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IMPACT OF THE SHORT - CHAIN FATTY ACIDS ON THE MICROBIOTA - GUT - BRAIN AXIS

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ABSTRACT

Currently, there are many studies that corroborate the relationship between the microbiota and the gut – brain axis. This relationship is due through various mechanisms including the production of some metabolites by the microbiota, such as short – chain fatty acids. The microbiota – gut – brain axis consists in the bidirectional communication between the microbiota, the gut and the brain where changes in the microbiota can lead to changes in the gut and brain, and vice versa. The aim of the research is to study the impact of short – chain fatty acids on the axis. A bibliographic research was performed through some search engines. Studies show that short – chain fatty acids have different effects by increasing or decreasing the quantity of certain molecules such as GLP-1, peptide YY, insulin, glucagon, ghrelin, leptin and serotonin while they also have an impact on the nervous system. Also is needed to emphasize its role in certain neurological diseases such as Parkinson, autism spectrum disorder and multiple sclerosis. However, the current evidence still needs to be strengthened by further studies that will allow to define the mechanisms by which this relationship takes place and confirm the impact of this type of metabolites on the organism. At the same time, this will allow to develop new treatments for people with certain neurological diseases.
Key words: microbiota, microbiota – gut – brain axis, prebiotics, short – chain fatty acids, neurological diseases.

RESUM

A dia d'avui són molts els estudis que corroboren la relació entre la microbiota i l'eix intestí – cervell. Aquesta relació es dona mitjançant diversos mecanismes entre els quals hi ha la producció de certs metabòlits per part de la microbiota, com són els àcids grassos de cadena curta. L'eix microbiota – intestí – cervell consisteix en una comunicació bidireccional entre la microbiota, l'intestí i el cervell on modificacions a nivell de la microbiota poden donar lloc a canvis a nivell intestinal i cerebral i viceversa. L'objectiu de la recerca consisteix en l'estudi de l'impacte dels àcids grassos de cadena curta sobre l'eix. Per fer-ho s'ha realitzat una recerca bibliogràfica mitjançant alguns motors de

cerca. Els estudis mostren que els àcids grassos de cadena curta tenen accions a diferents nivells incrementant o disminuint la quantitat de certes molècules com el GLP-1, pèptid YY, insulina, glucagó, grelina, leptina i serotonina a la vegada que també tenen un impacte sobre el sistema nerviós. Cal destacar també, el seu paper en certes malalties neurològiques com el Parkinson, trastorn de l'espectre autista i l'esclerosis múltiple. No obstant, l'evidència actual encara necessita ser reforçada per més estudis que permetin acabar de definir els mecanismes pels quals es dona aquesta relació i confirmar l'impacte d'aquest tipus de metabòlits a diferents nivells de l'organisme. A la vegada, també permetrà generar nous tractaments per a persones que presentin certes malalties neurològiques.

Paraules clau: microbiota, eix microbiota – intestí – cervell, prebiòtics, àcids grassos de cadena curta, malalties neurològiques.

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ABREVIATIONS

SCFA	Short – Chain Fatty Acids
CNS	Central Nervous System
GI	Gastrointestinal
BBB	Blood – Brain Barrier
VN	Vagus Nerve
NT	Neurotransmitters
ASD	Autism Spectrum Disorder
EEC	Enteroendocrine Cells
GLP-1	Glucagon-like peptide 1
PYY	Peptide YY
FFAR	Free Fatty Acid Receptor
NS	Nervous System
ENS	Enteric Nervous System
IS	Immune System
LPS	Lipopolysaccharide
TLR	Toll-like receptors
GPCR	G protein – coupled receptor
AT	Adipose tissue
Treg	Regulatory T cell

1. INTRODUCTION

This final degree project consists in conducting bibliographic research on current scientific evidence about the relationship between short – chain fatty acids (SCFAs) and the microbiota – gut – brain axis.

The project below includes the definition of SCFAs and the microbiota – gut – brain axis. There are also described different mechanisms that relate both concepts and scientific evidence about their role in certain neurological disorders.

This is an area that is increasingly being studied due to its impact on human pathophysiology. Recent studies show how the gut microbiota influences the functioning of the central nervous system (CNS). Through the production of hormones, immune factors and metabolites it influences both brain behavior and cognitive development. This fact paves the way for a possible therapeutic route (1).

