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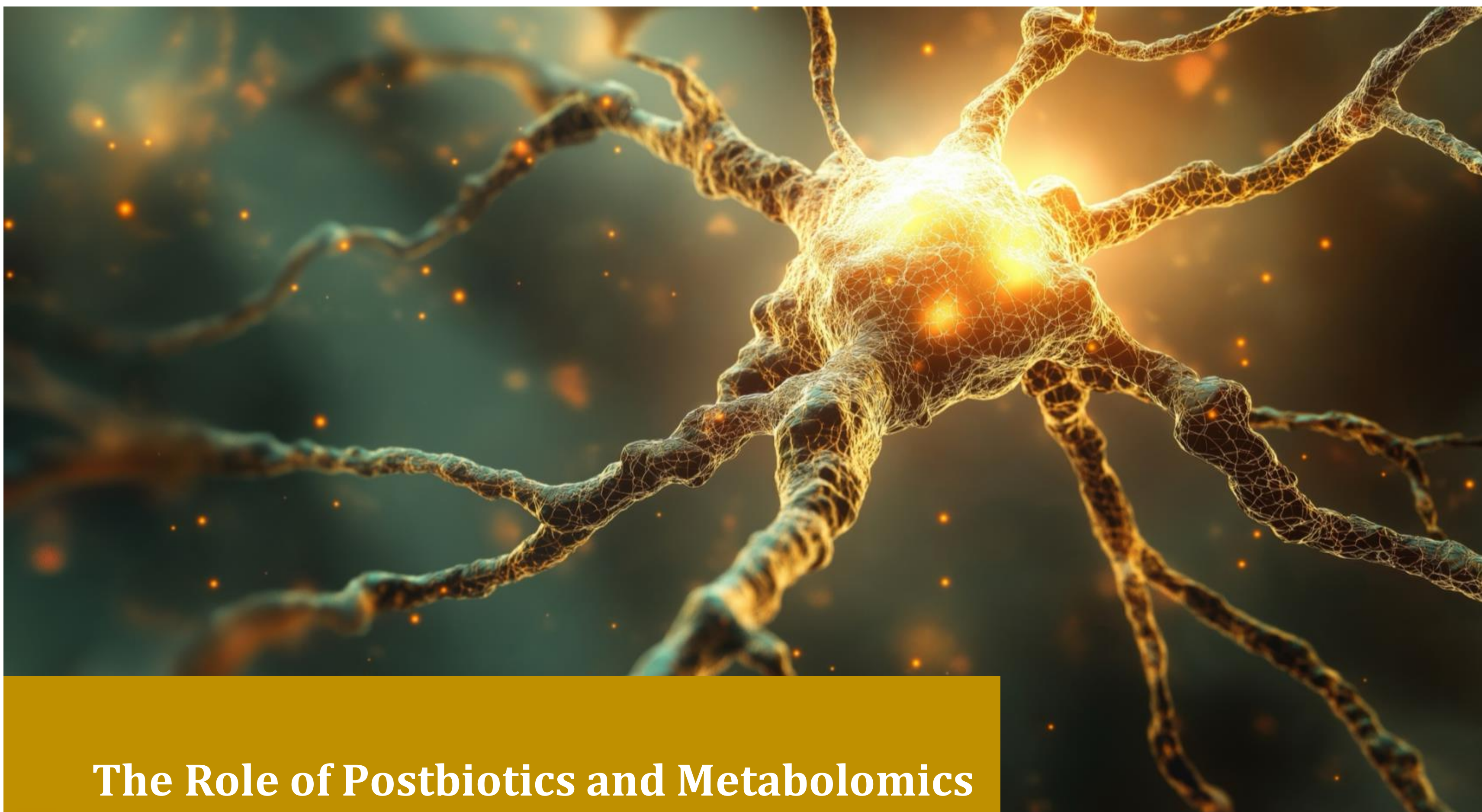

The Role of Postbiotics and Metabolomics in Modulating the Gut-Brain Axis

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The Complexity of the Gut-Brain Axis and the Evolution of Interventions

Human health is a complex ecosystem where physiological systems interact in intricate and, at times, surprising ways. Among these interactions, the gut-brain axis has emerged as a bidirectional communication pathway of paramount importance, influencing everything from digestion and metabolism to mood, cognition, and behavior (Cryan et al., 2020). This connection is mediated by a multifaceted network that includes the enteric nervous system, the vagus nerve, the endocrine system, the immune system, and, crucially, the vast community of microorganisms inhabiting the gastrointestinal tract: the gut microbiota (Carabotti et al., 2015).

