Review

The Role of the Gut Microbiome Dysbiosis in Metabolic Dysfunction: A Mini Review

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The Role of the Gut Microbiome Dysbiosis in Metabolic Dysfunction: A Mini Review

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Highlights

What are the main findings?

- In addition to its role in regulating glucose metabolism, it also has an emerging potential to modulate the gut microbiome beneficially, accordingly, Metformin may indirectly support improved brain health.

What is the implication of the main finding?

- Metformin has a promising therapeutic role in promoting cognitive and neurological well-being.

Abstract

Objectives: This review provides a comprehensive overview of the complex and dynamic bacterial composition of the human gastrointestinal (GI) microbiota and explores its integral role in the microbiome-gut-brain axis. **Methods**: It discusses the physiological and molecular pathways through which the gut microbiota communicates with the central nervous system, highlighting key barriers that can impede effective signaling along this axis. The review also delves into the influence of the microbiota on brain health, including cognitive function, mood regulation, and neuroinflammation, and considers how disruptions in this system—known as dysbiosis—can contribute to metabolic and neurological dysfunction. **Results**: A central focus of the article is the role of the commonly prescribed antidiabetic drug Metformin, not only in regulating glucose metabolism but also in its emerging potential to beneficially modulate the gut microbiome. By doing so, Metformin may indirectly support improved brain health. **Conclusions**: Ultimately, the article seeks to inform both healthcare practitioners and patients about the promising therapeutic implications of microbiome-targeted strategies, particularly the use of Metformin, in promoting cognitive and neurological well-being.

Keywords: brain health; gut-brain axis; metformin; metabolic dysfunction; microbiota; probiotics

1. Gut Microbiota

This term refers to the various microorganisms residing in the human intestine, whose collective genomes and metabolites form the microbiome [1,2]. Dominant phyla include Bacteroidetes and Firmicutes, which produce short-chain fatty acids (SCFAs) critical for gut integrity and host metabolism [3,4]. These microbes assist in digesting nutrients, synthesizing vitamins, and regulating immune responses and metabolic pathways. They also protect against pathogens by maintaining epithelial barriers and producing antimicrobial compounds [5]. Disruptions in microbial composition (i.e., dysbiosis) contributed to various diseases, prompting interest in probiotics for therapeutic use..

2. Gut-Brain Axis (GBA)

The gut microbiota plays a critical role in the GBA. Microbe-derived signals reach the central nervous system (CNS) either directly through systemic circulation or indirectly via receptors on enteroendocrine cells (EECs), enterochromaffin cells (ECCs) in the gut, or the mucosal immune system [6], which in turn trigger a CNS response through the autonomic nervous system (ANS), and the hypothalamic-pituitary-adrenal (HPA) axis [7]. Strong evidence of microbiota and brain linkages in clinical practice is that gut dysbiosis has been causally associated with neurological illnesses such as autism and anxiety-depressive behaviors, as well as functional gastrointestinal disorders, including irritable bowel syndrome [8,9]. Numerous channels of communication, including immunological, endocrine, neuronal, and metabolic pathways, have been identified along the GBA [10–13].

2.1. Microbiota and Neurotransmitters Synthesis

Various neurotransmitters, such as acetylcholine, noradrenaline, serotonin, and dopamine are synthesized by numerous bacterial species residing in the gastrointestinal tract [14–17], contribute to the intricate communication network between the gut and the brain [18]. Gamma-aminobutyric acid (GABA) is synthesized by Bifidobacterium and Lactobacillus species; Noradrenaline is synthesized by the species Bacillus, Escherichia, and Saccharomyces; serotonin by Streptococcus, Escherichia, Candida, and Enterococcus species, while acetylcholine is synthesized by Lactobacillus and dopamine by Bacillus [15]. These microbiota-generated neurotransmitters cross the intestinal mucosal barrier; however, their effects on brain function are thought to be mediated indirectly via interactions with the enteric nervous system (ENS) [19,20].

