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Review

Diagnostic Value of Short-Chain Fatty Acids in Psychoneurology and Methodological Aspects of Quantitative Assessment

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Abstract: Increasing evidence suggests that bidirectional communication between the gut microbiome and the central nervous system, also known as the microbiota-gut-brain axis, plays a key role in brain development and function. Short-chain fatty acids (SCFAs), as one of the main microbial metabolites, have a broad multifactorial effect on many physiological and pathophysiological processes in the body, including the central nervous system. It is known that there are correlations between the phenotype of patients with a nervous system disorder and the SCFAs profile. Currently, the most informative and reliable method for the quantitative assessment of SCFAs is gas chromatography (GC), however, such studies of the SCFAs profile in the case of diseases of the nervous system are limited, and until now scientific experience in this area has not been generalized. In this regard, the purpose of this review is to summarize the diagnostic value of SCFAs profile in the case of nervous and mental disorders, as well as to demonstrate the capabilities of gas chromatography for studying the metabolic profile of these diseases.

Keywords: *short-chain fatty acids, intestinal microbiota, gas chromatography, metabolomic profiling, molecular diagnostics, neuropsychiatric disorders.*

1. Introduction

The human body is inhabitat by huge number of microbes, consisting of viruses, bacteria and fungi, which together make up the human microbiome. Microbial communities participate in human metabolic processes and play a central role in the maturation of the immune system, central nervous system and gastrointestinal tract [1].

The gut microbiota contributes to various pathogenesis pathways. Recent publications report that the composition of the gut microbiota depends on various factors, including genetic predisposition, environmental factors, stress, diet, antibiotics and other medications. Changes in gut microbiome composition can lead to increasing of intestinal permeability, systemic inflammation and may cause the onset of neurological diseases such as Alzheimer's disease, Parkinson's disease, autism spectrum disorder, schizophrenia, depressive disorders, etc. [2-4].

Increasing evidence suggests that bidirectional communication between the gut microbiome and the central nervous system, also known as the microbiota-gut-brain axis, plays a key role in brain development and function. Thus, changes in the gut microbiota are associated with neurodegenerative and psychiatric disorders, and modulation of the microbiota-gut-brain axis by probiotics, prebiotics or diet causes preventive and therapeutic effects. The current interpretation of the mechanisms underlying this relationship

is based on parallel molecular pathways of the central nervous system, endocrine and immune systems that interact with each other [5,6].

The impact of intestinal microbiota on the brain occurs in three main directions. Firstly, through the produced metabolites (SCFAs, bile acids, amino acids) [2,7]; directly by neurotransmitters, such as dopamine, serotonin, norepinephrine [2,8]; and indirectly by influencing the release of intestinal hormones [9,10]. The most important direction is related to the production of microbial metabolites, first of all, SCFA.

The main source of SCFA is the fermentation of dietary fiber in the intestines or direct intake from fermented foods. Endogenous sources of SCFAs include host metabolism of long-chain fatty acids, pyruvate to acetate, and some proteins. The formation of a specific type of SCFA depends on the enzymes of which bacteria will cleave the substrate, which makes it possible to assess the functional activity of certain representatives of the intestinal microbiota [11]. Levels of acetate, propionate and butyrate in human feces typically correspond to a ratio of 60:20:20 [12].

SCFAs have a broad multifactorial effect on many physiological and pathophysiological processes in the body. Normal SCFA metabolism can be considered as one of the main conditions for maintaining the homeostasis of the macroorganism as a whole. SCFAs can play a significant role in the development of intestinal dysbiosis, metabolic syndrome, chronic gastrointestinal pathologies [13], and also affect many systems, including the central nervous system [2,11].

SCFAs are metabolized in cells through the Krebs cycle to produce energy. All SCFAs have an inhibitory effect on histone deacetylase, while butyrate affects specific receptors (GPR43/FFAR2; GPR41/FFAR3; GPR109a/HCAR2) and transporters (MCT1/SLC16A1; SMCT1/SLC5A8). For this reason, butyrate has been proposed for use as an experimental drug for neuropsychiatric disorders [14]. In addition, it has been found that butyrate prevents the breakdown of the blood-brain barrier (hereinafter referred to as the BBB) and promotes neurogenesis [16]. It has also been noted that SCFAs obtained from a high-fiber diet have the potential to reduce the risk of Alzheimer's disease due to insulin resistance [15]. Sodium butyrate was previously synthesized for use as a drug for the treatment of epilepsy, and has recently been considered for the treatment of various neurodegenerative diseases, such as Alzheimer's disease, Huntington's disease and Parkinson's disease [17,18].

