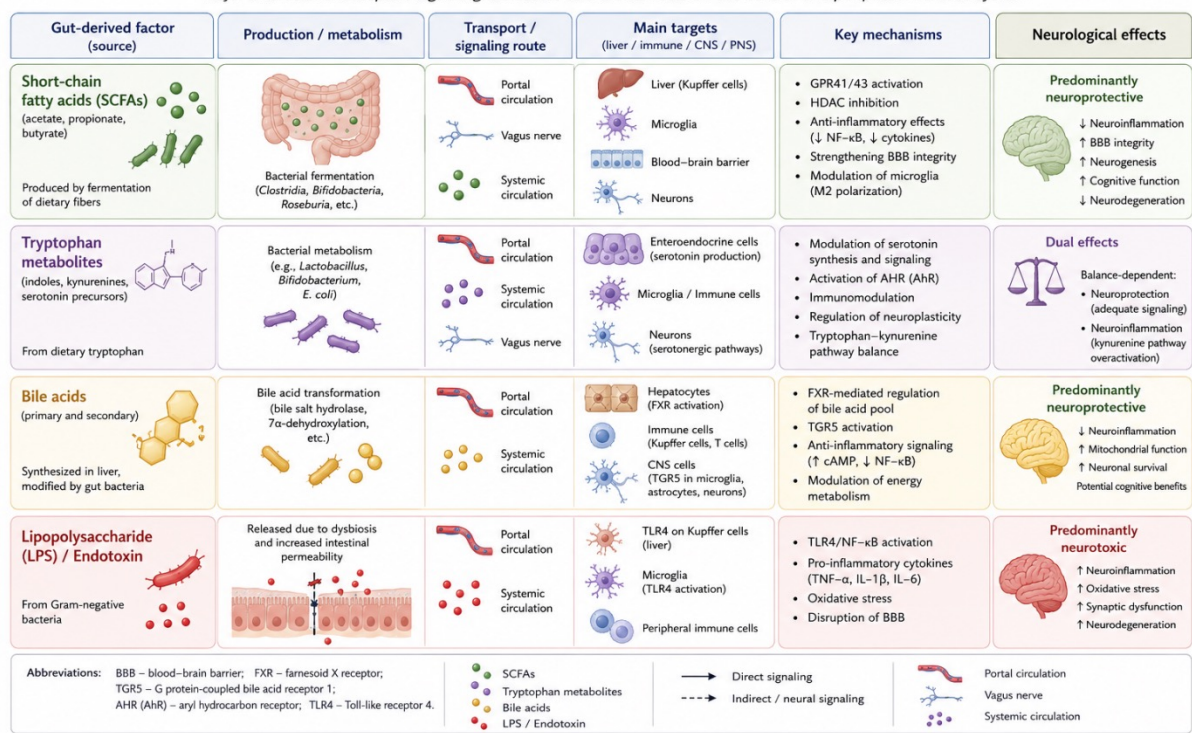


Figure 2. Molecular Mediators Connecting the Gut and Nervous System

Overview of major microbial and hepatic signaling molecules involved in gut–liver–brain communication. Short-chain fatty acids (SCFAs), tryptophan-derived metabolites, bile acids, and lipopolysaccharides (LPS) represent key mediators linking intestinal microbial activity with neural function. These molecules reach target tissues through portal, systemic, and neural pathways and interact with hepatocytes, immune cells, microglia, neurons, and the blood–brain barrier. Their biological effects include modulation of neuroinflammation, immune signaling, neurotransmitter synthesis, metabolic regulation, and neuronal survival. While SCFAs and bile acids predominantly exert neuroprotective and anti-inflammatory effects, excessive endotoxin exposure promotes neuroinflammation and neurodegeneration. The effects of tryptophan metabolites appear context-dependent and are influenced by the balance of microbial and host metabolic pathways.

Methods

Literature Search Strategy

A narrative literature review was conducted to examine current evidence regarding the interactions among the gut microbiota, liver, immune system, and nervous system. Relevant literature was identified through searches of PubMed/MEDLINE, Scopus, Web of Science, and Google Scholar, covering publications available up to May 2026.

The search strategy incorporated combinations of keywords and Medical Subject Headings (MeSH) terms related to the gut–liver–nerve axis, including gut–brain axis, gut–liver axis, microbiota, neurodegeneration, neuroregeneration, neuroinflammation, bile acids, TGR5, FXR, short-chain fatty acids, tryptophan metabolism, intestinal permeability, endotoxemia, peripheral nerve regeneration, metabolic dysfunction-associated fatty liver disease, cognitive impairment, and intervertebral disc degeneration. Boolean operators (“AND” and “OR”) were applied to refine the searches and identify relevant publications.

Literature Selection

Priority was given to peer-reviewed original research articles, systematic reviews, meta-analyses, and high-quality narrative reviews addressing mechanistic, translational, or clinical aspects of gut microbiota–liver–nervous system interactions. Both experimental and clinical studies were considered when they contributed meaningful evidence regarding microbial, hepatic, immune, or neural signaling pathways.

Publications were selected according to their scientific relevance to the objectives of the review. Articles not directly related to the biological communication between the gut microbiota, liver, immune system, and nervous system were not considered. Conference abstracts, editorials, commentaries, and publications lacking sufficient methodological or scientific detail were excluded. Only publications written in English were included.

A total of 35 publications were included in the final qualitative synthesis.

Analiza i sinteza podataka

Odabrana literatura analizirana je kvalitativno, sa posebnim naglaskom na biološke mehanizme koji povezuju aktivnost crevne mikrobiote, hepatičnu signalizaciju, neuroinflamaciju, neurodegeneraciju i neuroregeneraciju. Posebna pažnja posvećena je putevima koji uključuju mikrobne metabolite, signalizaciju žučnih kiselina, imunološku modulaciju, poremećaj integriteta crevne barijere i sistemske inflamatorne odgovore.

Rezultati su sintetizovani narativno i organizovani u tematske celine koje obuhvataju komunikaciju između creva i mozga, interakcije na relaciji crevo–jetra, neuroinflamatorne mehanizme, regeneraciju perifernih nerava, degeneraciju intervertebralnog diska, metaboličku bolest jetre i potencijalne terapijske primene. S obzirom na heterogenost dizajna studija, ispitivanih populacija, intervencija, eksperimentalnih modela i praćenih ishoda u dostupnoj literaturi, kvantitativno objedinjavanje podataka nije smatrano odgovarajućim. Cilj ovog pregleda bio je pružanje integrisanog konceptualnog prikaza osovine crevo–jetra–nervni sistem i njenog potencijalnog značaja za neurološko zdravlje, neurodegeneraciju i neuroregeneraciju.

Osovina crevo–mozak i neurodegeneracija

Osovina crevo–mozak postala je jedno od značajnih područja savremenih istraživanja, ukazujući na postojanje dvosmerne komunikacije između gastrointestinalnog trakta i centralnog nervnog sistema. Ova kompleksna mreža obuhvata nervne, imunološke, endokrine i metaboličke puteve putem kojih crevna mikrobiota može uticati na razvoj mozga, njegovu funkciju i procese povezane sa razvojem bolesti (1,4).