2.2. Microbiota and Enteroendocrine Signaling

Bacterial metabolites interact with the gut epithelium, prompting EECs to create active amines through the intracellular decarboxylation of active amine precursors. These are subsequently deposited in secretory vesicles [21]. EECs are considered crucial sensors of gut microbiota and/or microbial metabolites, playing a vital role in maintaining mucosal immunity and gut barrier function, visceral hyperalgesia, and gastrointestinal (GI) motility in health and disease [13,22–24].

The brain controls the functions of intestine functional effector cells, including enteric neurons, interstitial cells of Cajal, immune cells, epithelial cells, smooth muscle cells, and enterochromaffin cells, through a combination of neurological and hormonal channels of communication. On the other hand, the gut microbiota, which is involved in the gut-brain reciprocal connections, also influences these same cells. It’s currently emerging that a microbiome GBA exists [7].

2.3. Microbiota Metabolites

The gut microbiota produces a remarkably diverse array of metabolites derived from the anaerobic fermentation of dietary components and endogenous chemicals produced by both the host and microbes [33]. Many of these resulting compounds hinder the growth of their rivals, thus maintaining the diversity of commensal species and eliminating pathogenic bacteria [26]. Furthermore, these gut microbiota metabolites have roles in a variety of key physiological processes, such as host energy metabolism and immunology as well as other unknown activities, composing the human metabolome [34].

Colonic bacteria possess carbohydrate-active enzymes, enabling them to break down complex carbohydrates and produce metabolites such as SCFAs [35]. Propionate, butyrate, and acetate are the three most common SCFAs in the GI tract, with a 1:1:3 ratio [36]. These SCFAs are quickly absorbed by epithelial cells in the GI tract, where they regulate cellular processes such as gene expression, chemotaxis, differentiation, proliferation, and cell death [37].

3. Barriers to Microbiota-Gut-Brain (MGB) Signaling

The intestinal barrier and the BBB are the two primary obstacles to MGB signaling. Gut flora, inflammatory signals, and stress influence the permeability of both dynamic barriers. In a healthy condition, these tight barriers inhibit microbiome-related immunological signals reaching the brain [38,39].

3.1. Intestinal Barrier

The intestinal barrier comprises multiple layers. The outer layer is composed of mucus, commensal gut flora, and defense proteins, including secretory immunoglobulin A (sIgA) and antimicrobial proteins (AMPs). The intermediate layer consists of intestinal epithelial cells (IECs), whereas the inner layer is made up of innate and adaptive immune cells [40]. The mucus layer is divided into two layers: a loose outside layer (lumen-facing) and an interior layer linked to the epithelial tissues. Commensal microorganisms mostly occupy the outer layer, both because it is their preferred habitat for biofilm formation and because it provides microbes with nutrients (glycans) in the absence of dietary fiber [41]. Dietary fiber deficiency, which is characteristic of the traditional American diet, causes thinning of the outer layer, resulting in greater permeability of microorganisms through the outer layer [42]. The inner layer is normally devoid of bacteria and protects the epithelial cells from the microbiota through innate immune mechanisms (antimicrobial peptides), adaptive immune mechanisms (secretory immunoglobulin A), and physical separation [43]. Fortunately, diet- or chronic stress-induced shrinkage of the outer layer increases the likelihood that commensal bacteria cell wall components interact with TLRs on dendritic cell extensions, resulting in cytokine release from these cells and stimulation of other cells in the gut-associated immune system [44]. Cytokine production may also loosen the tight connections between epithelial cells, permitting microorganisms to pass across the intestinal barrier through microfold cells, which in turn allows more local immune cell activation and dissemination all through the systemic circulation, a condition known as metabolic endotoxemia [45]. Similarly, SCFAs generated by specific gut microorganisms play an important role in preserving intestinal structural integrity by keeping cell junctions tight and limiting the activation of gut-associated immune cells [46].

3.2. Blood–Brain Barrier (BBB)

The BBB controls the transport of substances from the circulatory system to the cerebrospinal fluid [47]. The BBB is composed of capillary endothelial cells with tight junctions, astrocytes, and pericytes. Tight junction proteins, which limit the paracellular transport of water-soluble compounds from the blood to the brain [48], are mostly composed of transmembrane proteins such as claudins, tricellulin, and occluding [49].