The microbiota, composed of trillions of bacteria, fungi, viruses, and archaea, is not merely a passive collection of inhabitants; it is an active metabolic organ, capable of producing a myriad of bioactive compounds from the digestion of nutrients not absorbed by the host.

The balance and diversity of this microbial community are fundamental for maintaining homeostasis. Imbalances, known as dysbiosis, have been consistently associated with a growing range of health conditions, including gastrointestinal disorders, metabolic diseases, and, increasingly evident, neuropsychiatric disorders such as depression, anxiety, and Autism Spectrum Disorder (ASD) (Martins et al., 2022; Foster et al., 2017).

Historically, strategies to modulate the gut microbiota and, consequently, influence the gut-brain axis have focused on the administration of beneficial live microorganisms (probiotics) and indigestible dietary fibers that serve as substrates for these microorganisms (prebiotics) (Gibson et al., 2017). Although probiotics and prebiotics have demonstrated significant benefits in various clinical contexts, their application can be limited by issues of viability, stability, safety, and specificity. The viability of probiotics, for example, can be compromised by gastric acidity and bile salts, reducing the number of live microorganisms reaching the intestine (Yao et al., 2020).

In this scenario, science is advancing towards a new generation of interventions: postbiotics. These are defined as "preparations of inactivated microorganisms and/or their components that confer a health benefit on the host" (Salminen et al., 2021). The shift in focus from live microorganisms to their metabolic products and structural components represents a paradigmatic leap, offering greater stability, safety, and the possibility of more rigorous standardization. In parallel, metabolomics, the large-scale study of metabolites present in a biological system, emerges as an indispensable tool for unraveling the complex "chemical language" of the microbiota and its interactions with the host. By mapping metabolic profiles, metabolomics allows for the identification of biomarkers, elucidation of mechanisms of action, and paves the way for precision nutrition and the development of personalized therapies (Nicholson et al., 2012).

Definition and Classification of Postbiotics

The definition of postbiotic has evolved, but the most widely accepted currently, proposed by the International Scientific Association of Probiotics and Prebiotics (ISAPP), emphasizes that they are "preparations of inactivated microorganisms and/or their components that confer a health benefit on the host" (Salminen et al., 2021). This definition encompasses a wide range of compounds, which can be categorized as follows:

- **Microbial Metabolites**: These are products of bacterial metabolism, such as short-chain fatty acids (SCFAs), vitamins (e.g., B12, B9), neurotransmitters (e.g., GABA, serotonin), enzymes, antimicrobial peptides, and organic acids.
- **Inactivated Cellular Components**: These include fragments of bacterial cells, such as peptidoglycans, teichoic acids, lipopolysaccharides (LPS in controlled concentrations and less immunogenic forms), exopolysaccharides (EPS), and surface proteins.
- **Cell Lysates**: These are extracts obtained after the lysis (rupture) of microbial cells, containing a mixture of intracellular and cell wall components.
- **Extracellular Vesicles (EVs)**: These are small structures released by bacteria that contain proteins, lipids, nucleic acids, and metabolites, acting as vehicles for intercellular communication and with the host (Ma et al., 2021)

The main distinction from probiotics is the absence of live microorganisms, which gives postbiotics advantages in terms of stability (do not require refrigeration), safety (no risk of bacterial translocation or infection in immunocompromised individuals), and ease of formulation and standardization (Aguilar-Toalá et al., 2018).