Sve veći broj dokaza ukazuje na to da promene u sastavu crevne mikrobiote, koje se zajednički označavaju kao disbioza, mogu doprineti patogenezi neurodegenerativnih poremećaja. Metagenomske studije pokazale su postojanje specifičnih mikrobnih obrazaca kod pacijenata sa bolestima kao što su Alchajmerova i Parkinsonova bolest, pri čemu se često uočava smanjenje zastupljenosti korisnih bakterija koje proizvode kratkolančane masne kiseline, uz povećanu zastupljenost proinflamatornih mikroorganizama. Ove promene mogu doprineti sistemske inflamaciji, narušavanju integriteta crevne i krvno–moždane barijere i aktivaciji neuroinflamatornih odgovora (2,3).

Mikrobni metaboliti predstavljaju važnu meha-

nističku vezu između creva i mozga. Kratkolančane masne kiseline, derivati žučnih kiselina i drugi mikrobni produkti mogu modulisati imunološku aktivnost, funkciju mikroglije i neuronsku homeostazu. Poremećaj ovih signalnih puteva povezan je sa intenziviranjem neuroinflamacije i progresijom neurodegenerativne patologije (1,2).

Kliničke studije dodatno podržavaju povezanost između crevne mikrobiote i kognitivnog pada. Sistematski pregled koji je obuhvatio pacijente sa blagim kognitivnim poremećajem i demencijom pokazao je konzistentne promene u sastavu crevnih mikrobni zajednica u poređenju sa kognitivno zdravim osobama, što ukazuje na potencijalnu ulogu mikrobioma kako biomarkera, ali i kao terapijskog cilja kod neurodegenerativnih bolesti [9].

Zbirno posmatrano, dostupni dokazi ukazuju na to da crevna mikrobiota predstavlja aktivnog učesnika u neurodegenerativnim procesima, a ne samo pasivnog posmatrača. Iako se precizni uzročno–posledični odnosi i dalje istražuju, modulacija crevnog mikrobioma nameće se kao perspektivan pravac budućih preventivnih i terapijskih strategija usmerenih na neurodegeneraciju (1–3,9).

Osovina crevo–jetra

Osovina crevo–jetra predstavlja visoko integrisani sistem dvosmerne komunikacije koji povezuje crevnu mikrobiotu, intestinalnu barijeru, portnu cirkulaciju i imunološke odgovore jetre. S obzirom na to da jetra najveći deo krvi prima putem portne vene, ona je kontinuirano izložena mikrobnim produktima, metabolitima i jedinjenjima poreklom iz hrane koja dospevaju iz gastrointestinalnog trakta (5,6).

U fiziološkim uslovima, intestinalna barijera ograničava translokaciju bakterija i njihovih komponenti u cirkulaciju. Međutim, disbioza i povećana intestinalna permeabilnost mogu omogućiti prolazak lipopolisaharida, bakterijske DNK i drugih molekularnih obrazaca povezanih sa patogenima do jetre, gde mogu aktivirati Kupfferove ćelije i druge imunološke puteve. Ovaj proces može podstaći hroničnu inflamaciju i doprineti oštećenju i fibrozi jetre (5,10).

Crevna mikrobiota takođe reguliše metabolizam žučnih kiselina, obradu nutrijenata i produkciju bioaktivnih metabolita koji utiču na hepatičnu homeostazu. Poremećaji ovih puteva dovedeni su u vezu sa razvojem i progresijom različitih bolesti jetre, naročito nealkoholne masne bolesti jetre (NAFLD).

Data Analysis and Synthesis

The selected literature was analyzed qualitatively, with emphasis placed on biological mechanisms linking gut microbial activity, hepatic signaling, neuroinflammation, neurodegeneration, and neuroregeneration. Particular attention was given to pathways involving microbial metabolites, bile acid signaling, immune modulation, intestinal barrier dysfunction, and systemic inflammatory responses.

Findings were synthesized narratively and organized into thematic sections covering gut–brain communication, gut–liver interactions, neuroinflammatory mechanisms, peripheral nerve regeneration, intervertebral disc degeneration, metabolic liver disease, and potential therapeutic applications. Given the diversity of study designs, populations, interventions, experimental models, and outcomes across the available literature, quantitative pooling of data was not considered appropriate. The objective of this review was to provide an integrated conceptual overview of the emerging gut–liver–nerve axis and its potential relevance to neurological health, neurodegeneration, and neuroregeneration.

Gut–Brain Axis and Neurodegeneration

The gut–brain axis has emerged as a major focus of neuroscience research, highlighting the bidirectional communication between the gastrointestinal tract and the central nervous system. This complex network involves neural, immune, endocrine, and metabolic pathways through which the gut microbiota can influence brain development, function, and disease processes (1,4).

Growing evidence suggests that alterations in gut microbial composition, commonly referred to as dysbiosis, contribute to the pathogenesis of neurodegenerative disorders. Metagenomic studies have demonstrated distinct microbial signatures in patients with conditions such as Alzheimer’s disease and Parkinson’s disease, often characterized by reduced populations of beneficial short-chain fatty acid producing bacteria and increased abundance of pro-inflammatory microorganisms. These changes may promote systemic inflammation, disrupt intestinal and blood–brain barrier integrity, and facilitate neuroinflammatory responses. (2,3).

Microbial metabolites represent an important mechanistic link between the gut and the brain. Short-chain fatty acids, bile acid derivatives, and other microbial products can modulate immune activity, microglial function, and neuronal homeosta-

sis. Dysregulation of these pathways has been associated with enhanced neuroinflammation and the progression of neurodegenerative pathology (1,2).

Clinical studies further support the relationship between gut microbiota and cognitive decline. A systematic review of patients with mild cognitive impairment and dementia reported consistent alterations in gut microbial communities compared with cognitively healthy individuals, suggesting a potential role for the microbiome as both a biomarker and a therapeutic target in neurodegenerative diseases (9).

Collectively, current evidence indicates that the gut microbiota is an active participant in neurodegenerative processes rather than a passive bystander. Although the precise causal relationships remain under investigation, modulation of the gut microbiome has emerged as a promising avenue for future preventive and therapeutic strategies targeting neurodegeneration. (1,2,3,9)

Gut–Liver Axis

The gut–liver axis represents a highly integrated bidirectional communication system linking the intestinal microbiota, intestinal barrier, portal circulation, and hepatic immune responses. Because the liver receives the majority of its blood supply from the portal vein, it is continuously exposed to microbial products, metabolites, and dietary compounds originating from the gastrointestinal tract (5,6).

Under physiological conditions, the intestinal barrier limits the translocation of bacteria and their components into the circulation. However, dysbiosis and increased intestinal permeability can facilitate the passage of lipopolysaccharides, bacterial DNA, and other pathogen-associated molecular patterns to the liver, where they activate Kupffer cells and other immune pathways. This process promotes chronic inflammation and contributes to hepatic injury and fibrosis (5,10).