The gut microbiota, which modulates the intestinal barrier, may affect BBB permeability. The gut microbiome boosts the synthesis of tight junction proteins like Claudin-5 and occludin, which reduces BBB permeability [50]. The Colonization of the gut with SCFA-producing bacteria also reduces the permeability of the BBB, indicating that SCFAs play a crucial role in the development and maintenance of the BBB [51] - Figure 1.

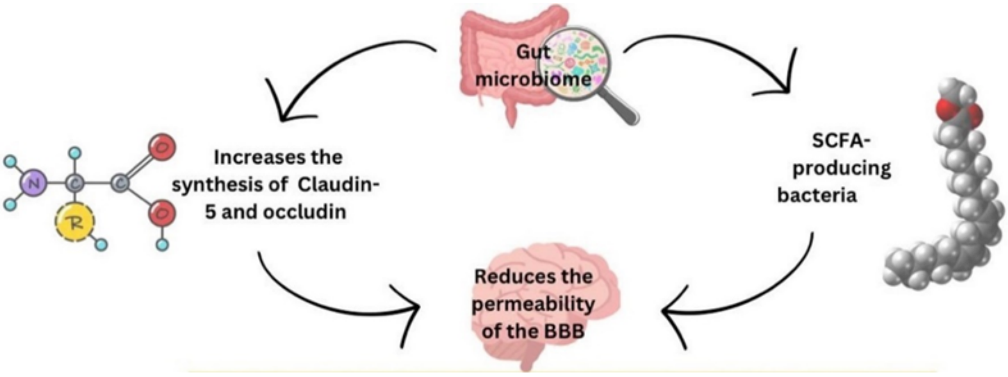

Figure 1. This diagram shows the effect of the gut microbiome on the blood-brain barrier. BBB: Blood-Brain Barrier - SCFA: Short-Chain Fatty Acid.

4. Role of the Gut Microbiota in Health

With its extensive genetic makeup and metabolic diversity, the gut microbiota offers several beneficial characteristics to the host. Among these bacteria's most significant functions are their assistance in preserving the mucosal barrier's integrity, their provision of nutrients including vitamins, and their defense against infections. Furthermore, for the immune system to operate properly, commensal microbiota and the mucosal immune system must interact [52].

The alterations in gut bacterial composition and disruption of gut homeostasis, which have been linked to the etiology of gut-brain diseases, are frequently brought on by dietary patterns, antibiotic use, and viral and bacterial infections [53].

SCFAs are signaling molecules produced only by gut microorganisms during the fermentation of dietary fiber, since humans lack the enzymes necessary to digest fiber [54]. Once absorbed by colonic epithelial cells, SCFAs activate free fatty acid 2 (FFA2), FFA3, GPR109a, and Olfr78 receptors, and act on a variety of targets. SCFAs have been linked to various physiological processes, including neuroplasticity, gene expression, dietary intake, and immune system modulation [55,56].

The GI microbiota is also important for the de novo production of critical vitamins that the host can't generate [57]. Lactic acid bacteria are essential for the creation of vitamin B12, which cannot be generated by animals, plants, or fungus [58]. Bifidobacteria are the primary providers of folate, a vitamin involved in essential host metabolic processes such as DNA synthesis and repair [59]. Vitamin K, riboflavin, biotin, nicotinic acid, pantothenic acid, pyridoxine, and thiamine are other vitamins that human gut bacteria have been demonstrated to manufacture [60]).

The GI microbiota is vital to the development of both the intestinal mucosal and systemic immune system, evidenced by the lack of different immune cell types and lymphoid structures expressed by germ-free organisms [61,62].

5. Role of GBA in Health

Bacterial colonization of the gut is essential for the formation and maturity of both the ENS and the CNS. The lack of microbial colonization leads to changes in gene expression and neurotransmitter turnover in both the CNS and ENS. Additionally, it results in altered gut sensory-motor functions, resulting in delayed gastric emptying and intestinal transit [7].

Microbiota regulates the HPA axis set point, which generates glucocorticoids such as cortisol in humans and corticosterone in rodents, which modulates stress reactivity and anxiety-like behavior [63]. Several mental disorders and behavioral changes have been linked to alterations in the HPA axis [64,65].