Although short-chain fatty acids can have significant effects on the nervous system, SCFAs levels are not routinely measured in clinical practice and analyzed to provide additional evidence when diagnosing disease onset or progression.

In this review, we provide a deeper understanding of the diagnostic value of the SCFA profile in the case of nervous and mental disorders, and also consider the possibilities of gas chromatography as an instrumental chromatographic method for studying the metabolic profile of these diseases, and primarily the SCFAs profile.

2. Materials and Methods

We searched and analyzed scientific papers published on eLibrary, PubMed, Google Scholar on the association between SCFAs and nervous system for all time till end of 2023 year. For this we used keywords: Gas chromatography, SCFAs, brain-gut axis, neuropsychiatric disorders, schizophrenia, autism, Alzheimer's disease, Parkinson's disease.

3. Results

3.1. *Diagnostic Value of Short-Chain Fatty Acids for Neuropsychiatric Disorders*

Short-chain fatty acids, also known as volatile fatty acids, are saturated fatty acids containing six or fewer carbon atoms, mainly including acetic acid (acetate), propionic

acid (propionate), butyric acid (butyrate), valeric acid (valerate), and caproic acid (caproate). Among them, acetate, propionate and butyrate are the most abundant and make the largest contribution to the total pool of short-chain fatty acids [2]. SCFAs are the main metabolites of the intestinal microbiota and have important biological functions: energy [19], anti-inflammatory [20], immunoregulatory and maintenance of intestinal integrity [21].

A large number of studies have shown that changes in the SCFAs profile are observed in most neuropsychiatric disorders (Table 1).

Table 1. Changes of short-chain fatty acids profile in selected neuropsychiatric disorders

Neuropsychiatric disorders	Biosample	SCFAs	Direction of change compared to control group	Reference
Parkinson's disease	feces	C_2, C_3,C_4	↓	[22], [23]
	plasma	C_2, C_3,C_4	↑	[24], [25], [26]
Alzheimer's disease	feces	C_2, C_3, C_4, C_5, C_6 (terminal stage)	↑	[27]
	feces	C_2, C_3, iC_4, C_4, iC_5, C_5	↓	[31]
Autism	feces	C_2,C_3,C_4	↓	[33]
		C_5	↑	
	feces	C_2, C_3, C_4, C_5	↓	[35]
	feces	C_2, C_3, iC_4, C_4, iC_5, C_5, C_6	↑	[36]
Schizophrenia	serum	C_4	↑	[43]
	serum	C_2, C_3, C_4,C_2/C_3	↑	[44]

3.1.1. Parkinson's Disease

Parkinson's disease (PD) is an increasingly common age-related neurodegenerative disease clinically characterized by motor and non-motor symptoms. Since the gastrointestinal tract is the main site of exposure to pathogens and absorption of antiparkinsonian drugs, the role of the intestinal microbiota and, in particular, the role of SCFAs, which may be indicators of cognitive impairment in PD, is increasing [22,23].

Thus, it is noted that in patients with PD, compared with controls of the same age, when studying fecal biomaterial, a decrease in the absolute content of acetic, butyric and propionic acids, as well as the relative content of butyric acid, was observed [22,23]. The authors of the studies believe that a decrease in SCFAs can cause changes in the intestinal (enteric) nervous system and contribute to impaired gastrointestinal motility in PD [22].

Studies of plasma SCFAs profiles have shown that patients with PD have a significant increase in acetic and propionic acid levels compared to controls [24,25]. In addition, recent studies have noted that the SCFAs profile is not only associated with Parkinson's

disease, but also correlates with the severity of the disease and the use of antiparkinsonian drugs [24].

According to the authors [26], the plasma SCFAs profile, in contrast to the fecal profile, better reflects the proportion of SCFAs entering the bloodstream and may be involved in the pathogenesis of multiple system atrophy.