The gut microbiota also regulates bile acid metabolism, nutrient processing, and the production of bioactive metabolites that influence hepatic homeostasis. Alterations in these pathways have been implicated in the development and progression of several liver disorders, particularly nonalcoholic fatty liver disease (NAFLD). The contemporary “multiple parallel hits” hypothesis proposes that gut-derived inflammatory signals, metabolic dysfunction, insulin resistance, and microbiome alterations act simultaneously to drive liver disease progression

Savremena hipoteza „multiple parallel hits“ pretpostavlja da inflamatorni signali poreklom iz creva, metabolička disfunkcija, insulinska rezistencija i promene mikrobioma deluju istovremeno i zajednički doprinose progresiji bolesti jetre, umesto da postoji jedan izolovani patogenetski mehanizam (11).

Sve veći broj dokaza stoga identifikuje osovinu crevo–jetra kao važan regulator gastrointestinalnog i sistemskog zdravlja. Pored njene ustanovljene uloge u bolestima jetre, poremećaji unutar ove osovine mogu imati značajne posledice po ekstrahepatične organe, uključujući nervni sistem, čime se pruža mehanistička osnova za širi koncept osovine crevo–jetra–nervni sistem (5,6,10,11).

Žučne kiseline i međuorganska signalizacija

Žučne kiseline se sve više prepoznaju kao signalni molekuli čija funkcija značajno prevazilazi njihovu klasičnu ulogu u varenju i apsorpciji lipida. Interakcijom sa receptorima kao što su farnesoid X receptor (engl. *Farnesoid X Receptor* – FXR) i receptor za žučne kiseline spregnut sa G-proteinom (engl. *Takeda G protein-coupled Receptor 5* – TGR5), žučne kiseline učestvuju u regulaciji metaboličke homeostaze, imunoloških odgovora i komunikacije između creva, jetre i nervnog sistema (8).

Sastav ukupnog pula žučnih kiselina značajno je uslovljen crevnom mikrobiotom. Crevne bakterije transformišu primarne žučne kiseline sintetisane u jetri u različite sekundarne žučne kiseline, čime oblikuju signalna svojstva enterohepatične cirkulacije. Ove mikrobne biotransformacije predstavljaju važnu funkcionalnu vezu između aktivnosti crevne mikrobiote i sistemske fiziološke regulacije (12).

Novija istraživanja pokazala su da signalizacija posredovana žučnim kiselinama utiče i na centralni nervni sistem. Receptori za žučne kiseline ekspimirani su u različitim neuronskim i glijalnim ćelijskim populacijama, gde učestvuju u regulaciji neuroinflamacije, preživljavanja neurona i metaboličke signalizacije. Posebno je aktivacija TGR5 receptora povezana sa antiinflamatornim efektima u mozgu i potencijalno doprinosi neuroprotektivnim odgovorima u patološkim stanjima (7).

Eksperimentalni dokazi dodatno ukazuju na to da ursodeoksiholna kiselina (engl. *Ursodeoxycholic acid* – UDCA) može ublažiti aktivaciju mikroglije i inhibirati inflamatornu signalizaciju putem mehanizama posredovanih TGR5 receptorom. Ovi nalazi podržavaju koncept prema kojem žučne kiseline predstavljaju značajne molekularne glasnike unutar

mreže crevo–jetra–mozak i mogu predstavljati perspektivne terapijske ciljeve kod neurodegenerativnih i neuroinflamatornih poremećaja (7,13).

Regeneracija perifernih nerava

Periferni nervi poseduju izuzetnu sposobnost regeneracije u poređenju sa centralnim nervnim sistemom. Nakon povrede aktivira se koordinisan niz ćelijskih i molekularnih događaja koji omogućavaju ponovni rast aksona, reinervaciju ciljnih struktura i funkcionalni oporavak. Centralnu ulogu u ovom procesu ima transformacija zrelih Schwannovih ćelija u specijalizovane reparativne Schwannove ćelije, koje uklanjaju ćelijski detritus, sekretuju neurotrofne faktore i obezbeđuju usmeravajuće signale za regenerišuće aksone (14,15).

Regenerativni odgovor takođe u velikoj mери zavisi od interakcije između Schwannovih ćelija i imunoloških ćelija. Nakon povrede nerva, makrofagi infiltriraju oštećeno tkivo i zajedno sa Schwannovim ćelijama učestvuju u uklanjanju mijelinskog detritusa, modulaciji inflamacije i stvaranju mikrookruženja pogodnog za regeneraciju aksona. Ravnoteža između proinflamatorne i proregenerativne signalizacije predstavlja jednu od ključnih determinanti uspešne reparacije nerva (16).

Nastajući dokazi ukazuju na mogućnost da crevna mikrobiota utiče na regeneraciju perifernih nerava putem svojih efekata na sistemski imunitet, inflamatorne medijatore i mikrobne metabolite. Promene u sastavu mikrobiote mogu menjati imunološke odgovore domaćina i potencijalno uticati na ćelijske mehanizme uključene u reparaciju nerva. Iako je ova oblast još u ranoj fazi razvoja, rastuće interesovanje za odnos između perifernog nervnog sistema i mikrobioma proširilo je tradicionalni pogled na regeneraciju nerva, koja se više ne posmatra isključivo kao lokalni tkivni proces (17).

Zajedno posmatrano, reparacija perifernih nerava se sve više razume kao sistemski fenomen koji uključuje kompleksne interakcije između nervnih, imunoloških i metaboličkih puteva. Ova zapažanja pružaju osnovu za istraživanje mogućnosti da modulacija crevne mikrobiote unapredi regenerativne ishode nakon povrede perifernog nerva (14–17).

Neuroinflamacija i imunološka signalizacija

Neuroinflamacija se sve više prepoznaje kao centralni mehanizam koji povezuje periferne fiziološke poremećaje sa neurodegenerativnim bolestima. Dok akutni inflamatorni odgovor može imati

rather than through a single pathogenic mechanism (11).

Accumulating evidence therefore identifies the gut–liver axis as a central regulator of both gastrointestinal and systemic health. Beyond its established role in liver disease, disturbances within this axis may have important consequences for extrahepatic organs, including the nervous system, providing a mechanistic foundation for the broader gut–liver–nerve axis concept (5,11,6,10).

Bile Acids and Interorgan Signaling

Bile acids are increasingly recognized as signaling molecules that extend far beyond their classical role in lipid digestion and absorption. Through interactions with receptors such as the farnesoid X receptor (FXR) and the G protein–coupled bile acid receptor TGR5, bile acids regulate metabolic homeostasis, immune responses, and interaction between the gut, liver, and nervous system (8).

The composition of the bile acid pool is strongly influenced by the intestinal microbiota. Gut bacteria transform primary bile acids synthesized in the liver into a diverse range of secondary bile acids, thereby shaping the signaling properties of the enterohepatic circulation. These microbial biotransformations create an important functional link between gut microbial activity and systemic physiological regulation (12).

Recent studies have demonstrated that bile acid signaling also affects the central nervous system. Bile acid receptors are expressed in various neural and glial cell populations, where they participate in the regulation of neuroinflammation, neuronal survival, and metabolic signaling. In particular, activation of TGR5 has been associated with anti-inflammatory effects within the brain and may contribute to neuroprotective responses under pathological conditions (7).