Cortisol can influence the MGB axis via several routes. Cortisol receptors are present on various gut cells, such as epithelial cells, immune cells, and EECs, suggesting a direct impact of cortisol on gut function [7,66,67]. By modifying gut transit time, intestinal permeability, and nutritional availability, cortisol can impact the gut microbiota, which in turn affects its diversity and composition. Central effects of cortisol occur by binding to glucocorticoid receptors in the prefrontal cortex, amygdala, and hippocampus. Additionally, there is proof that microorganisms in the stomach can trigger stress circuits in the CNS and ENS by means of the vagus nerve and sensory neurons, respectively.

Microbiota also regulate serotonergic pathways in the limbic system [7,68,69]. It has a strong influence on the EECs, which synthesize and secrete around 90% of serotonin. Furthermore, the gut microbiome has been discovered to influence hippocampal serotonin levels, possibly by affecting the peripheral availability of tryptophan [70]. Gut-derived serotonin cannot penetrate the BBB, but serotonin derivatives (N-acetyl serotonin and melatonin) and their precursor (5-hydroxytryptophan) can, and can affect the CNS [71].

Stress, anxiety, and violence are all triggered by serotonin (5-HT). Research has shown that disorders related to gut microbes and serotonergic system have a major influence on the etiology of neuropsychiatric and neurological illnesses [72]. They are linked to numerous CNS diseases, such as Alzheimer’s disease [73], Parkinson’s disease [74], and amyotrophic lateral sclerosis [75]. As a result, gut microbe disorders are thought to be a major cause of dementia.

6. Dysbiosis of the Gut Microbiome Contributes to Metabolic Dysfunction

Gut microbiota is a major environmental factor in the regulation of human metabolism, leading to the occurrence and development of chronic illnesses, such as obesity, diabetes, and atherosclerosis [76]. Reported causes include increases in systemic LPS, changes in bile acid metabolism [77], changes in SCFAs synthesis [37,78,79], changes in gut hormone secretion [80–82] and changes in circulating branched chain amino acids [83–85].

6.1. Lipopolysaccharide (LPS)

LPS, or endotoxin, is a bacterial cell wall component primarily found in Gram-negative bacteria that triggers an inflammatory response by activating TLR-4 and transforming growth factor (TGF)-mediated pathways [86,87]. Increases in systemic LPS or lipoprotein binding protein have been linked to low-grade, chronic inflammation in obesity [88], metabolic syndrome [89], and type 2 diabetes [90].

Several potential routes by which the gut microbiota may influence circulating LPS levels. These include: 1) Changes in the balance and types of intestinal bacteria can affect LPS bioavailability. For example, in diabetes, dysbiosis is characterized by a reduction in butyrate-producing, LPS-lacking, Gram-positive Clostridial species, and an increase in LPS-containing, Gram-negative opportunistic pathogens, including certain Bacteroidetes and Proteobacteria species [91–93]. 2) Increased intestinal permeability, often referred to as “leaky gut,” can enable LPS to move through intercellular pathways. The gut microbiome plays a key role in regulating gut permeability by supporting the health of intestinal cells, maintaining their tight junctions, and preserving a protective mucous layer. This regulation is partly achieved by supplying nutrients, such as SCFAs, to the epithelial cells [94–96].

Probiotics, such as Streptococcus thermophilus and Lactobacillus acidophilus, have been shown to prevent TNF-α and Interferon Gamma (IF꩜)-induced increase in human intestinal epithelial cells’ permeability in vitro. This highlights the important role certain bacteria play in maintaining a healthy intestinal barrier [97,98].

6.2. Bile Acids

The gut microbiome plays a vital role in bile acid metabolism. Bile acids are initially synthesized from cholesterol in the liver and conjugated with glycine or taurine to form bile salts. These salts are secreted into the small intestine, where roughly 95% are reabsorbed in the ileum and transported back to the liver via enterohepatic circulation. However, around 400–600 mg of bile salts reach the large intestine, where anaerobic bacteria convert them into secondary bile acids, such as deoxycholic acid and lithocholic acid. These secondary bile acids can exert widespread effects, including on the brain [99,100].

