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BIOCHEMICAL AND BIOPHYSICAL FOUNDATIONS OF THE MICROBIOME–BRAIN AXIS

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ABSTRACT

The gut–brain axis represents a complex and highly dynamic bidirectional communication network that integrates neural, endocrine, immune, and metabolic signaling pathways, enabling continuous interaction between the gastrointestinal tract and the central nervous system (CNS). This integrative system operates through multiple interconnected routes, including the vagus nerve, hypothalamic–pituitary–adrenal (HPA) axis, immune mediators, and circulating microbial metabolites. Recent advances in biophysics and biochemistry have demonstrated that microbial-derived compounds, membrane transport mechanisms, and electrophysiological processes play fundamental roles in modulating CNS function at both cellular and systemic levels. From a biophysical perspective, microbiota influence neuronal excitability by altering ion channel dynamics, membrane potential stability, and synaptic transmission efficiency. Changes in ionic gradients and membrane conductivity, often mediated by microbial metabolites such as short-chain fatty acids, directly affect action potential generation and propagation. In parallel, biochemical mechanisms involve the synthesis and regulation of neuroactive molecules, including neurotransmitters, neuromodulators, and metabolic intermediates that can cross or influence the blood–brain barrier. Furthermore, microbial regulation of host metabolism contributes to energy homeostasis and mitochondrial function in neural cells, thereby impacting ATP-dependent processes essential for maintaining electrochemical gradients. The interaction between microbial products and host signaling pathways also modulates inflammatory responses, which in turn can influence neuronal plasticity and network activity. This study aims to synthesize contemporary findings on the biophysical and biochemical mechanisms underlying microbiome-mediated regulation of neural activity, with particular emphasis on molecular signaling pathways, ion channel modulation, membrane transport processes, and metabolic interactions that collectively shape brain function.

KEYWORDS: Gut–brain axis; microbiome; biofizika; biokimya; neyromediatorlar; ion kanalları; metabolitlər; elektrofiziologiya; siqnal ötürülməsi.

INTRODUCTION

The gut–brain axis (GBA) is increasingly recognized as a key regulatory system linking gastrointestinal physiology with brain function. It encompasses a highly coordinated network of bidirectional communication pathways that integrate neural, endocrine, immune, and metabolic signals, thereby maintaining systemic homeostasis. This interaction is mediated through complex signaling routes, including the vagus nerve, hypothalamic–pituitary–adrenal (HPA) axis, circulating hormones, immune mediators, and a wide range of microbiota-derived metabolites. These pathways enable rapid and long-term adaptations of brain function in response to changes within the gut environment.

From a biophysical perspective, neuronal excitability and signal transmission are tightly regulated by ionic gradients across cellular membranes, membrane potentials, and synaptic activity, all of which are sensitive to modulation by microbiota-derived compounds.[1] Alterations in ion channel conductance, particularly those involving calcium, potassium, and sodium channels, can significantly affect action potential generation and propagation. In addition, microbial

metabolites can influence membrane fluidity and receptor dynamics, thereby modulating synaptic efficacy and neural network activity.

Biochemically, gut microbiota produce a diverse array of neuroactive substances, including short-chain fatty acids (SCFAs), neurotransmitters such as gamma-aminobutyric acid (GABA), serotonin precursors, and dopamine-related compounds, as well as amino acid derivatives that directly or indirectly affect brain function.[2] These molecules can interact with host receptors, influence intracellular signaling cascades, and modulate gene expression related to neurotransmission and neuroplasticity. Furthermore, microbial metabolites play a critical role in regulating mitochondrial activity and energy metabolism in neurons, thereby supporting ATP-dependent processes essential for maintaining electrochemical gradients.

Recent research indicates that dysbiosis—an imbalance in microbial composition—can lead to significant disruptions in these finely tuned processes. It has been shown that dysbiosis can alter membrane permeability, impair neurotransmitter synthesis, and dysregulate inflammatory signaling pathways, ultimately contributing to the pathophysiology of neurological disorders such as depression, epilepsy, and neurodegenerative diseases.[3] In particular, increased intestinal permeability and compromised blood–brain barrier integrity may facilitate the translocation of pro-inflammatory molecules, further exacerbating neural dysfunction.

Moreover, emerging evidence suggests that chronic dysbiosis can induce long-term changes in synaptic plasticity, neural circuitry, and behavioral responses through both direct biochemical interactions and indirect immunological mechanisms. These findings highlight the importance of maintaining microbial homeostasis for optimal neurophysiological function. Therefore, understanding the integration of biophysical and biochemical mechanisms within the GBA is essential not only for elucidating fundamental physiological processes but also for developing innovative therapeutic strategies targeting microbiome–brain interactions.

MATERIALS AND METHODS

This study was conducted as a narrative review integrating data from peer-reviewed articles published between 2020 and 2025. Scientific databases including PubMed, Scopus, and Web of Science were systematically searched using keywords such as “gut-brain axis,” “microbiome,” “electrophysiology,” “ion channels,” and “neurotransmitters.” Inclusion criteria encompassed experimental, clinical, and computational studies focusing on molecular, cellular, and systemic mechanisms of microbiome-brain interactions. Studies with insufficient methodological clarity or lacking relevance to biophysical or biochemical mechanisms were excluded.