Experimental evidence further suggests that ursodeoxycholic acid (UDCA) can attenuate microglial activation and suppress inflammatory signaling through TGR5-mediated pathways. These findings support the concept that bile acids serve as important molecular messengers within the gut–liver–brain network and may represent promising therapeutic targets for neurodegenerative and neuroinflammatory disorders (7,13).

Peripheral Nerve Regeneration

Peripheral nerves possess a remarkable regen-

erative capacity compared with the central nervous system. Following injury, a coordinated sequence of cellular and molecular events promotes axonal regrowth, target reinnervation, and functional recovery. Central to this process is the transformation of mature Schwann cells into specialized repair Schwann cells, which clear debris, secrete neurotrophic factors, and provide guidance cues for regenerating axons (14,15).

The regenerative response is also critically dependent on interactions between Schwann cells and immune cells. Following nerve injury, macrophages infiltrate the damaged tissue and cooperate with Schwann cells to remove myelin debris, modulate inflammation, and create a microenvironment conducive to axonal regeneration. The balance between pro-inflammatory and pro-regenerative signaling is a key determinant of successful nerve repair (16).

Emerging evidence suggests that the gut microbiota may influence peripheral nerve regeneration through its effects on systemic immunity, inflammatory mediators, and microbial metabolites. Changes in gut microbial composition can alter host immune responses and potentially affect cellular mechanisms involved in nerve repair. Although this field remains in its early stages, growing interest in the relationship between the peripheral nervous system and the microbiome has expanded the traditional view of nerve regeneration beyond local tissue processes alone (17).

Taken together, peripheral nerve repair is increasingly understood as a systemic phenomenon involving complex interactions among neural, immune, and metabolic pathways. These observations provide a rationale for investigating whether modulation of the gut microbiota could enhance regenerative outcomes following peripheral nerve injury (14–17).

Neuroinflammation and Immune Signaling

Neuroinflammation is increasingly recognized as a central mechanism linking peripheral physiological disturbances to neurodegenerative disease. While acute inflammatory responses may serve protective functions, chronic activation of innate immune pathways can promote neuronal dysfunction and progressive neurodegeneration (18,19).

Microglia, the resident immune cells of the central nervous system, play a pivotal role in this process. Under pathological conditions, activated microglia release pro-inflammatory cytokines, reactive

zaštitnu ulogu, hronična aktivacija urođenih imunoloških puteva može doprineti neuronskoj disfunkciji i progresivnoj neurodegeneraciji (18,19).

Mikroglija, rezidentne imunološke ćelije centralnog nervnog sistema, ima ključnu ulogu u ovom procesu. U patološkim stanjima, aktivirana mikroglija oslobađa proinflamatorne citokine, reaktivne vrste kiseonika i druge medijatore koji mogu doprineti oštećenju neurona. Dugotrajna aktivacija mikroglije dovedena je u vezu sa patogeneom različitih neurodegenerativnih bolesti, uključujući Alchajmerovu bolest (20).

Sve veći broj dokaza ukazuje na to da periferni inflamatorni signali poreklom iz creva i jetre mogu uticati na centralne imunološke odgovore. Shodno tome, neuroinflamacija se danas sve češće posmatra kao sistemski proces koji uključuje kontinuiranu komunikaciju između perifernih organa i mozga, pružajući mehanističku osnovu za koncept osovine crevo–jetra–nervni sistem (18–20).

Degeneracija intervertebralnog diska

Degeneracija intervertebralnog diska (engl. *intervertebral disc degeneration*, IVDD) predstavlja multifaktorski proces koji karakteriše progresivna degradacija ekstracelularnog matriksa, ćelijska disfunkcija i hronična inflamacija unutar mikrookruženja diska. Ove promene dovode do strukturne degeneracije, pojave bola i narušavanja funkcije kičmenog stuba (21,22). Proinflamatorni citokini imaju važnu ulogu u patogenezi IVDD, jer podstiču razgradnju matriksa, ubrzavaju ćelijsko starenje i narušavaju tkivnu homeostazu. Zbog toga je inflamatorna signalizacija postala jedno od centralnih područja istraživanja mehanizama degeneracije diska (21).

Novije studije Mendelove randomizacije identifikovale su potencijalnu vezu između sastava crevne mikrobiote i predispozicije za razvoj IVDD. Ovi nalazi pokazuju da mikrobnii faktori mogu uticati na zdravlje intervertebralnog diska putem sistemskih inflamatornih, metaboličkih i imunoloških mehanizama, podržavajući koncept prema kojem na degeneraciju diska mogu uticati procesi koji prevazilaze lokalno okruženje kičmenog stuba (23,24).

Metabolička disfunkcija povezana sa masnom bolešću jetre i povezanost jetra–mozak

Metabolička disfunkcija povezana sa masnom bolešću jetre (engl. *metabolic dysfunction-associated fatty liver disease*, MAFLD) sve se više prepozna-

je kao sistemski poremećaj čije posledice prevazilaze samu jetru. Pored metaboličkih i kardiovaskularnih komplikacija, sve veći broj dokaza ukazuje na to da MAFLD može doprineti kognitivnom oštećenju i razvoju neurodegenerativnih bolesti (25,26).

Predloženo je nekoliko mehanizama koji mogu objasniti ovu povezanost, uključujući hroničnu inflamaciju niskog stepena, insulinsku rezistenciju, oksidativni stres i izmenjenu produkciju metabolita poreklom iz jetre. Ovi faktori mogu podstaći neuroinflamatorne odgovore i nepovoljno uticati na funkciju neurona (25,27).

Novija istraživanja ukazala su na povećan rizik od kognitivnog pada i demencije kod osoba sa MAFLD, naglašavajući značaj jetre kao aktivnog učesnika u održavanju zdravlja mozga. Ova zapažanja dodatno podržavaju koncept osovine jetra–mozak i ukazuju na mogućnost da hepatična disfunkcija utiče na neurološke ishode putem višestrukih međusobno povezanih mehanizama (25–27).

Kratkolančane masne kiseline i mikrobnii metaboliti

Kratkolančane masne kiseline (engl. *short-chain fatty acids*, SCFA), prvenstveno acetat, propionat i butirat, spadaju među najvažnije metabolite koje proizvode crevna mikrobiota. Nastaju fermentacijom dijetetskih vlakana i ostvaruju različite efekte na imunološku regulaciju, metabolizam i funkciju nervnog sistema (28).

U okviru nervnog sistema, SCFA doprinose održavanju integriteta krvno–moždane barijere, modulaciji aktivnosti mikroglije i regulaciji neuroinflamatornih odgovora. Eksperimentalne studije pokazuju da promene u produkciji SCFA mogu uticati na predispoziciju za neurološke poremećaje i tok bolesti (29).

S obzirom na to da SCFA predstavljaju jedan od glavnih komunikacionih puteva između crevnih mikroorganizama i udaljenih organa, sve više se smatraju ključnim medijatorima interakcija na relaciji crevo–jetra–mozak i potencijalnim terapijskim ciljevima kod neurodegenerativnih bolesti (28,29).