Secondary bile acids activate the farnesoid X receptor (FXR) in the ileum [101,102], which stimulates the production of fibroblast growth factor 19 (FGF19). FGF19 then enters the bloodstream, crosses the BBB, and activates the arcuate nucleus of the hypothalamus [103]. This hypothalamic activation enhances glucose metabolism regulation and reduces HPA axis activity. The antidiabetic effects of vertical sleeve gastrectomy, a type of bariatric surgery, have been shown to rely on FXR signaling [104]. Similarly, an intestinal FXR agonist has been demonstrated to improve insulin sensitivity [105]. In the pancreas, FXR activation influences insulin transport and secretion [106] and may also provide protection to islets against lipotoxicity [107].

L cells in the ileum express Takeda G protein-coupled receptor 5 (TGR5), which is activated by secondary bile acids. These secondary bile acids are exclusively produced by intestinal bacteria and their levels are influenced by the composition of the gut microbiota [108]. Activation of TGR5 enhances glucose homeostasis by stimulating L cells to release glucagon-like peptide-1 (GLP-1). This increase in GLP-1 regulates ingestive behavior and food intake [109].

6.3. Short Chain Fatty Acid (SCFAs)

Nondigestible carbohydrates are fermented by bacteria in the colon to produce SCFAs, with butyrate, acetate, and propionate being the main products. Dietary fiber content, microbiota, and SCFAs interact because diets high in oligosaccharides change the makeup of microorganisms, produce more SCFAs, and lower the pH of the luminal fluid [55,56].

Preclinical and clinical research have demonstrated that the synthesis of SCFAs induces the ileum’s L cells to release the satiety hormone GLP-1, resulting in behavioral changes and altered satiety perceptions [110]. Additionally, SCFAs influence how 5-HT, or serotonin, is synthesized in ECCs [111]. By stimulating AMP kinase and free fatty acid receptors 2 and 3 (FFAR2 and 3), sometimes referred to as G-protein coupled receptors 43 and 41 [112], SCFAs behave as signaling molecules. SCFAs was shown to prevent de novo development of non-alcoholic fatty liver disease by stimulating fatty acid oxidation [113].

More attention has been paid to butyrate as a possible helpful intermediary; in people with diabetes, butyrate-producing bacteria are less prevalent [114,115]. Supplementing mice with butyrate was shown to increase their sensitivity to insulin.

6.4. Gut Hormone Secretion

The release of gut hormones like GLP-1 and peptide YY (PYY), which regulate energy balance and glucose metabolism, is linked to SCFAs [80]. In response to dietary intake, proglucagon undergoes tissue-specific processing to produce GLP-1, which enhances insulin secretion from pancreatic β-cells. Both GLP-1 and PYY act in the hypothalamus to suppress food intake [116]. These hormones are also thought to contribute to the metabolic benefits observed after gastric bypass surgery, with GLP-1 playing a role in Metformin’s glucose-lowering effect [117,118].

PYY, like GLP-1, is synthesized by L-cells in the ileum and colon and regulates satiety by activating Agouti-related peptide (AgRP) neurons in the hypothalamus and Y2 receptors on neuropeptide Y (NPY). This suppresses appetite by disinhibiting the satiety-inducing proopiomelanocortin/alpha-melanocyte stimulating hormone (POMC/α-MSH) pathway [119]. The gut microbiota’s influence on PYY secretion is significant for understanding obesity and metabolic diseases [120]. Additionally, secondary bile acids stimulate PYY secretion via pathways like those for GLP-1 [121].

6.5. Microbial Synthesis of Amino Acids

The human microbes take part in the synthesis of amino acids and serum amino acid levels [122]. Bacteria may serve as a source of branched-chain amino acids (BCAAs), as these are more abundant in bacterial cells compared to eukaryotic ones. Notably, bacteria can synthesize all 20 amino acids required for protein production. Various lines of evidence suggest that gut microbiota influence both the composition and levels of amino acids absorbed by the host. Circulating amino acids play a role in maintaining glucose homeostasis by promoting the release of insulin and glucagon. BCAAs, in particular, appear to have a distinct role in glucose regulation, which may be linked to an increased risk of diabetes. A prospective, nested case-control study found that plasma concentrations of five branched-chain and aromatic amino acids (isoleucine, leucine, valine, tyrosine, and phenylalanine) predicted the development of diabetes, independent of traditional risk factors [123].