Data extraction focused on microbial metabolites, membrane transport processes, electrophysiological changes, and biochemical signaling pathways. Comparative analysis was performed to identify consistent patterns and emerging trends.

RESULTS AND DISCUSSION

Microbial metabolites, particularly short-chain fatty acids (SCFAs), including butyrate, propionate, and acetate, play a central role in modulating neuronal activity.[4,12] These metabolites influence membrane potential by regulating ion channel conductance, especially potassium and calcium channels, thereby altering neuronal excitability and the threshold for action potential generation.[4,13] In addition to direct electrophysiological effects, SCFAs can interact with G-protein-coupled receptors and intracellular signaling pathways, further modulating neuronal responsiveness. Butyrate has also been shown to enhance mitochondrial ATP production, supporting the maintenance of electrochemical gradients across neuronal membranes and ensuring the proper functioning of ion pumps such as Na^+/K^+-ATPase.[5,14] Moreover, its role as a histone deacetylase inhibitor suggests an epigenetic dimension in the regulation of genes involved in synaptic plasticity and neuronal survival.

From a biophysical perspective, microbiota can affect the integrity of the blood–brain barrier (BBB) by modulating tight junction proteins, which alters ion permeability and molecular transport between the peripheral circulation and the central nervous system.[6,15] Changes in BBB permeability can influence the diffusion of ions, metabolites, and signaling molecules, thereby impacting neuronal homeostasis. Experimental studies indicate that disruption of microbiota composition leads to measurable changes in neuronal firing patterns and synaptic plasticity, particularly in hippocampal regions associated with learning and memory.[7,16] These alterations are often accompanied by modifications in dendritic spine density and synaptic connectivity, reflecting deeper structural and functional changes in neural circuits.

Biochemically, gut microbiota are involved in the synthesis of neurotransmitters such as serotonin, dopamine precursors, and gamma-aminobutyric acid (GABA).[8,17] These neuroactive compounds can influence both peripheral and central signaling pathways, either by direct interaction with neural receptors or indirectly via vagal nerve stimulation. It has been demonstrated that microbial regulation of tryptophan metabolism significantly influences serotonin biosynthesis and signaling pathways, affecting mood, cognition, and behavior.[10,18] In addition, microbial metabolites can modulate enzyme activity involved in neurotransmitter synthesis and degradation, thereby fine-tuning synaptic transmission and neurochemical balance.

Inflammatory mechanisms also play a crucial role in microbiome–brain interactions. Lipopolysaccharides (LPS), components of Gram-negative bacterial cell walls, activate systemic immune responses, leading to cytokine-mediated alterations in neuronal excitability and synaptic transmission.[9,19] Elevated levels of pro-inflammatory cytokines such as IL-6 and TNF-α can disrupt synaptic signaling, impair long-term potentiation, and alter neuronal network dynamics. Chronic neuroinflammation has been linked to long-term electrophysiological changes, including shifts in resting membrane potential and synaptic strength, as well as to the progression of neurodegenerative processes.[19,20] Furthermore, sustained inflammatory signaling may contribute to oxidative stress and mitochondrial dysfunction, creating a feedback loop that exacerbates neuronal damage and functional decline.

CONCLUSION

The gut–brain axis represents a multifaceted and highly integrated system in which biophysical and biochemical mechanisms converge to regulate neural function across multiple organizational levels, from molecular interactions to complex neural networks. Within this framework, microbial metabolites act as key modulators of ion channel activity, membrane dynamics, and neurotransmitter synthesis, thereby directly influencing neuronal excitability, synaptic transmission, and overall signaling efficiency in the central nervous system. These interactions are not isolated but occur within a tightly regulated environment where electrical properties of membranes, intracellular signaling cascades, and metabolic pathways are dynamically interconnected.

At the biophysical level, the modulation of ion channel kinetics and membrane conductivity by microbial-derived compounds contributes to alterations in action potential generation, propagation, and synaptic integration. Simultaneously, biochemical processes such as the synthesis and regulation of neurotransmitters, neuromodulators, and metabolic intermediates ensure the fine-tuning of neuronal communication and plasticity. The integration of these processes highlights the importance of considering both electrical and chemical dimensions of neural regulation when studying the gut–brain axis.

Advances in electrophysiology, molecular biology, and computational modeling have significantly enhanced our understanding of these complex interactions. High-resolution techniques such as patch-clamp recordings, multi-electrode arrays, and imaging methods have provided detailed insights into how microbial signals influence neuronal activity at the cellular level. In parallel, molecular and omics-based approaches, including genomics, metabolomics, and proteomics, have enabled the identification of key signaling molecules and pathways involved in microbiome–brain communication. Computational modeling and systems biology approaches further allow the integration of large datasets to predict functional outcomes and identify potential therapeutic targets.

Importantly, these developments open new avenues for translational research aimed at harnessing microbiome-based strategies for the prevention and treatment of neurological disorders. Targeted interventions such as probiotics, prebiotics, dietary modulation, and microbiota transplantation hold promise for restoring physiological balance within the gut–brain axis. Future research should therefore focus not only on elucidating fundamental mechanisms but also on developing clinically applicable approaches that integrate biophysical and biochemical insights to modulate neural function and improve patient outcomes.

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