3.1.2. Alzheimer's Disease

Alzheimer's disease (AD) is the most common form of dementia, in which the brain loses its functions due to cell death and disruption of neural connections. As the disease progresses, cognitive impairment occurs, affecting memory, language skills, the ability to perceive the environment, navigate space, time and self, problem-solving skills, and self-sufficiency. Ultimately, loss of body functionality leads to death.

It is known that acetate, propionate and butyrate beneficially modulate the peripheral and central nervous system; they have been suggested to play a major role in AD [27]. In particular, SCFAs may attenuate AD by serving as substrates for energy metabolism [12,28] and provide an alternative energy source to counteract brain hypometabolism that contributes to neuronal dysfunction in AD [29]. The authors [30] reported that acetate and valerate in AD patients were positively correlated with brain amyloid deposition and anti-inflammatory factors. Therefore, it is possible that short-chain fatty acids and lipopolysaccharides may be mediators between intestinal dysbiosis and amyloid pathology in Alzheimer's disease [30].

Among the metabolites, fecal volatile organic compounds (hereinafter VOCs), the main of which are SCFAs, are considered potential biomarkers of Alzheimer's disease (AD). At the same time, the qualitative and quantitative profile of SCFA in combination with other VOCs may vary depending on the stage of AD.

Thus, the authors [31] established a relationship between the profile of fecal VOCs, including SCFAs, and the progression of cognitive impairment in Alzheimer's disease. In the early stage of AD, the most significant VOCs with higher content are SCFAs and their producing bacteria, *Faecalibacterium* and *Lachnoclostridium*. Along with the development of dementia in patients with AD, there is a parallel increase in the levels of heptanoic acid and *Peptococcus*. In later stages of AD, the microbiota and VOCs shift toward the fecal SCFAs profile with an increase in hexanoic acid, as well as *Ruminococcus* and *Blautia*. Other studies have shown a decrease in SCFAs (except hexane) from amnestic mild cognitive impairment (aMCI) to AD [32].

Thus, fecal SCFA changes are associated with the presence and progression of AD and provide a potential target for a personalized approach to the prevention of patients with AD. On the other hand, a large body of evidence suggests that intestinal SCFAs production may represent a biological mechanism by which the gut microbiota may influence Alzheimer's disease.

3.1.3. Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a complex behavioral syndrome characterized by speech and language impairment, intellectual impairment, and learning and motor impairments. Research suggests that the gut microbiota and its metabolites, especially SCFAs, play an important role in gastrointestinal disorders and the pathogenesis of ASD. Many children with ASD experience gastrointestinal disorders, which are associated with altered gut microbiota composition [33,34]. Thus, lower levels of fecal acetic acid and butyrate and higher levels of fecal valeric acid were found in children with ASD [33]. Among the same cohort, a decrease in the abundance of the main butyrate-producing taxa (*Ruminococcaceae, Eubacterium, Lachnospiraceae* and *Erysipelotrichaceae*) and an increased abundance of valeric acid-associated bacteria (*Acidobacteria*) were detected. The authors noted that children with ASD had a gastrointestinal disorder – constipation, which is the most common symptom in this disorder of the nervous system [33,34].

It should be noted that some studies of fecal SCFAs in autism have had conflicting results. [35] reported lower SCFAs concentrations in children with ASD compared to a healthy cohort. The authors of other studies, on the contrary, found increased levels of these metabolites in the feces of autistic patients [36]. It is likely that this discrepancy may be due to specific changes in the intestinal microbiota in different countries.

A number of studies have reported that the accumulation of SCFAs, in particular propionate, can induce autistic behavior in children with ASD [37]. At the same time, lower levels of butyrate are known in ASD, which can positively modulate the expression of neurotransmitter genes and eliminate behavioral abnormalities [38]. The scientific literature reports that patients with ASD appear to have both elevated levels of fecal and serum SCFAs concentrations and elevated levels of SCFA-producing bacteria (*Clostridia*, *Desulfovibrio*, and *Bacteroides*) [33,36,39]. Thus, translocation across the blood-brain barrier via transporters or by passive diffusion may have potential effects on the brain and lead to the development of some symptoms of ASD [39,40].