In addition, the microbiota – gut – brain axis is gaining importance in the investigation of psychiatric, neurodevelopmental, neurodegenerative and age - related disorders (2).

The microbiota has also been shown to play a key role in the regulation of energy homeostasis and obesity. Different studies show the relationship between dysbiosis and obesity and the role of the microbiota in eating behavior (3).

Starting from this point, it must be considered that there are several factors that can affect the composition of the microbiota such as the type of birth, breastfeeding, antibiotic intake, type of feeding, the presence of stressful elements, among others (2).

The SCFAs are one of the major metabolites of the intestinal microbiota and perform various functions in humans (4). These functions and some of their mechanisms are described below.

In order to understand the mechanisms surrounding the effects of SCFAs on this axis, it is necessary to continue conducting further studies, and thus develop microbiota – based intervention strategies (2).

2. OBJECTIVES

The main objective of this report is to conduct bibliographic research about the evidence on the involvement of SCFAs, produced by the gut microbiota, in the microbiota – gut – brain axis, a topic with many papers published in the last few years. This study will be based on the understanding of different items:

- Definition of the dietary fiber and prebiotics concepts.
- Study of the synthesis of short – chain fatty acids by gut microbiota from dietary fiber consumption.
- Study of the functioning of the microbiota – gut – brain axis.
- Analysis of the impact of short – chain fatty acids on the microbiota – gut – brain axis.
- Research on the role of short – chain fatty acids in different neurological disorders.

3. MATERIALS AND METHODS

This final degree project is based on an exhaustive bibliographic research. As this is a very current topic, the work of nutritional intervention in humans is not very extensive, so a fairly inclusive search has been carried out in order to comprise as much information as possible and then focus on what is really useful. The main databases used were Pubmed and Scopus, where the "5 years" and "review" filters were applied, as well as Google Scholar to expand the information.

First, a general search was made with the terms: “microbiota AND (gut – brain axis)”, “microbiota AND brain” and “fiber AND microbiota AND brain”. From all the papers published, a selection of the most relevant was performed and analyzed.

From then on, a more specific search was made using terms such as “fiber AND microbiota AND metabolism ” and “microbiota AND brain AND (short chain fatty acids)”. It should be noted that many of the articles used were taken from the category "Similar articles” shown in Pubmed and the own bibliography of some of the articles used.

4. RESULTS

4.1. The dietary fiber and prebiotics

To date, there is still no definition of dietary fiber that is unified by different organisms. Historically, dietary fiber was considered to be those polysaccharides with a degree of polymerization greater than 10 that are resistant to both digestion and absorption in the gut (5). In some recent studies, those substrates with a degree of polymerization between 3 - 9 units have been considered as they seem to have the same physiological activities as polysaccharides with a degree greater than 10 (6).

The Regulation (UE) 1169/2011 of the European Union about the provision of food information to consumers has defined fiber as «carbohydrate polymers with three or more monomeric units, which are neither digested nor absorbed in the human small intestine and belong to the following categories:

- edible carbohydrate polymers naturally occurring in the food as consumed,
- edible carbohydrate polymers which have been obtained from food raw material by physical, enzymatic or chemical means and which have a beneficial physiological effect demonstrated by generally accepted scientific evidence,
- edible synthetic carbohydrate polymers which have a beneficial physiological effect demonstrated by generally accepted scientific evidence» (7).

On the other hand, the current definition of prebiotic was developed by "The International Scientific Association for Probiotics and Prebiotics" in 2016. Prebiotic is defined as: «Substrate that is used selectively by host microorganisms conferring a benefit for the health». With this definition it is clear that in order to be considered prebiotic it is necessary to demonstrate that there is a health benefit. Moreover, this health benefit must be given through the selective use of the substrate by host microorganisms. In addition, it also expands the concept that the substrate may not belong to the category of carbohydrates (8).