Više klasa mikrobnii i metabolita poreklom iz jetre identifikovano je kao značajni medijatori komunikacije između gastrointestinalnog trakta i nervnog sistema. Ovi signalni molekuli uključuju kratkolančane masne kiseline, metabolite triptofana, žučne kiseline i bakterijske endotoksine, pri čemu svaki od njih ostvaruje specifične efekte na imunološku regulaciju, neuronsku funkciju i neuroinflamatorne puteve (slika 2).

oxygen species, and other mediators that contribute to neuronal injury. Sustained microglial activation has been implicated in the pathogenesis of several neurodegenerative disorders, including Alzheimer's disease (20).

Accumulating evidence suggests that peripheral inflammatory signals originating from the gut and liver can influence central immune responses. Consequently, neuroinflammation is now viewed as a systemic process involving continuous communication between peripheral organs and the brain, providing a mechanistic framework for the gut–liver–nerve axis (18–20).

Intervertebral Disc Degeneration (IVDD)

Intervertebral disc degeneration (IVDD) is a multifactorial process characterized by progressive extracellular matrix degradation, cellular dysfunction, and chronic inflammation within the disc microenvironment. These changes contribute to structural deterioration, pain, and impaired spinal function (21,22). Pro-inflammatory cytokines play a critical role in IVDD by promoting matrix breakdown, accelerating cellular senescence, and disrupting tissue homeostasis. As a result, inflammatory signaling has become a major focus of research into the mechanisms underlying disc degeneration (21).

Recent Mendelian randomization studies have identified potential associations between gut microbiota composition and susceptibility to IVDD. These findings suggest that microbial factors may influence disc health through systemic inflammatory, metabolic, and immune pathways, supporting the concept that disc degeneration may be affected by processes extending beyond the spine itself (23,24).

Metabolic dysfunction - associated fatty liver disease and the Liver–Brain Connection

Metabolic dysfunction – associated fatty liver disease (MAFLD) is increasingly recognized as a systemic disorder with consequences extending beyond the liver. In addition to its metabolic and cardiovascular complications, growing evidence suggests that MAFLD may contribute to cognitive impairment and neurodegenerative diseases (25,26).

Several mechanisms have been proposed to explain this association, including chronic low-grade inflammation, insulin resistance, oxidative stress, and altered production of liver-derived metabolites. These factors may promote neuroinflammatory

responses and adversely affect neuronal function (25,27).

Recent studies have reported an increased risk of cognitive decline and dementia among individuals with MAFLD, highlighting the importance of the liver as a contributor to brain health. These observations reinforce the concept of a liver–brain axis and suggest that hepatic dysfunction may influence neurological outcomes through multiple interconnected pathways (25–27).

Short-Chain Fatty Acids and Microbial Metabolites

Short-chain fatty acids (SCFAs), primarily acetate, propionate, and butyrate, are among the most important metabolites produced by the gut microbiota. Generated through the fermentation of dietary fibers, SCFAs exert diverse effects on immune regulation, metabolism, and neural function (28).

Within the nervous system, SCFAs contribute to the maintenance of blood–brain barrier integrity, modulation of microglial activity, and regulation of neuroinflammatory responses. Experimental studies indicate that alterations in SCFA production may influence susceptibility to neurological disorders and affect disease progression (29). Because SCFAs represent a major communication pathway between intestinal microorganisms and distant organs, they are increasingly considered key mediators of gut–liver–brain interactions and potential therapeutic targets for neurodegenerative diseases (28,29).

Several classes of microbial and hepatic metabolites have been identified as critical mediators of communication between the gastrointestinal tract and the nervous system. These signaling molecules include short-chain fatty acids, tryptophan-derived metabolites, bile acids, and bacterial endotoxins, each exerting distinct effects on immune regulation, neuronal function, and neuroinflammatory pathways (Figure 2).

Tryptophan Metabolism

Tryptophan metabolism constitutes another important mechanism through which the gut microbiota influences host physiology. Intestinal microorganisms regulate the conversion of tryptophan into a variety of bioactive metabolites that affect immune responses, intestinal homeostasis, and neural signaling (30).

One of the most significant pathways involves the synthesis and regulation of serotonin, a neu-

Metabolizam triptofana

Metabolizam triptofana predstavlja još jedan značajan mehanizam putem kojeg crevna mikrobiota utiče na fiziologiju domaćina. Crevna mikrobiota učestvuje u regulaciji konverzije triptofana u različite bioaktivne metabolite koji utiču na imunološke odgovore, intestinalnu homeostazu i nervnu signalizaciju (30).

Jedan od najznačajnijih puteva uključuje sintezu i regulaciju serotonina, neurotransmitera koji ima ključnu ulogu u raspoloženju, kogniciji i gastrointestinalnoj funkciji. Crevna mikrobiota može uticati na raspoloživost serotonina direktnim i indirektnim mehanizmima, čime utiče na komunikaciju između gastrointestinalnog trakta i centralnog nervnog sistema (31).

Pored puteva povezanih sa serotoninom, mikrobni metaboliti triptofana mogu modulirati inflamatornu signalizaciju i ostvarivati interakcije sa receptorima uključenim u neuroprotekciju i imunološku regulaciju. Ovi mehanizmi dodatno naglašavaju značaj mikrobnog metabolizma u regulaciji zdravlja i bolesti mozga (30,31).

Poremećaj funkcije barijere i endotoksemija

Intestinalna barijera predstavlja ključnu barijeru između spoljašnje sredine i unutrašnje cirkulacije organizma. U fiziološkim uslovima, ova barijera ograničava sistemsku diseminaciju mikroorganizama i potencijalno štetnih mikrobnih produkata, istovremeno omogućavajući selektivnu apsorpciju hranljivih materija (32).

Narušavanje integriteta barijere, koje se često označava kao povećana intestinalna permeabilnost, omogućava translokaciju bakterijskih komponenti, poput lipopolisaharida, u krvotok. Ovaj fenomen doprinosi sistemskoj inflamaciji i doveden je u vezu sa različitim metaboličkim, hepatičnim i neurološkim poremećajima (32,33).

Koncept metaboličke endotoksemije opisuje hronično prisustvo niskih koncentracija bakterijskih endotoksina u cirkulaciji. Takva dugotrajna izloženost može aktivirati urođene imunološke puteve, podstaći inflamatornu signalizaciju i doprineti disfunkciji više organskih sistema, uključujući jetru i mozak (33).

Integrativna perspektiva osovine crevo–jetra–nervni sistem

Sve veći broj dokaza koji povezuju crevnu mikrobiotu sa neurološkim i sistemskim bolestima doveo

je do razvoja sve integrativnijih modela interakcije domaćin–mikrobiom. Umesto da funkcionišu kao izolovani sistemi, creva, jetra, imunološki sistem i nervni sistem danas se sve više razumeju kao delovi dinamičke i međusobno povezane biološke mreže (34,35).

Produkcijom metabolita, modulacijom imunoloških odgovora, regulacijom integriteta bioloških barijera i uticajem na neuroendokrinu signalizaciju, crevna mikrobiota ostvaruje efekte koji značajno prevazilaze granice gastrointestinalnog trakta. Ove interakcije mogu oblikovati fiziološku homeostazu i progresiju bolesti u različitim organskim sistemima (34).