Thus, there is a bidirectional influence between the microbiota and diet through the production of metabolites, in particular SCFAs, which can be characterized using metabolomics and which may help identify new therapeutic strategies in patients with autism.

3.1.4. Schizophrenia

Schizophrenia is an endogenous polymorphic mental disorder, literally meaning "early dementia", characterized by the breakdown of thinking processes and emotional reactions. Schizophrenia may arise from neuroevolutionary and neurodegenerative pathophysiological processes.

The main biomaterial for studying changes in the SCFAs profile in patients with schizophrenia is blood serum. Acetate, propionate and butyrate are the three most abundant SCFAs, accounting for 85–89% of total SCFAs in human serum [41]. Accumulating evidence in the literature strongly suggests that butyrate can cross the blood-brain barrier [42] and may play a beneficial role in several neuropsychiatric conditions, including schizophrenia [43].

A study of serum butyric acid levels in drug-naive patients with first-episode schizophrenia found a positive association between increased butyric acid levels after 24 weeks of risperidone treatment and improvement in schizophrenia patients on the Positive and Negative Syndrome Scale (PANSS) [43].

Recently published studies reported that serum levels of total SCFAs, as well as acetic acid and the acetic acid/propionic acid ratio were significantly higher in schizophrenia compared with controls [44]. These findings are consistent with a report of urine samples from patients with chronic schizophrenia [45]. A significant correlation was observed between the acetic acid/propionic acid ratio and working memory scores or the reasoning and problem solving subscale [44]. Studies have also shown that lipid metabolism and serum SCFAs levels may be independently or interactively associated with cognitive dysfunction [44]. At the same time, cognitive dysfunction, as well as abnormal levels of SCFA, occur already at the early stage of schizophrenia [44].

3.2. Application of Gas Chromatography Method for Determination of Short-Chain Fatty Acids

In recent years, the most informative and reliable method for diagnosing the state of intestinal microflora, including for assessing the condition of patients with various forms of neuropsychiatric disorders, is gas chromatography. The state of the intestinal microflora is assessed based on the quantitative content and profile of SCFAs in patients and healthy individuals, with analysis of possible correlations between the composition of SCFAs and the clinical phenotype of patients.

The analytical platform based on gas chromatography allows you to cover a wide range of studies of various biological samples, while using additional instrumental

capabilities and a variety of sample preparation options. In this review, we tried to summarize the experience of previous publications in this area (Table 2).

Table 2. Determination of short-chain fatty acids in various biomaterials using the gas chromatography method

Biosample	Sample preparation	Type of method based on gas chromatography	Chromatography column type	Reference
Feces	Without derivatization HCOOH, acetone, centrifugation	GC-FID	Stabilwax-DA 30м х 0,25мм х 0,5 мкм	[22]
Feces	Without derivatization HCl, vortexing	HS-SPME-GC-MS	CPWax-57CB 50м х 0,25 мм х 0,20 мкм	[31]
Feces	With derivatization NaOH, centrifuge, PrOH/Py mixture: propyl chloroformate, vortexing, hexane extraction	GC-MS	HP-5MS 30м х 0,25 мм х 0,25 мкм	[32]
Feces	Without derivatization HCl, vortexing	GC-FID	Chromosorb W-AW, 80-100 меш (183 см х 3 мм)	[35]
Feces	Without derivatization Heptane acid (pH=7), centrifugation, vacuum distillation	GC-FID	ZB-FFAP 30м х 0,53 мм х 1мкм	[36]
Feces	Without derivatization H2O deionized, HCl, centrifugation, acetonitrile, dioxane	GC-FID	Carbowax 30м х 0,32 мм х 1мкм	[46]
Feces	Without derivatization H2O deionized, mixture of (NH4)2SO4 and KH2PO4 (4:1)	HS-GC-MS	VF-WAX MS 30м х 0,25 мм х 0,25 мкм	[46]
Feces	Without derivatization H2O, stirring, HCl to pH=2-3, centrifugation	GC-FID	DB-FFAP 30 м × 0,53 мм × 0,5 мкм	[49]
Feces	Without derivatization H2O, stirring, H3PO4, H2SO4, extraction Et2O : heptane (1:1), centrifugation	GC-FID	HP-FFAP 30м х 0,53 мм х 1 мкм	[50]
Feces	With derivatization H2O, stirring, incubation, vortexing, HCl to pH=2, Et2O, centrifugation, Na2SO4 (water removal) extraction, BSTFA, shaking, incubation at 70 °C 20-40 min.	GC-FID	HP-5MS 30м х 0,25 мм х 0,25 мкм	[51]
Plasma	Without derivatization, sulfosalicylic acid, HCl, Et2O extraction, supernatant + H3PO4	GC-FID	HP-FFAP 25м х 0,32 мм х 0,5 мкм	[24]
Plasma	Without derivatization H2SO4, Et2O, extraction, centrifugation, incubation	GC-MS	HP-FFAP 30м х 0,25 мм х 0,25 мкм	[26]