Postbiotics: The Bioactive Messengers of the Gut Microbiota

The understanding that the health benefits conferred by probiotics do not depend exclusively on the viability of the microorganisms, but also on their metabolites and cellular components, has propelled the field of postbiotics. These represent a diverse class of substances that act as "messengers" of the microbiota, communicating with the host and modulating various physiological functions.

Mechanisms of Action of Postbiotics in Gut-Brain Axis Modulation

Postbiotics exert their beneficial effects through multiple mechanisms that directly impact the complex communication between the gut and the brain:

Modulation of Immune Response and Inflammation

Chronic low-grade inflammation is a common factor in various neuropsychiatric conditions, including depression, anxiety, and ASD (Madore et al., 2016). Postbiotics, especially SCFAs like butyrate, are potent immunomodulators. Butyrate, for example, acts as a histone deacetylase (HDAC) inhibitor, influencing gene expression and promoting an anti-inflammatory profile in immune cells (Koh et al., 2016). It can reduce the production of pro-inflammatory cytokines (such as IL-6 and TNF-α) and increase the production of anti-inflammatory cytokines (such as IL-10). The reduction of inflammatory biomarkers, such as C-Reactive Protein (CRP) and fecal calprotectin, observed in studies with probiotics (Shaaban et al., 2018), suggests that postbiotics may be the main mediators of these effects. Bacterial cell wall components, such as LPS (in controlled doses and non-toxic forms), can also interact with Toll-like receptors (TLRs) on immune cells, inducing a regulatory immune response that "trains" the host's immune system to be less reactive to inflammatory stimuli (Rook et al., 2017).

Strengthening the Intestinal Barrier

The integrity of the intestinal epithelial barrier is crucial for preventing the translocation of toxins, pathogens, and microbial components into the bloodstream. A compromised barrier, or "leaky gut," is associated with systemic inflammation and neuroinflammation (Fiorentino et al., 2016). Postbiotics, such as butyrate, are the main energy source for colonocytes (colon cells), promoting their proliferation and differentiation, and strengthening the tight junctions between epithelial cells (Peng et al., 2009). By improving barrier function, postbiotics reduce the systemic inflammatory load, protecting the brain from neurotoxic substances and inflammatory mediators that could cross the blood-brain barrier. The measurement of fecal calprotectin, a marker of intestinal inflammation, is a way to monitor barrier health (D'Amico et al., 2021).

Modulation of Neurotransmitters and Neuromodulators

The gut microbiota is capable of producing and metabolizing a vast range of neurotransmitters and neuromodulators that can directly influence brain function. Postbiotics derived from these processes play a fundamental role. For example, gut bacteria can metabolize tryptophan, an essential amino acid, into metabolites that affect the serotonin pathway, a crucial neurotransmitter for mood, sleep, and appetite regulation (Yano et al., 2015). Other microbial metabolites, such as GABA (gamma-aminobutyric acid), can also be produced and influence neural activity (Bravo et al., 2011). The literature highlights the importance of compounds like S-adenosylmethionine (SAMe), vitamin B12, and vitamin B9 in the methylation cycle and neurotransmitter synthesis, processes that are intrinsically linked to microbial activity and the availability of their metabolites (Bottiglieri, 2002; O'Leary & Samman, 2010; Bailey & Gregory, 1999). The modulation of these neurochemical systems by postbiotics can explain the beneficial effects observed in parameters such as mood, focus, and stress reduction.

Antioxidant and Neuroprotective Effects

Oxidative stress is a contributing factor to neural dysfunction, brain aging, and the progression of neurodegenerative diseases (Lobo et al., 2010). Some postbiotics, such as certain peptides and bacterial exopolysaccharides, possess direct antioxidant properties, neutralizing free radicals and protecting cells from oxidative damage (Wang et al., 2019). Furthermore, by reducing systemic inflammation and strengthening the intestinal barrier, postbiotics indirectly contribute to neuroprotection, decreasing the brain's exposure to pro-oxidant and inflammatory compounds.