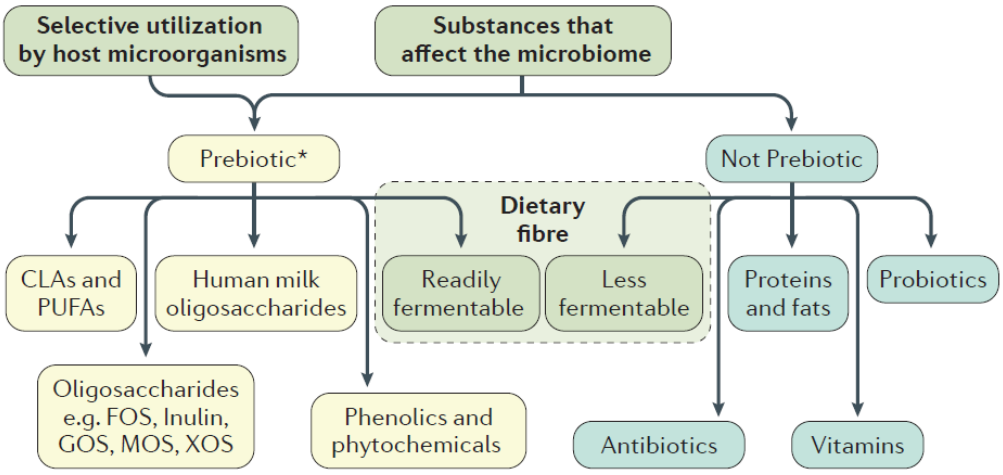

Figure 1. Distinction of what is considered a prebiotic from Gibson GR. et al. (8)

Unifying both concepts, some types of dietary fiber are candidates to act as prebiotics as they are used selectively by the microbiota and produce a beneficial effect. However, it can be difficult to categorize dietary fiber as a prebiotic because it also depends on some factors such as the host and whether there is a microbiota at the target site capable of using it selectively (8). It can be concluded, therefore, that although many of the prebiotics belong to the dietary fiber category, not all dietary fiber can be considered prebiotic (9).

4.2. Dietary fiber metabolism to short – chain fatty acids

The physicochemical characteristics of the fiber are fermentability, solubility and viscosity. The types of fermentable fiber include β-glucans, pectins, inulin, fructooligosaccharides , resistant maltodextrins, resistant starch, among others (9).

Dietary fiber plays an important role in the composition, diversity and metabolism of the microbiota that produce different metabolites which provide various beneficial physiological effects (10). This is a turning point that defines the modulation of the microbiota from the food pattern due to the substrate it has available and how it will influence its growth and the metabolites produced (9).

Substrates that have not been able to be digested by human enzymes are candidates to be metabolized by the microbiota. It must be considered that there is a difference between the microbiota metabolic capacity according to his type of glucosidases. The main metabolites resulting from bacterial fermentation are SCFAs and H_2 and CO_2

gases (9). The SCFAs generated are mainly acetate, propionate and butyrate. These are mostly generated in the colon, but the concentration of SCFAs changes along the gastrointestinal (GI) tract, being greater in the proximal colon and decreasing in the distal colon (9,10). This decrease may be due to an increase in absorption by SLC5A8[1] and SLC16A1[2] (11).

When the amount of dietary fiber that arrives is deficient, bacteria move on to metabolizing other substrates such as dietary or endogenous proteins and dietary fats. These are energetically less favorable substrates for growth and, in addition, cause a decrease in the production of SCFAs (11).

4.2.1. Synthesis, absorption and distribution of short – chain fatty acids

Dietary fiber is fermented by a variety of gut microbiota specific enzymes leading to SCFAs as the main products. Each SCFA has its own synthesis pathway:

- **Acetate:** can be produced from pyruvate by the acetyl – CoA pathway and also by the Wood – Ljungdahl pathway (11).
- **Butyrate:** is synthesized from two molecules of acetyl – CoA and the consequent reduction to butyryl – CoA. Butyrate is obtained from the butyryl – CoA molecule through the classical pathway. However, it has been shown that some bacteria are also able to obtain butyrate from acetate and lactate (11,12).
- **Propionate:** its synthesis can be carried out through three pathways. From phosphoenolpyruvate there is the acrylate pathway where lactate is reduced to propionate and the succinate pathway where it is produced from succinate. The third pathway is the propylene glycol one where the synthesis is carried out from sugars of deoxyhexose type (11).

It is estimated that approximately 90–99% of SCFAs are absorbed or used by the microbiota (9). SCFAs can diffuse through the intestinal epithelium in a non-ionized

[1] SLC5A8: Sodium – coupled monocarboxylate transporter 1
[2] SLC16A1: Monocarboxylate transporter 1 (MCT1)

form or through certain transporters such as: SLC16A1, SLC16A3[3], SLC5A8 and, specifically butyrate, SLC22A9[4] (2).