Plasma	Without derivatization H3PO3, vortexing	GC-FID	HP-FFAP 30м х 0,53 мм	[30]
Plasma	Without derivatization CH3COOH, HCl, shaking, cold MTBE, vortexing, centrifugation, extraction	GC-MS	DB-WAXUI 30м х 0,25 мм х 0,25 мкм	[47]
Serum	Without derivatization H3PO4, ether, centrifugation	GC-MS	HP-INNOWAX 30м х 0,25 мм х 0,25 мкм	[43]
Serum	Without derivatization H3PO4, ether, centrifugation	GC-MS	HP-INNOWAX 30м х 0,25 мм х 0,25 мкм	[44]
Serum	Without derivatization precipitator, centrifugation, i-PrOH, homogenization	GC-MS	Nukol-fused silica 30м х 0,25 мм	[48]
Serum	Without derivatization H3PO3, centrifugation, H2SO4, Et2O extraction, centrifugation	GC-FID	HP-FFAP 30м х 0,53 мм х 1 мкм	[50]

As can be seen from Table 2, the quantitative determination of SCFAs is carried out by gas chromatography with flame ionization [22,24,30,35,36,46,49,50] or mass spectrometry [26,31,32,43,44,46-48,51] detection by introducing both liquid [22,24,26,30,32,35,36,43,44,46-51] and vapor phases [31,46]. Instrumental research is preceded by sample preparation, which is carried out either without derivatization [22,24,26,30,35,36,43,44,46-50] or with derivatization [32,51]. The sample preparation option directly influences the choice of the chemically grafted capillary column phase used. Let us note in this regard that sample preparation based on the introduction of vapor samples makes it possible to determine not only the SCFAs profile, but also to screen all volatile organic marker compounds present in the sample.

4. Conclusions

Thus, SCFAs can be considered as the most important diagnostic indicator in patients suffering from various forms of neurological and psychiatric disorders, such as schizophrenia, Alzheimer's disease, Parkinson's disease, autism spectrum disorder, etc. It has been established that changes in the content of some short-chain fatty acids and metabolic profile of SCFAs in general may indicate the onset and progression of neurological and psychiatric disorders. The generalized results of publications indicate the applicability of gas chromatography for reliable, accurate and timely quantitative assessment of SCFAs in various biomaterials for the purpose of diagnosing neuropsychiatric diseases, as well as in the selection of personalized therapy.

A personalized approach to the diagnosis and treatment of diseases associated with nervous system disorders can be provided by studying the profile of not only SCFAs, but also other metabolites that can be determined in various biomaterials of patients using an analysis method based on gas chromatography.

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Abbreviations

GC-MS - gas chromatography - mass spectrometry

GC-FID – gas chromatography with flame ionization detection

HS-GC-MS – gas chromatography - mass spectrometry with headspace dosing

SPME – Headspace solid-phase microextraction

HCOOH – formic acid

HCl – hydrochloric acid

NaOH – sodium hydroxide

PrOH – propanol-1 (propyl alcohol)

i-PrOH – 2-propanol (isopropyl alcohol)

Py – pyridine

(NH4)2SO4 – ammonium sulfate

KH2PO4 – potassium dihydrogen orthophosphate

H2SO4 – sulfuric acid

Et2O – diethyl ether

Na2SO4 – sodium sulfate

BSTFA – N,O-bis(trimethylsilyl)trifluoroacetamide

H3PO4 – orthophosphoric acid

H3PO3 – metaphosphoric acid

CH3COOH – acetic acid

MTBE – methyl tert-butyl ether

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