Table 1 demonstrates the diversity of postbiotics, which include metabolites such as short-chain fatty acids (SCFAs) and neurotransmitters like GABA, as well as bacterial structural components and vitamins. Each type of postbiotic exerts specific mechanisms of action on the gut-brain axis, such as inflammation modulation, intestinal barrier strengthening, and influence on neurotransmitter synthesis. These mechanisms contribute to a range of potential benefits, including improved cognitive function, reduced anxiety, and support for intestinal and immune health, highlighting the fundamental role of these compounds in gut-brain communication.

Category	Probiotics	Prebiotics	Synbiotics	Postbiotics
Definition	Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host.	Substrates that are selectively utilized by host microorganisms conferring a health benefit.	A mixture comprising live microorganisms and substrate(s) selectively utilized by host microorganisms that confers a health benefit on the host.	A preparation of inanimate microorganisms and/or their components that confers a health benefit on the host.
Main Mechanism	Colonization of the gut, production of antimicrobial substances, modulation of the immune system.	Fermented by beneficial gut bacteria, leading to the production of SCFAs and promoting the growth of these bacteria.	Combines the benefits of probiotics and prebiotics, improving the survival and implantation of live microorganisms.	Direct modulation of host responses through microbial components and metabolites, without requiring live cells.
Examples	*Lactobacillus spp., Bifidobacterium spp.*	Fructo-oligosaccharides (FOS), galacto-oligosaccharides (GOS), inulin.	Combination of *Bifidobacterium lactis*with FOS.	Heat-inactivated bacteria, cell-free supernatants, purified metabolites (e.g., butyrate).
State at Administration	Live cells.	Non-digestible fibers/compounds.	Live cells + non-digestible substrate.	Inanimate cells or cell components/metabolites.
Key Advantages	Well-established clinical efficacy for certain conditions.	Stimulates endogenous beneficial bacteria.	Synergistic effect that enhances probiotic efficacy.	Greater stability, safety profile, and defined composition, facilitating standardization and regulation.

Source: Compilation and adaptation by the author based on scientific literature (Aguilar-Toalá et al., 2018; Salminen et al., 2021; Cryan et al., 2020; Koh et al., 2016; Yano et al., 2015; Ma et al., 2021).

Metabolomics: The Key to Unraveling the Biochemical Language of the Gut-Brain Axis

If postbiotics are the "messengers" of the microbiota, metabolomics is the tool that allows us to "read" and "interpret" the biochemical language of these messengers and their interactions with the host. Metabolomics is the systematic and large-scale study of metabolites, the small molecules that are products of cellular metabolism. It offers a functional "snapshot" of the physiological state of an organism at a given moment, reflecting the interaction between genetics, environment, and microbiota (Nicholson et al., 2012).

Techniques and Approaches of Metabolomics

Metabolomics employs a variety of advanced analytical techniques to identify and quantify metabolites in biological samples (blood, urine, feces, saliva, tissues). The most common platforms include:

- **Mass Spectrometry (MS)**: Often coupled with liquid chromatography (LC-MS) or gas chromatography (GC-MS), MS allows for the identification and quantification of thousands of metabolites with high sensitivity and specificity. It is particularly useful for the analysis of low-abundance metabolites and for the elucidation of new metabolic pathways.

- **Nuclear Magnetic Resonance (NMR)**: A non-destructive technique that allows for real-time metabolite analysis and the identification of molecular structures. Although less sensitive than MS for some metabolites, NMR is excellent for quantifying abundant metabolites and for metabolic flux studies.

Metabolomic analysis can be performed in two main ways:

- **Targeted Metabolomics**: Focuses on the precise quantification of a predefined set of known metabolites, usually involved in specific metabolic pathways.
- **Untargeted Metabolomics**: Aims to identify and quantify the largest possible number of metabolites in a sample, without bias, allowing for the discovery of new biomarkers and unexpected metabolic pathways.