But only a small part is detected in blood circulation, mainly acetate and propionate, unlike the butyrate which is used locally as a colonocytes energy source (9). Some studies have shown that there is a preference in the SCFAs metabolism: butyrate > propionate > acetate. The remaining butyrate and most of the propionate are metabolized in the liver. The acetate, apart from being the SCFA which is found in higher concentrations in peripheral blood, it has also been shown to be able to cross the blood – brain barrier (BBB) as certain levels have been detected in the cerebrospinal fluid (2,9,11).

Within the cell, SCFAs can be used as an energy source as they are metabolized primarily by the Krebs cycle. As a result, the activity of mTOR, which acts as a sensor of the cellular energy levels and is involved in brain physiology and behavior, is increased (2).

It has been shown that the microbiota belonging to the Bacteroidetes phylum produces mainly acetate and propionate unlike the Firmicutes phylum which mainly produces butyrate (13).

4.3. The gut microbiota

The microbiota is the whole set of microorganisms which are found in different parts of the organism where a symbiotic relationship takes place. Of the whole microbiota, the one located in the GI tract has the greatest involvement in health due to the different functions it performs, some of them vital (4,14). The microbiome is estimated to be 100 times larger than the human genome (15).

Among all the microorganisms that inhabit the GI tract, bacteria stand out as the majority group. In adulthood it is mainly composed by the Firmicutes and Bacteroidetes phylum, with less from the Actinobacteria, Proteobacteria, Fusobacteria, Verrucomicrobia and Cyanobacteria phylum (15).

[3] SLC16A3: Monocarboxylate transporter 4 (MCT 4)
[4] SLC22A9: Organic anion transporter 7 (OAT 7)

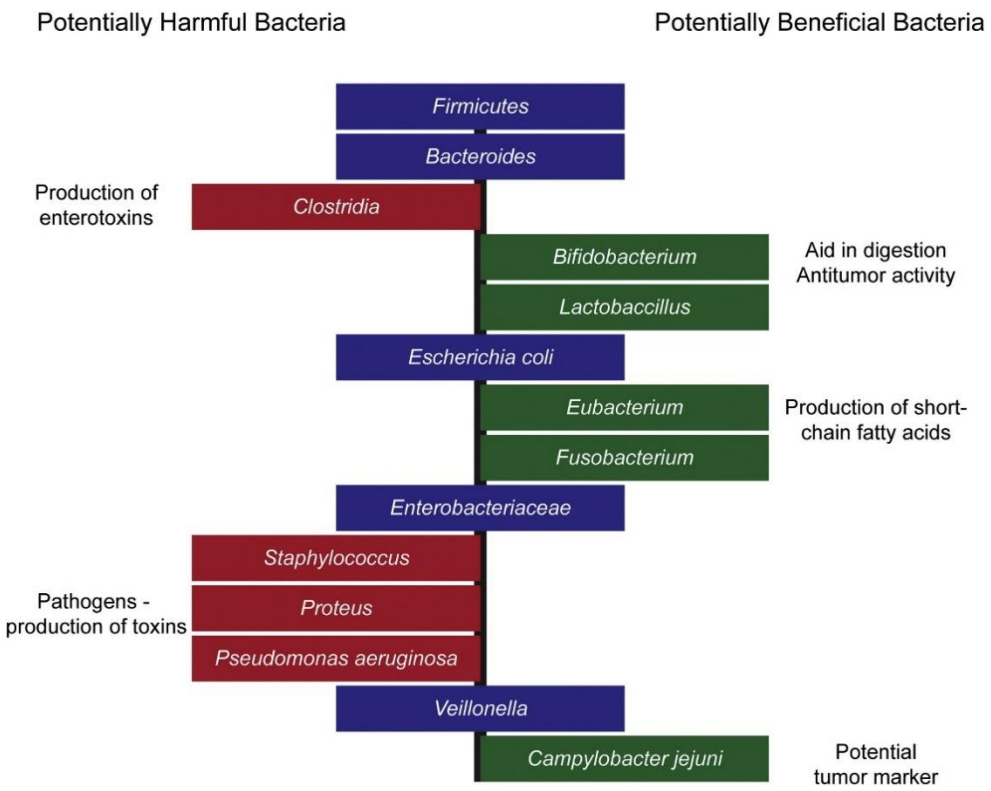

Figure 2. Schematic representation of the gut microbiota from Ghaisas S. et al. (4)

Its composition is not static as it changes throughout life due to factors such as age, diet, lifestyle, antibiotics intake, and so on. During the first years of life, the microbiota is conditioned by the type of birth and the food the baby receives, whether it is breastfeeding or formulas (14). In regard to the diet, changes in the food pattern have been seen to cause changes in the microbiota rapidly, even changes are observed 24 hours after changing a plant – based diet to a diet based on the consumption of animal – derived foods and vice versa (13).

