Central Asian Journal of Medicine

THE RELATIONSHIP BETWEEN PARKINSON'S DISEASE AND SHORT-CHAIN FATTY ACIDS

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ABSTRACT

Over the past ten years, growing evidence from research has emphasized the potential impact of bacterial communities in the human gut microbiota and their metabolites on both health and disease. Research has demonstrated that disruptions in gut bacteria, known as dysbiosis, can lead to disease and changes in the production of bacterial metabolites, which in turn can disrupt the immune system and metabolism. Short-chain fatty acids (SCFAs), including butyrate, acetate, and propionate, are produced through bacterial fermentation in the gut. Changes in the gut microbiota's metabolites have been linked to the development of various neurological disorders, such as Alzheimer's disease, multiple sclerosis, Parkinson's disease, amyotrophic lateral sclerosis, as well as mental health conditions like stress, anxiety, depression, autism, vascular dementia, schizophrenia, stroke, and neuromyelitis optica spectrum disorders, among others. Deciphering the mechanisms of regulation of neuronal function using propionic, butyric and acetate acids will allow us to identify new pharmacological targets for the treatment of various diseases of the central nervous system.The purpose of this review is to prove that the intestinal microbiota and its metabolites as short—chain fatty acids are a separate functioning system of the body.

Key words: gut microbiota, bacterial metabolites, SCFAs, inflammation, Parkinson's disease.

INTRODUCTION

The intestinal microbiota is a distinctive and intricate ecosystem made up of bacteria, fungi, viruses, and protozoa. The intestine is the area with the highest concentration of bacteria, hosting around 1,800 different genera and roughly 40,000 species of bacteria[1]. The microbiota–gut–brain axis provides a bidirectional connection between the enteric and central nervous systems [2]. The communication between the intestine and the brain occurs through several mechanisms, including:

Neural Pathways: The vagus nerve is a major pathway that transmits signals between the gut and the brain [3]. It relays information about gut function, such as nutrient presence or inflammation, to the brain, influencing mood and behavior.

Hormonal Signaling: The gut produces various hormones, like ghrelin, leptin, and serotonin, which can affect brain function. These hormones play roles in appetite regulation, mood, and stress responses.[4]

Immune System: The gut microbiota influences immune signaling, which can affect brain health. Inflammatory cytokines produced by gut bacteria can travel through the bloodstream to the brain, potentially influencing neurological function and behavior [5].

Microbial Metabolites: The gut microbiota produces metabolites such as short-chain fatty acids (SCFAs), which can cross the blood-brain barrier and impact brain function, including cognition, mood, and stress response.

Short-chain fatty acids (SCFA) are among the key bacterial metabolites in the intestine that link changes in the composition of the microbiota and disruption of brain function [6], which can regulate the transmission of signals through free fatty acid receptors located on colonocytes of enteroendocrine cells, as well as immune cells, internal and external neurons [7].

Properties of short-chain fatty acids derived from microbiota. It is known that SCFAs are aliphatic monocarboxylic acids with a chain length from 1 to 6 carbon atoms [8]. The main pathway of SCFA formation is the anaerobic saccharolytic enzymatic breakdown of dietary fiber by bacteria [9]. Such species as Lactobacillus spp., Bifidobacterium spp., Akker mansia muciniphila, Faecalibacterium prausnitzi, Clostridium leptum, C. butyricum [10,11] and others participate in the synthesis of SCFA. There are significantly more bacteria that produce butyric acid, since the bacteria Actinobacteria, Bacteroidetes, Fusobacteria, Proteobacteria, Spirochaetes, and Thermotogae are potential butyrate producers, expressing butyryl-CoA dehydrogenases, butyryl-CoA transferase, and butyrate kinase [12]. Acetate (C2), propionate (C3), and butyrate (C4) are short-chain fatty acids (SCFAs) produced daily in the human gut in a ratio of 60:20:20, respectively. The production of these SCFAs depends on the fiber content in the diet and the composition of the microbiota [14]. After their formation, short-chain fatty acids (SCFAs) are absorbed by colonocyte cells primarily through H+-linked monocarboxylate transporters (MCTs) and sodium-linked monocarboxylate transporters (SMCTs) [15]. SCFAs that are not metabolized within colonocyte cells are transferred into the portal circulation, where they serve as an energy source for hepatocyte cells [16]. As a result, only a small portion of butyrate, acetate, and propionate can enter the systemic circulation. Resistant starch, inulin,

oat bran, wheat bran, cellulose, guar gum and pectin are the main substrates for the production of SCFA by gut microbiota [17]. It has been shown that a high fiber content in the diet can increase the level of SCFA and contribute not only to improving cognitive functions, but also to the prevention of dementia[18]. The main SCFAs are acetate, propionate, and butyrate,[6] accounting for 95% of all SCFA [19]. After formation, SCFAs diffuse through the plasma membrane of colonocytes and act as energy substrates in mitochondria [6]. Unmetabolized SCFAs enter the portal venous system, from where they enter the lungs, brain, and liver[8]. The highest concentration of SCFA in humans is observed in the proximal colon, where it can range from 50 to 150 mmol/L [20].