Zajedno posmatrano, savremeni nalazi podržavaju koncept osovine crevo–jetra–nervni sistem, u okviru koje se mikrobni, hepatični, imunološki i nervni putevi međusobno prepliću i zajednički utiču na procese neuroregeneracije i neurodegeneracije. Ovaj integrativni okvir predstavlja osnovu za razvoj novih translacionih strategija usmerenih na modulaciju međusobno povezanih bioloških sistema, umesto na izolovano delovanje na pojedinačne organe (34,35).

Terapijska modulacija osovine crevo–jetra–nervni sistem

Identifikacija međusobno povezanih mikrobnih, hepatičnih, imunoloških i nervnih puteva pruža racionalnu osnovu za istraživanje terapijskih strategija koje osovinu crevo–jetra–nervni sistem posmatraju kao integrisani biološki sistem. Dostupni dokazi u okviru ovog koncepta naročito ukazuju na terapijski značaj mikrobnih metabolita, signalizacije žučnih kiselina, funkcije intestinalne barijere i inflamatornih puteva. Međutim, većina dostupnih dokaza i dalje je pretežno mehanističke ili pretkliničke prirode, dok su direktni klinički dokazi o neuroregenerativnoj efikasnosti ograničeni.

Mikrobni metaboliti kao terapijski ciljevi

Mikrobni metaboliti predstavljaju važne medijatore komunikacije između gastrointestinalnog trakta i udaljenih organa. Kratkolančane masne kiseline, metaboliti poreklom od triptofana i mikrobne modifikacije žučnih kiselina mogu uticati na imunološku regulaciju, intestinalnu homeostazu, sistemski metabolizam i funkciju nervnog sistema. Dostupna literatura stoga ukazuje na mogućnost da ovi metaboliti predstavljaju farmakološki relevantne ciljeve za modulaciju neuroinflamatornih i neurodegenerativnih procesa (28–31).

rotransmitter that plays essential roles in mood, cognition, and gastrointestinal function. The gut microbiota can influence serotonin availability both directly and indirectly, thereby affecting communication between the gut and the central nervous system (31).

In addition to serotonin-related pathways, microbial tryptophan metabolites can modulate inflammatory signaling and interact with receptors involved in neuroprotection and immune regulation. These mechanisms further emphasize the importance of microbial metabolism in the regulation of brain health and disease (30,31).

Barrier Dysfunction and Endotoxemia

The intestinal barrier serves as a critical interface between the external environment and the internal circulation. Under normal conditions, this barrier restricts the systemic dissemination of microorganisms and potentially harmful microbial products while allowing selective nutrient absorption (32).

Disruption of barrier integrity, often referred to as increased intestinal permeability, facilitates the translocation of bacterial components such as lipopolysaccharides into the bloodstream. This phenomenon contributes to systemic inflammation and has been implicated in a variety of metabolic, hepatic, and neurological disorders (32,33).

The concept of metabolic endotoxemia describes the chronic presence of low concentrations of bacterial endotoxins in the circulation. Such exposure can activate innate immune pathways, promote inflammatory signaling, and contribute to dysfunction across multiple organ systems, including the liver and brain (33).

Integrative Perspective of the Gut–Liver–Nerve Axis

The growing body of evidence linking the gut microbiota to neurological and systemic diseases has led to the development of increasingly integrative models of host–microbe interactions. Rather than functioning as isolated systems, the gut, liver, immune system, and nervous system are now understood to operate within a dynamic and interconnected biological network (34,35).

Through the production of metabolites, modulation of immune responses, regulation of barrier integrity, and influence on neuroendocrine signaling, the gut microbiota exerts effects that extend far beyond the gastrointestinal tract. These interactions

can shape both physiological homeostasis and disease progression across multiple organs (34).

Taken together, current findings support the concept of a gut–liver–nerve axis in which microbial, hepatic, immune, and neural pathways converge to influence neuroregeneration and neurodegeneration. This integrative framework provides a foundation for the development of novel translational strategies aimed at targeting interconnected biological systems rather than individual organs in isolation (34,35).

Therapeutic Modulation of the Gut–Liver–Nerve Axis

The identification of interconnected microbial, hepatic, immune, and neural pathways provides a rationale for investigating therapeutic strategies that target the gut–liver–nerve axis as an integrated biological system. Current evidence within this framework particularly supports the therapeutic relevance of microbial metabolites, bile acid signaling, intestinal barrier function, and inflammatory pathways. However, the available evidence remains predominantly mechanistic or preclinical, and direct clinical evidence for neuroregenerative efficacy is limited.

Microbial Metabolites as Therapeutic Targets

Microbial metabolites represent important mediators of communication between the gastrointestinal tract and distant organs. Short-chain fatty acids (SCFAs), tryptophan-derived metabolites, and microbial modifications of bile acids may influence immune regulation, intestinal homeostasis, systemic metabolism, and neural function. The existing literature suggests that these metabolites may therefore represent pharmacologically relevant targets for modulation of neuroinflammatory and neurodegenerative processes (28–31).

SCFAs, particularly acetate, propionate, and butyrate, are generated predominantly through microbial fermentation of dietary fibers and participate in metabolic and immune regulation. Within the nervous system, SCFAs have been associated with maintenance of blood–brain barrier integrity, modulation of microglial activity, and regulation of neuroinflammatory responses (28,29). These observations provide a mechanistic basis for investigating interventions capable of restoring or modifying microbial metabolite production. Nevertheless, the available evidence does not currently establish

SCFA, naročito acetat, propionat i butirat, nastaju pretežno kao rezultat mikrobne fermentacije dijetetskih vlakana i učestvuju u regulaciji metabolizma i imunoloških odgovora. U nervnom sistemu povezane su sa održavanjem integriteta krvno-moždane barijere, modulacijom aktivnosti mikroglije i regulacijom neuroinflamatornih odgovora (28,29). Ova zapazanja pružaju mehanističku osnovu za istraživanje intervencija koje bi mogle obnoviti ili modifikovati produkciju mikrobnih metabolita. Ipak, trenutno dostupni dokazi ne potvrđuju postojanje specifične terapije zasnovane na SCFA koja bi se mogla smatrati dokazanom neuroregenerativnom terapijom.

Metabolizam triptofana predstavlja još jedan proces potencijalno podložan terapijskoj modulaciji. Intestinalni mikroorganizmi učestvuju u stvaranju bioaktivnih metabolita triptofana koji mogu uticati na imunološke odgovore, intestinalnu homeostazu i nervnu signalizaciju. Modulacija raspoloživosti serotoninu zavisna od mikrobiote, kao i drugih puteva povezanih sa triptofanom, dodatno pokazuje na koji način mikrobni metabolizam može uticati na komunikaciju na relaciji crevo–mozak (30,31). Stoga ovi putevi mogu predstavljati potencijalne ciljeve budućih farmakoloških i mikrobiomski usmerenih intervencija.