The current evidence shows the great involvement of the microbiota in having a good state of health as it is associated with multiple effects that lead to the maintenance of homeostasis. Moreover, this can play a key role in certain pathologies (4,15–17).

It has been seen that the microbiota can play a key role in regulating metabolism and appetite control through CNS, so it has the ability to affect the eating behavior in some eating disorders and metabolic disorders, such as obesity and malnutrition (15).

4.4. The microbiota – gut – brain axis

The gut – brain axis consists in the bidirectional connection between the GI tract and the CNS that is given by afferent neurons of the spinal cord and the vagus nerve (VN) thanks to some peptides (neuropeptide Y, cholecystokinin, ghrelin and leptin) and neurotransmitters (NT) (dopamine, serotonin, GABA, acetylcholine and glutamate) (4). It is a physiological system that integrates the endocrine, immune, GI system, different neural pathways, and the brain (13).

In the recent years, due to the evidence about the microbiota impact on the axis and the CNS, the microbiota has been incorporated into this concept, leading to what is called the microbiota – gut – brain axis. It has also been studied as potential diagnostic and therapeutic tool on various diseases such as Parkinson, Alzheimer, amyotrophic lateral sclerosis, autism spectrum disorder (ASD), depressive disorder, and so on (4,17–21). Alterations in this axis can lead to immunological, neurological, and psychiatric illness (13).

4.4.1. Enteroendocrine cells

Related to the microbiota – gut – brain axis concept and in order to understand the functioning of the different communication pathways and, later, the effects of the SCFAs on the axis, it is important to talk about enteroendocrine cells (EEC). These, although they represent only 1% of the epithelial cells of the GI tract, play a very important role. 10 types of EEC have been described and all of them act as a luminal content sensor leading to different responses through the production of certain signaling molecules and hormones (2,13).

Two types of cells can be highlighted: enteroendocrine L cells and enterochromaffin cells. L enteroendocrine cells, located mostly in the distal small intestine and colon, have an apical brush border which is in contact with the intestinal lumen. As for the basolateral membrane, it is in contact with the vascular and lymphatic pathways allowing secreted hormones to get into circulation rapidly (2,22).

These cells are able to secrete the "Glucagon-like peptide 1" (GLP-1) and the peptide YY (PYY), which have an anorexigenic effect as they are involved in the regulation of appetite. Among other substrates, these can be activated by SCFAs through the free

fatty acid receptor (FFAR) 2 and FFAR3 receptors that stimulate GLP-1 and PYY secretion (2,22).

In regard to enterochromaffin cells, they are the main producers of serotonin from the tryptophan ingested. However, there is less information about its relationship with the microbiota (2).

4.5. Communication mechanisms:

The communication between the intestinal microbiota and the CNS is carried out through several systems such as the autonomic nervous system (NS), enteric nervous system (ENS), immune system (IS) and some microbiota metabolites. Bacteria are able to activate the secretion of local NT, peptides, hormones and IS mediators. There are three different pathways through which information is transmitted: neuronal, circulatory and immune pathway (13,23).

4.5.1. The neural pathway

The gut is innervated by the sympathetic and parasympathetic NS where the afferent fibers transmit information from the gut to the brain unlike the efferent ones that project the information to the smooth muscle of the intestine (13). The signals can be transmitted to the CNS by afferent nerves originated in the nodular and dorsal root ganglia through the VN and the spinal sensory nerves respectively (23).

The VN belongs to the parasympathetic NS and is the main one involved in the communication. This one ends on the intestinal mucosa and transmits information from the intestine to the brainstem, so it is a key element of the effects that the microbiota has on neurophysiological function (13,24). Besides, it is able to maintain homeostasis between the gut and the brain because, among other functions, regulates the secretion of NT in the GI system against various pathophysiological conditions (24).