Applications of Metabolomics in the Context of the Gut-Brain Axis

The application of metabolomics has been fundamental in advancing our understanding of how the microbiota influences brain and mental health:

a) Identification of Biomarkers and Metabolic

"Fingerprints" Metabolomics allows for the identification of metabolic patterns ("fingerprints") that are characteristic of different health or disease states. In the context of the gut-brain axis, this means identifying metabolites or groups of metabolites that are altered in conditions such as ASD, depression, or neurodegenerative diseases (Cryan et al., 2020). For example, metabolomics can reveal changes in SCFA levels, tryptophan metabolites, or bile acids in patients with gut-brain axis dysfunctions. These biomarkers can be used for diagnosis, prognosis, or to monitor response to interventions.

b) Elucidation of Mechanisms of Action

By analyzing changes in metabolic profiles before and after an intervention (such as supplementation with postbiotics or probiotics), metabolomics can elucidate the molecular mechanisms by which these interventions exert their effects. If a probiotic supplement leads to behavioral improvements, metabolomics can reveal whether this is due to increased butyrate production, modulation of inflammatory pathways, or alteration of neurotransmitter-related metabolites. This is crucial for understanding the depth of effects observed in studies that correlate improvements in inflammatory and behavioral biomarkers with supplementation (Hsiao et al., 2013; Tomova et al., 2015).

c) Discovery of New Postbiotics and Bioactive Compounds

Untargeted metabolomics is a powerful tool for the discovery of new bioactive compounds produced by the microbiota. By analyzing the "metabolome" of different bacterial strains or fecal samples, researchers can identify unknown metabolites with therapeutic potential, which can then be isolated, characterized, and developed as new postbiotics.

d) Personalization of Interventions and Precision Nutrition

Metabolomics is a cornerstone of precision nutrition. By correlating an individual's metabolic profile with their response to different dietary or supplementary interventions, it is possible to develop highly personalized recommendations (Zeevi et al., 2015). If a patient has a metabolic profile indicative of low butyrate production, an intervention with a butyrate-rich postbiotic or a prebiotic that promotes its production may be more effective. This personalized approach maximizes benefits for neurocognitive health and well-being, aligning with the trend towards more targeted interventions.

The Intersection of Postbiotics, Metabolomics, and Advanced Biotechnology

True innovation in the field of gut-brain axis modulation lies in the synergy between postbiotics, metabolomics, and cutting-edge biotechnological technologies, such as nanotechnology.

Optimization of Postbiotic Delivery via Nanotechnology

Although postbiotics exhibit greater stability than live probiotics, optimizing their delivery and absorption remains a challenge. Nanotechnology offers innovative solutions to this problem. Nanoencapsulation, for example, can protect sensitive postbiotics from degradation in the gastrointestinal tract, ensure their segmented release at specific sites (such as the small intestine, where many metabolites are absorbed), and increase their systemic bioavailability (Yao et al., 2020).

- **Nanoencapsulation**: Postbiotics can be encapsulated in lipid nanoparticles, polymeric nanoparticles, or biointelligent delivery systems. This not only protects the compound from enzymatic and acidic degradation but can also improve its solubility and permeation through cell membranes, resulting in a higher concentration of the active compound at the site of action (Mozafari, 2005). The concept of lipid microencapsulation for bioactive compounds, aiming for release in the small intestine and increased bioavailability, is a significant advance that can be applied to postbiotics (Lichtenstein et al., 2021).

- **Segmented Release Systems**: The proposed segmented release, which allows for the delivery of active compounds to different parts of the gastrointestinal tract (oral mucosa, stomach, intestine), can be applied to postbiotics. This enables a more targeted and efficient action, maximizing their absorption and interaction with the enteric immune system and the enteric nervous system (Wang et al., 2020).