Signalizacija žučnih kiselina i putevi TGR5/FXR

Žučne kiseline predstavljaju dodatnu farmakološki relevantnu vezu između creva, jetre, imunološkog i nervnog sistema. Primarne žučne kiseline sintetisane u jetri podležu opsežnoj mikrobnoj transformaciji u crevima, pri čemu nastaju sekundarne žučne kiseline sa različitim signalnim svojstvima. Ovi metaboliti stupaju u interakciju sa receptorima, uključujući FXR i TGR5, čime utiču na metaboličku homeostazu, imunološke odgovore i međuorgansku komunikaciju (7,8,12).

Potencijalni neurološki značaj signalizacije žučnih kiselina podržan je dokazima da su njihovi receptori eksprimirani u neuronskim i glijalnim populacijama i da mogu učestvovati u regulaciji neuroinflamacije i neuronske homeostaze (7). Eksperimentalni nalazi dalje ukazuju na mogućnost da ursodeoksiholna kiselina modulira mikroglijalnu inflamaciju putem mehanizama povezanih sa TGR5 receptorom nakon cerebralne ishemije (13). Ovi nalazi opravdavaju dalja istraživanja signalizacije žučnih kiselina kao potencijalnog terapijskog cilja, naročito kod neuroloških stanja koja karakteriše perzistentna neuroinflamacija.

Međutim, navedene nalaze trenutno treba tumačiti prvenstveno kao mehanističke i pretkliničke dokaze. Da li farmakološka modulacija FXR, TGR5 ili specifičnih metabolita žučnih kiselina može proizvesti klinički značajne neuroregenerativne efekte, tek treba da bude utvrđeno.

Mikrobiom i regeneracija perifernih nerava

Potencijalni terapijski značaj mikrobioma prevladava centralni nervni sistem. Regeneracija perifernog nerva zavisi od koordinisanih interakcija između Schwannovih ćelija, makrofaga, inflamatornih medijatora i neurotrofne signalizacije. Reparativne Schwannove ćelije podržavaju regeneraciju aksona uklanjanjem ćelijskog detritusa, produkcijom neurotrofnih faktora i obezbeđivanjem usmeravajućih signala, dok makrofagi učestvuju u uklanjanju detritusa i remodelovanju regenerativnog mikrokruženja (14–16).

Nastajući dokazi ukazuju na mogućnost da crevna mikrobiota indirektno utiče na ove procese putem sistemske imunološke regulacije, inflamatornih medijatora i mikrobnih metabolita. Odnos između perifernog nervnog sistema i crevne mikrobiote stoga predstavlja novu oblast interesovanja u regenerativnim neuronaukama (17). Iako su direktni dokazi o terapijskoj efikasnosti i dalje ograničeni, ovaj koncept ukazuje na mogućnost da modulacija sistemskih mikrobnih i imunoloških puteva u budućnosti predstavlja dopunu lokalnim regenerativnim strategijama.

Translacijska perspektiva

Zajedno posmatrano, literatura uključena u ovaj pregledni rad identifikuje nekoliko komponenti osovine crevo–jetra–nervni sistem koje su potencijalno pogodne za ciljanu terapiju. Mikrobni metaboliti, naročito SCFA i metaboliti poreklom od triptofana, predstavljaju potencijalne medijatore signalizacije na relaciji crevo–mozak i sistemske komunikacije, dok putevi žučnih kiselina koji uključuju FXR i TGR5 predstavljaju jasnije definisan farmakološki signalni sistem. Mikrobiom dodatno može uticati na regeneraciju perifernih nerava putem imunoloških i metaboličkih mehanizama.

Međutim, trenutni dokazi ne bi trebalo da se tumače kao potvrda da manipulacija mikrobiomom ili modulacija žučnih kiselina predstavljaju ustanovljene terapijske postupke za neurodegenerativne ili neuroregenerativne poremećaje. Većina dostupnih dokaza i dalje je mehanističke, opservacione ili pret-

a specific SCFA-based intervention as an effective neuroregenerative therapy.

Tryptophan metabolism represents another potentially modifiable pathway. Intestinal microorganisms participate in the generation of bioactive tryptophan-derived metabolites that can influence immune responses, intestinal homeostasis, and neural signaling. Microbiota-dependent modulation of serotonin availability and other tryptophan-related pathways further illustrates how microbial metabolism may affect gut–brain communication (30,31). These pathways may therefore represent candidate targets for future pharmacological and microbiome-directed interventions.

Bile Acid Signaling and TGR5/FXR Pathways

Bile acids provide an additional pharmacologically relevant link between the gut, liver, immune system, and nervous system. Primary bile acids synthesized in the liver undergo extensive microbial transformation within the intestine, generating secondary bile acids with distinct signaling properties. These metabolites interact with receptors including FXR and TGR5, thereby influencing metabolic homeostasis, immune responses, and interorgan communication (7,8,12).

The potential neurological relevance of bile acid signaling is supported by evidence that bile acid receptors are expressed in neural and glial populations and may participate in the regulation of neuroinflammation and neuronal homeostasis (7). Experimental findings further indicate that ursodeoxycholic acid can modulate microglial inflammation through TGR5-associated mechanisms following cerebral ischemia (13). These observations support further investigation of bile acid signaling as a potential therapeutic target, particularly in neurological conditions characterized by persistent neuroinflammation.

At present, however, these findings should be interpreted primarily as mechanistic and preclinical evidence. Whether pharmacological modulation of FXR, TGR5, or specific bile acid metabolites can produce clinically meaningful neuroregenerative effects remains to be established.

Microbiome and Peripheral Nerve Regeneration

The potential therapeutic relevance of the microbiome extends beyond the central nervous system. Peripheral nerve regeneration depends on

coordinated interactions among Schwann cells, macrophages, inflammatory mediators, and neurotrophic signaling. Repair Schwann cells support axonal regeneration by clearing cellular debris, producing neurotrophic factors, and providing guidance signals, while macrophages contribute to debris clearance and remodeling of the regenerative microenvironment (14–16).

Emerging evidence suggests that the gut microbiota may influence these processes indirectly through systemic immune regulation, inflammatory mediators, and microbial metabolites. The relationship between the peripheral nervous system and gut microbiota has therefore become an emerging area of interest in regenerative neuroscience (17). Although direct therapeutic evidence remains limited, this concept suggests that modulation of systemic microbial and immune pathways could potentially complement local regenerative strategies.

Translational Perspective

Taken together, the literature included in this review supports several potentially targetable components of the gut–liver–nerve axis. Microbial metabolites, particularly SCFAs and tryptophan-derived metabolites, represent candidate mediators of gut–brain and systemic signaling, whereas bile acid pathways involving FXR and TGR5 provide a more defined pharmacological signaling system. The microbiome may additionally influence peripheral nerve regeneration through immune and metabolic mechanisms.

However, the current evidence should not be interpreted as demonstrating that microbiome manipulation or bile acid modulation is an established treatment for neurodegenerative or neuroregenerative disorders. Most available evidence remains mechanistic, observational, or preclinical. The major translational challenge is therefore to determine whether modulation of these pathways can produce reproducible changes in validated neurological outcomes.