7. The Role of Metformin in Modulating the Gut Microbiome

Metformin, a common medication for managing type 2 diabetes, has shown potential in altering gut microbiota, which plays a crucial role in glucose metabolism and overall metabolic health [124]. Dysbiosis, characterized by a reduced diversity of beneficial bacteria (e.g., Bifidobacterium spp. and Akkermansia muciniphila) and an increase in harmful bacteria (e.g., Firmicutes and Proteobacteria), has been linked to impaired glucose metabolism and insulin resistance [125] – Figure 2.

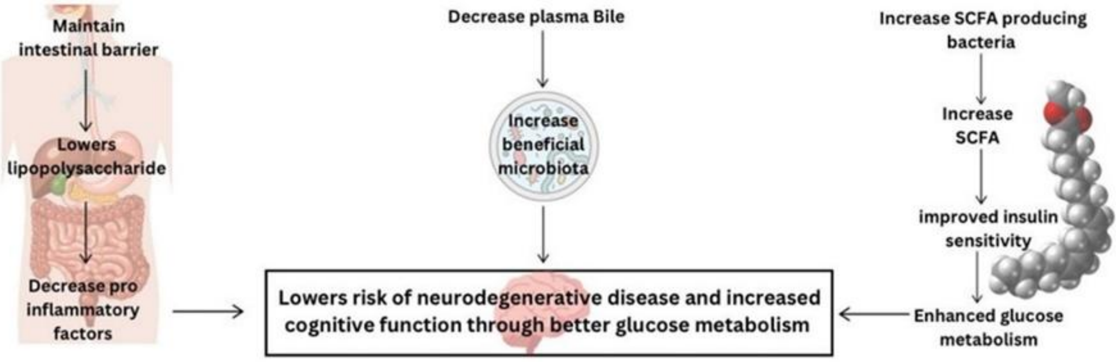

Figure 2. This diagram shows the role of Metformin in modulating the gut microbiome to improve human brain health. SCFA: Short-Chain Fatty Acid.

7.1. Metformin Mechanism of Action

Metformin primarily acts through the activation of AMP-activated kinase (AMPK), which influences various cellular processes [126]. It lowers glucose production in the liver and improves insulin sensitivity [127]. Additionally, Metformin exhibits strong anti-inflammatory and neuroprotective properties, potentially mediated by its effects on gut microbiota [128,129].

One of Metformin's key actions is maintaining intestinal barrier integrity, which reduces serum LPS levels and enhances glucose metabolism by preventing the migration of pro-inflammatory factors. The drug also promotes SCFAs production, improving insulin sensitivity by modulating substrate metabolism in peripheral tissues. This mechanism entails an increase in the population of SCFAs-producing bacteria, reinforcing Metformin's role in regulating glucose levels. Additionally, Metformin regulates bile acid levels, contributing to improved glucose metabolism. Studies have shown that it elevates plasma bile acid while altering gut microbiota to enhance metabolic outcomes. Its effect on gut microbiota composition, particularly through the promotion of beneficial bacteria such as Akkermansia muciniphila, plays a significant role in glucose homeostasis and overall metabolic health [4,130]. Metformin may influence glucose transfer from the intestinal lumen to the bloodstream and enhance glucose sensing in the gut. This highlights an additional mechanism by which Metformin contributes to its glucose-lowering effects.

Metformin's modulation of gut microbiota may have implications for brain health, potentially addressing cognitive disorders [128]. Through the GBA, Metformin's influence on gut microbiota opens possibilities for microbiome-targeted therapies that could offer cognitive benefits. These findings underline the importance of exploring Metformin's broader effects beyond its traditional role in metabolic regulation.