Metabolomics and Artificial Intelligence in Discovery and Optimization

The massive amount of data generated by metabolomics, combined with data from microbiota sequencing, genomics, and clinical trials, demands advanced computational tools. Artificial Intelligence (AI) and Big Data are essential for:

- **Identification of Complex Patterns**: Machine learning algorithms can identify subtle patterns in large metabolomic datasets that would be imperceptible to human analysis, correlating them with health or disease outcomes.
- **Prediction of Interactions**: AI can predict interactions between postbiotics, other supplements, and the host, optimizing formulations and minimizing adverse effects.
- **Accelerated Discovery**: AI-based predictive models can accelerate the discovery of new postbiotics and bioactive compounds, identifying promising candidates from vast libraries of microbial metabolites.
- **Personalization at Scale**: AI can process individual data (microbiome, metabolome, genome) to generate personalized recommendations for postbiotics and supplements on a large scale, making precision nutrition accessible to a wider audience.

Case Studies and Clinical Evidence: Postbiotics in Action

Although research on postbiotics is relatively recent, there is already promising evidence of their potential, often inferred from studies with probiotics that, in fact, act via postbiotic production.

Modulation of Stress Response and Well-being

Serum cortisol, a stress biomarker, is frequently evaluated in supplementation studies. The modulation of cortisol levels can be attributed, in part, to the action of postbiotics that influence the hypothalamic-pituitary-adrenal (HPA) axis and systemic inflammatory response (Babarro et al., 2023). Studies with probiotics have demonstrated a reduction in cortisol levels, suggesting the role of postbiotics in this effect (Zhang et al., 2020). The ability of postbiotics to reduce inflammation and strengthen the intestinal barrier contributes to a less stressful systemic environment, positively impacting well-being.

Postbiotics and Autism Spectrum Disorder (ASD)

Research on the relationship between gut microbiota and ASD has grown exponentially. Studies with probiotics in children with ASD have shown improvements in adaptive skills and reduction of inflammatory biomarkers, suggesting that the metabolites produced by probiotic strains and inactivated cellular components play a crucial role (Hsiao et al., 2013; Tomova et al., 2015; Shaaban et al., 2018). Microbiota modulation, with an increase in beneficial species like *Lactobacillus* spp. and a decrease in pathobionts like *Escherichia coli*, indicates a shift in the intestinal metabolic profile that favors the production of beneficial postbiotics (Kang et al., 2017). The optimization of the delivery of these compounds, through advanced technologies, is a promising area of research for the development of more effective interventions for ASD.

Optimization of Cognitive Performance

The literature already indicates that the combination of active compounds, such as caffeine and L-theanine, improves attention and reaction time (O'Neill et al., 2008). However, the synergistic action with other compounds and the optimization of absorption via nanotechnology can be enhanced by modulating the intestinal environment. Postbiotics that influence neurotransmitter synthesis or reduce neuroinflammation can contribute to a more sustained improvement in cognitive function, especially in contexts of sleep deprivation or prolonged stress. The modulation of the gut microbiota by probiotics and their metabolites has been associated with improvements in cognitive functions and reduction of fatigue (Tillisch et al., 2017).

Challenges and Opportunities in Clinical and Commercial Translation

Despite immense potential, the translation of postbiotics and metabolomics from research to clinical practice and the market faces significant challenges:

- **Standardization and Characterization**: The complexity of postbiotics, which can be mixtures of metabolites and cellular components, requires rigorous methods of standardization and characterization to ensure product consistency and reproducibility.

- **Robust Clinical Studies**: The need for randomized, double-blind, placebo-controlled clinical trials, with representative samples and well-defined outcomes, is crucial to validate the efficacy and safety of postbiotics in humans. Detailed protocols, including the measurement of biomarkers and behavioral assessments, are essential for this validation.
- **Regulation**: The classification and regulation of postbiotics are still evolving in many jurisdictions. A clear distinction between probiotics, prebiotics, and postbiotics is essential for the development of clear regulatory guidelines that ensure product safety and quality.
- **Complexity of Metabolomics**: The analysis and interpretation of metabolomic data are complex, requiring expertise in bioinformatics and biostatistics. The integration of data from different "omics" platforms (genomics, transcriptomics, proteomics) is a challenge, but also a great opportunity for a more holistic understanding.
- **Cost and Accessibility**: Advanced postbiotic production technologies and metabolomic analyses can still be expensive, which may limit their accessibility. Continuous research and process optimization are needed to make these interventions more widely available.