SCAFs and the brain. The high expression of monocarboxylate transporters in endothelial cells could aid in the passage of SCFAs across the blood-brain barrier (BBB), as previous studies in rats have shown that SCFAs can enter the brain after the injection of 14C-SCFAs into the carotid artery [21]. In a number of preclinical trials, it was found that oral administration of SCFA promotes the restoration of the integrity of the blood-brain barrier in case of its violations in the case of various pathologies of the central nervous system [20]. The blood-brain barrier functions as a regulator of the molecular transport between the cerebrospinal fluid and the circulatory system. Neurodegenerative and neuroinflammatory disorders are accompanied by damage to the blood-brain barrier. This is primarily due to oxidative stress and inflammation caused by numerous inflammatory mediators that act both from the passage of capillaries and from the parenchyma of the brain. The intestinal microbiota can modulate the permeability of the blood-brain barrier [20]. The idea that SCFAs control BBB function is supported by the fact that tight junction proteins like occludin and claudin are expressed less often in germ-free (GF) mice causing the BBB to become more permeable from prenatal life to maturity [22]. Additionally, the BBB is restored when these adult mice are recolonized with a diverse microbiota or monocolonized with bacterial strains that produce SCFA [22]. Likewise, administering propionate to an in vitro model of cerebrovascular endothelial cells reduces the permeabilizing effects of lipopolysaccharide (LPS) exposure [18].

Mechanisms of action of SCFA on cells of the CNS. Butyrate, propionate, and acetate activate several G protein-coupled receptors (GPCRs). The most studied of them are GUR43 and GPR41, later renamed free fatty acid receptors (FFA 2 and FAR 3) [23]. The selectivity of these receptors is determined by the length of the carbon chain of the SCFA. It is known that FFAR2 has a high affinity for acetate and propionate, SCFA with a shorter carbon chain, while FFAR3 prefers longer fatty acid molecules such as butyrate [24]. SCFAs are the only

known ligands for FEAR 2 receptors, which is involved in the regulation of inflammation through inhibition of adenylate cyclase and activation of phospholipase C [25]. In the brain, FAR2 mediates the anti-inflammatory effect of SCFA, which has been shown to mouse neuropathological models such as sepsis-associated encephalopathy, periodontal neurocognitive disorder, and Alzheimer's disease [23]. One of the important ways of regulating the functioning of a living cell is epigenetic modification [25]. The main epigenetic mechanisms include DNA methylation and demethylation, and histone acetylation and deacetylation. As it turned out, SCFAs are able to reduce the activity of histone deacetylase (HDAC) [18].

SCFAs and Parkinson's Disease. Parkinson's disease (PD), a synucleinopathy and multifactorial disorder with a strong environmental influence that manifests as bradykinesia, muscle rigidity, tremors, and altered gait, is controversially associated with SCFAs. It is believed that α-synuclein (αSyn) protein aggregation is the primary pathogenic event in Parkinson's disease (PD), which mostly impacts dopaminergic neurons. Because of disruptions in the enteric nerve system, the majority of PD patients also exhibit gastrointestinal symptoms. The connection between the gut microbiota and the onset of the illness has therefore attracted a lot of attention. Accordingly, when PD patients' fecal samples were sequenced, the microbiota showed lower populations of Bacteroidetes and Prevotellaceae compared to higher Enterobacteriaceae and lower SCFA synthesis when compared to matched controls [26]. However, in a mouse model of αSyn overexpression, the presence of gut microorganisms is required to trigger pathophysiological changes since removal of the Antibiotics combined with gut microbiota improved the illness. Fecal microbiota transplantation from PD patient donors, on the other hand, exacerbates the course of the disease, indicating the presence of certain microorganisms that promote disease [27]. Consequently, Li and associates verified that PD patients experience changes in their microbiota that correspond with the advancement of the disease, as there is a constant reduction in bacterial strains that break down fiber and a rise in pathobionts [28]. Endotoxin and neurotoxic synthesis rises and SCFA production likely declines as a result of this conversion. Growing evidence in favor of this theory has demonstrated that butyrate administration in animal models of Parkinson's disease (PD) and FMT from healthy donors alleviate dopamine deficit and motor dysfunction [28].

Conclusion. A better comprehension of the intricate microbiota-gut-brain interface is still needed, despite the fact that our knowledge of microbiota-host interactions has significantly improved in recent years. Understanding how these metabolites contribute to these intricate gut-brain interactions may help develop

new therapeutic targets for the treatment of CNS disorders, as SCFAs have the ability to directly and indirectly regulate CNS processes, which in turn shapes behavior and cognitive function.

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