7.2. Effects of Metformin on Cognition

Metformin has been associated with considerably reduced risk of dementia and neurodegenerative disorders, as well as enhancements in three cognitive domains: memory, semantic memory, and executive function [131,132]. Such neuroprotective benefits may occur via improving neuronal AMPK-induced energy homeostasis.

Metformin treatment was also shown to effectively counteract amyloid-beta-induced effects on human neural stem cells (hNSCs) by suppressing caspase activity and reducing cytosolic cytochrome c. Furthermore, co-treatment with Metformin played a key role in restoring mitochondrial structure in affected stem cells, bringing it closer to normal morphology [2]. Metformin-induced AMPK activation protected the stem cells against cytotoxicity caused by advanced glycation end products [133].

Metformin has been shown to reduce Alzheimer's disease-associated neuropathological alterations in differentiated mouse neuroblastoma cell lines, such as Neuro-2a [134]. It also inhibited the phosphorylation of tau protein in cultured neurons and in mice brains. Metformin was additionally shown to prevent apoptotic cell death in primary cortical neurons [135], and restore the decreased cell proliferation and neuroblast differentiation caused by type 2 diabetes in the dentate gyrus of the rat hippocampus [136].

In humans, Metformin was associated with a reduction in the incidence rate of dementia compared to those treated with sulfonylureas and thiazolidinediones. Combination therapy with Metformin and thiazolidinedione lowered the risk of all-cause dementia. Combination therapy with Metformin and sulfonylureas protected against all types of dementia over 2-year time [137].

Given that mitochondria-related metabolic disturbances and impaired molecular pathways play a role in the pathogenesis of multiple neurological degenerative diseases and manifest differently at different stages of disease progression, it is fundamental to precisely measure the altered mitochondria-related molecular pathways, which have great potential to serve as biomarkers to guide metformin-effective treatment for targeted therapy at the specific stage of disease [138].

8. Conclusions

The importance of microbiota in health cannot be overstated. Emerging research has highlighted the crucial role that the diverse community of microorganisms residing in our bodies plays in various physiological processes. These microbial populations play a crucial role in digestion, immune function, and the synthesis of essential nutrients.

Furthermore, microbiota influences the GBA, affecting mental health and cognitive function. Disruptions in microbial balance have been linked to a range of health issues, including gastrointestinal disorders, metabolic conditions, and even neurodegenerative diseases.

Metformin impacts gut microbiota composition, improving glucose regulation and potentially enhancing brain health. Since mitochondrial dysfunction contributes to various neurodegenerative diseases, precise measurements of altered mitochondrial pathways may help identify biomarkers to guide stage-specific metformin therapy. However, more research is needed to fully understand how Metformin influences gut microbiota and its role in managing type 2 diabetes and cognitive function. Future studies should investigate the microbial changes associated with therapeutic benefits, paving the way for new treatments for metabolic and cognitive disorders.

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Abbreviations

The following abbreviations are used in this manuscript:

AgRP	Agouti-related peptide
AMPs	Antimicrobial proteins
ANS	Autonomic nervous system
BBB	Blood-brain barrier
CNS	Central Nervous System
ECCs	Enterochromaffin cells
EECs	Enteroendocrine cells
ENS	Enteric nervous system
FFA2	Free fatty acid 2
FGF19	Fibroblast growth factor 19
FXR	Farnesoid X receptor
GABA	Gamma-aminobutyric acid
GALT	Gut-associated lymphoid tissues
GBA	Gut-Brain Axis
GI	Gastrointestinal
GLP-1	Glucagon-like peptide-1
hNSCs	Human neural stem cells
HPA	Hypothalamic-pituitary-adrenal
IECs	Intestinal epithelial cells
IF$^{\gamma}$	Interferon Gamma
IL-10	Interleukin 10
LPS	Lipopolysaccharide
NPY	Neuropeptide Y
PG	Peptidoglycan
POMC/α-MSH	proopiomelanocortin/alpha-melanocyte-stimulating hormone
PYY	Peptide YY
SCFAs	Short-chain fatty acids
sIgA	Secretory immunoglobulin A
TGF	Transforming growth factor
TGR5	Takeda G protein-coupled receptor 5
TLRs	Toll-like receptors

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