Despite these challenges, the opportunities are vast. The development of "precision postbiotics" — specific formulations of microbial metabolites or components targeted at specific physiological pathways — represents a new frontier for personalized medicine. The integration of metabolomics with AI will enable accelerated discovery of new compounds and optimization of interventions, paving the way for innovative solutions in neurocognitive health, well-being, and chronic disease management.

Future Perspectives: Towards Precision Nutrition and Personalized Interventions

The future of gut-brain axis modulation is promising and multifaceted. Research will continue to deepen the understanding of the mechanisms by which postbiotics interact with the host, identifying new metabolites with therapeutic potential and elucidating their signaling pathways.

The integration of data from various "omics" platforms (genomics, transcriptomics, proteomics, microbiomics, and metabolomics) will be fundamental for a systemic view of health. This holistic approach will enable the creation of individual "health profiles," which will guide the development of highly personalized interventions. Precision nutrition, based on these profiles, will offer dietary and supplementary recommendations (including postbiotics) that are optimized for each individual's genetics, microbiome, and metabolic state.

Biotechnology will continue to play a central role in developing advanced delivery systems, such as nanotechnology, to ensure that postbiotics reach their targets with maximum efficacy and safety. AI and Big Data will be indispensable tools for processing the vast amount of information generated, accelerating the discovery of new compounds, and optimizing formulations.

The focus will expand to primary prevention and early management of neuropsychiatric conditions, using postbiotics and metabolomics-based interventions to modulate the gut-brain axis before dysfunctions become established. Collaboration among researchers, industry, and regulatory bodies will be crucial to translate these scientific discoveries into clinical products and practices that improve people's quality of life on a global scale.

Conclusion

Postbiotics and metabolomics represent a significant evolution in the understanding and modulation of the gut-brain axis. By focusing on the bioactive products of the microbiota and the detailed analysis of the metabolic profile, biotechnology is unraveling new mechanisms and opening unprecedented avenues for the development of more effective, safe, and personalized supplements and therapies. The ability to influence inflammation, strengthen the intestinal barrier, and modulate neurotransmitter synthesis through postbiotics, combined with the diagnostic and monitoring precision of metabolomics, offers a powerful arsenal for optimizing neurocognitive health and mental well-being.

The synergy between these approaches and advanced biotechnological technologies, such as nanotechnology and artificial intelligence, is paving the way for an era of precision interventions. As research advances, the promise of more personalized and preventive health, driven by a deep understanding of the interactions between our gut, our microbiota, and our brain, becomes an increasingly tangible reality, consolidating the role of biotechnology as a transformative force in 21st-century healthcare.

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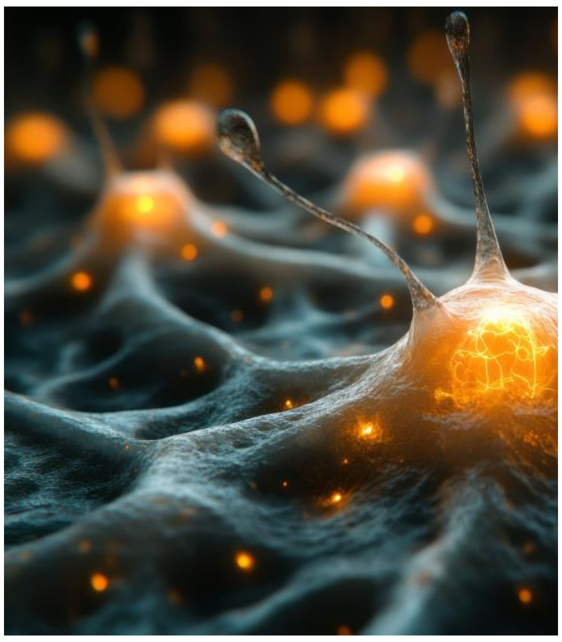

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