Future studies should combine microbiome profiling with metabolomic, inflammatory, and neurological endpoints and should distinguish correlations between microbial composition and disease from demonstrable causal therapeutic effects. Such an approach may facilitate the development of targeted strategies that modulate specific microbial metabolites, bile acid receptors, or immune pathways rather than attempting nonspecific modification of the entire microbiome.

kliničke prirode. Osnovni translacioni izazov stoga predstavlja utvrđivanje da li modulacija ovih puteva može dovesti do doslednih i klinički značajnih poboljšanja relevantnih neuroloških ishoda.

Buduća istraživanja trebalo bi da kombinuju profilisanje mikrobioma sa metabolomskim, inflamatornim i neurološkim parametrima, uz jasno razlikovanje korelacija između sastava mikrobiote i bolesti od dokazanih uzročno-posledičnih terapijskih efekata. Takav pristup mogao bi omogućiti razvoj ciljanih strategija usmerenih na specifične mikrobne metabolite, receptore za žučne kiseline ili imunološke puteve, umesto neselektivne modulacije celokupnog mikrobioma.

Budući pravci

Sve veći broj dokaza koji podržavaju postojanje interakcija između crevne mikrobiote, jetre i nervnog sistema ukazuje na nekoliko važnih pravaca budućih istraživanja. Iako su povezanosti između mikrobne disbioze i neurodegenerativnih poremećaja konzistentno opisivane, uzročni mehanizmi koji povezuju specifične mikrobne zajednice sa nastankom i progresijom bolesti još uvek nisu u potpunosti razjašnjeni. Neophodne su longitudinalne studije na ljudima koje objedinjuju profilisanje mikrobioma i kliničke ishode radi boljeg razumevanja ovih odnosa (2,3,9).

Mikrobni metaboliti predstavljaju posebno perspektivne ciljeve budućih istraživanja. Kratkolančane masne kiseline i metaboliti poreklom od triptofana izdvojili su se kao značajni medijatori komunikacije na relaciji crevo–mozak, ali njihova precizna uloga u neuroprotekciji, neuroinflamaciji i reparaciji nervnog tkiva još uvek nije dovoljno razjašnjena (28–31). Bolje razumevanje ovih puteva moglo bi omogućiti razvoj terapijskih intervencija zasnovanih na mikrobiomu, usmerenih na obnovu metaboličke homeostaze.

Signalizacija žučnih kiselina predstavlja još jednu oblast intenzivnog razvoja. Savremena saznanja o receptorima FXR i TGR5 ukazuju na to da žučne kiseline mogu predstavljati značajne molekularne veze između hepatičnih i neuroloških procesa (7,8). Eksperimentalni dokazi o antiinflamatornim efektima ursodeoksiholne kiseline putem mehanizama posredovanih TGR5 receptorom opravdavaju dalja translaciona i klinička istraživanja, posebno kod neurodegenerativnih bolesti koje karakteriše hronična aktivacija mikroglije (13).

Buduće studije trebalo bi takođe da ispituju

ulogu osovine crevo–jetra–nervni sistem u regenerativnoj medicini. Preliminarni dokazi ukazuju na mogućnost da mikrobni i imunološki posredovani mehanizmi utiču na regeneraciju perifernih nerava preko efekata na funkciju Schwannovih ćelija, aktivnost makrofaga i inflamatornu signalizaciju (14–17). Razumevanje ovih interakcija može identifikovati nove strategije za unapređenje regeneracije aksona nakon povrede.

Konačno, sve veći broj dokaza koji povezuju MAFLD, sistemsku inflamaciju, kognitivno oštećenje i demenciju ukazuje na to da jetru treba posmatrati kao aktivnog učesnika u neurološkim bolestima, a ne isključivo kao metabolički organ (25–27). Integrativni pristupi koji objedinjuju hepatologiju, neuronauku, imunologiju i istraživanja mikrobioma biće od ključnog značaja za prevođenje koncepta osovine crevo–jetra–nervni sistem u klinički relevantne dijagnostičke i terapijske primene.

Zaključak

Osovinu crevo–jetra–nervni sistem predstavlja kompleksnu biološku mrežu koja integriše mikrobne, metaboličke, imunološke i nervne signalne puteve. Savremeni dokazi ukazuju na to da crevna disbioza, poremećen metabolizam žučnih kiselina, narušen integritet bioloških barijera i hronična inflamacija mogu doprineti neurodegenerativnim procesima, ali istovremeno uticati i na regenerativne procese unutar nervnog sistema. Iako su ostvareni značajni pomaci u razumevanju osnovnih mehanizama, neophodna su dalja translaciona i klinička istraživanja radi utvrđivanja uzročno-posledičnih odnosa i identifikacije efikasnih terapijskih intervencija. Ciljana modulacija osovine crevo–jetra–nervni sistem može u budućnosti pružiti nove mogućnosti za prevenciju i lečenje različitih neuroloških poremećaja.

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Future Directions

The growing body of evidence supporting interactions among the gut microbiota, liver, and nervous system highlights several important directions for future research. Although associations between microbial dysbiosis and neurodegenerative disorders have been consistently reported, the causal mechanisms linking specific microbial communities to disease initiation and progression remain incompletely understood. Longitudinal human studies integrating microbiome profiling, and clinical outcomes are needed to clarify these relationships (2,3,9).

Microbial metabolites represent particularly promising targets for future investigation. Short-chain fatty acids and tryptophan-derived metabolites have emerged as key mediators of gut–brain communication, yet their precise roles in neuroprotection, neuroinflammation, and neural repair require further elucidation (28–31). Improved understanding of these pathways may facilitate the development of microbiome-based therapeutic interventions aimed at restoring metabolic homeostasis.

Bile acid signaling constitutes another rapidly expanding area of research. Recent findings regarding FXR and TGR5 receptors suggest that bile acids may function as important molecular links between hepatic and neurological processes (7,8). Experimental evidence demonstrating anti-inflammatory effects of ursodeoxycholic acid through TGR5-mediated pathways warrants further translational and clinical investigation, particularly in neurodegenerative diseases characterized by chronic microglial activation (13).

Future studies should also examine the role of the gut–liver–nerve axis in regenerative medicine. Preliminary evidence suggests that microbial and immune-mediated mechanisms may influence peripheral nerve regeneration through effects on Schwann cell function, macrophage activity, and inflammatory signaling (14–17). Understanding these interactions may identify novel strategies to enhance neural repair following injury.

Finally, increasing evidence linking MAFLD, systemic inflammation, cognitive impairment, and dementia suggests that the liver should be considered an active participant in neurological disease rather than merely a metabolic organ (25–27). Integrative approaches combining hepatology, neuroscience, immunology, and microbiome research will be essential for translating the gut–liver–nerve axis concept into clinically meaningful diagnostic and therapeutic applications.

Conclusion

The gut–liver–nerve axis represents a complex biological network integrating microbial, metabolic, immune, and neural signaling pathways. Current evidence indicates that gut dysbiosis, altered bile acid metabolism, impaired barrier function, and chronic inflammation contribute to neurodegeneration while also influencing regenerative processes within the nervous system. Although important mechanistic insights have been established, further translational and clinical studies are required to clarify causality and identify effective therapeutic interventions. Targeting the gut–liver–nerve axis may offer promising opportunities for the prevention and treatment of neurological disorders.

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