Although it is known that the VN plays an important role in the microbiota – gut – brain axis, is not entirely clear whether the microbiota or its metabolites are those who can activate it directly. Since the nerve fibers under physiological conditions have no contact with the lumen content, direct activation would occur as a result of an alteration in

intestinal permeability. Hence, because the microbiota remains in the intestinal lumen, the communication with the afferent pathway is through indirect mechanisms (23).

The microbiota is capable of producing certain metabolites such as SCFAs, secondary bile acids, lipopolysaccharide (LPS), among others that are neuronal modulators (23).

The GI barrier is made up of a layer of epithelial cells and avoid the lumen content to pass through the tissue. The microbiota can secrete some products that stimulate the EEC of the intestinal epithelium through certain receptors that are expressed on its surface. These cells act as sensors for the lumen content and subsequently send signals through the afferent nerves producing different neurohormones such as cholecystokinin, GLP-1, PYY and serotonin. That allows, among other functions, to regulate the intake, digestion and absorption of nutrients. In addition, metabolites produced by the microbiota act as a signal of the enterochromaffin cells and regulate serotonin synthesis that activates the VN pathway (23,24).

It is also necessary to emphasize the existence of the ENS. The ENS and CNS are in constant communication via neural pathways. The communication between the microbiota and the ENS is performed by metabolites such as SCFAs which are able to cross the epithelium to act directly on the ENS. Once they reach the lamina propria, are capable of interacting with certain receptors as Toll-like receptors (TLR) and G protein – coupled receptor (GPCR) (25).

4.5.2. The circulatory pathway

Another way through which the microbiota and the CNS are in contact, is the circulatory pathway through intestinal hormones, NT, inflammatory and immunological signals, and so on (23). The EEC of the gut are able to secrete certain peptides that communicate with the CNS through the afferent nerves in the intestine (neuronal pathway) or they reach the brain through bloodstream. It should be noted that through circulation not only the flow of microbial metabolites is regulated but also the information that reaches the brain from the intestinal microbiota (13).

Unlike other metabolites such as amino acids, sugars and vitamins that are absorbed by active mechanisms through specific transporters, microbiota metabolites can be

absorbed by both active and passive mechanisms. In regard to SCFAs, they can be absorbed by monocarboxylate transporters or via diffusion. However, in case of a leaky gut, a third mechanism is added: the paracellular via (between cells) which can lead to an alteration in the microbiota composition and an inflammatory response (13).

Neurohormones such as serotonin, catecholamines, dopamine… are released to circulation by neuroendocrine cells from the intestine. Among these, one of the most studied is serotonin, which has been proved to be produced in 90% in the intestine under microbiota regulation. However, the peripheral serotonin is not able to cross the BBB. In contrast, SCFAs produced by the microbiota once in the bloodstream are able to cross the BBB and reach the hypothalamus where they develop different effects (14).

Compounds capable of crossing the BBB are those with a low molecular weight, little or no charge, and have lipid-soluble properties. Therefore, those microbial metabolites that meet these physicochemical properties are likely to be able to diffuse into the BBB and, as a consequence, develop their effects on the brain (24).

In addition, it has also been shown that SCFAs that are in the bloodstream can increase the production of tight junction proteins called claudin-5 and occludin increasing the BBB integrity that limits the access of undesirable metabolites and, at the same time, regulates the transmission of more microbiota signals from the gut to the brain (16,24).

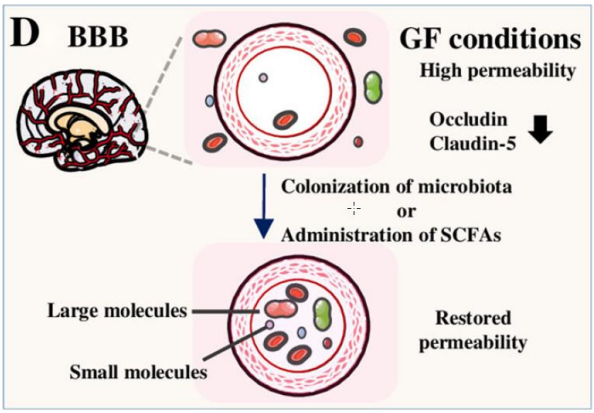

Figure 3. Effect of the SCFAs on BBB permeability from Ma Q. et al. (24)

4.5.3. The immune pathway

As a result of the constant communication between the NS and the IS, the effects that the microbiota has on the NS cannot be dissociated from those it has on the IS (26).

The microbiota is usually found in areas where there is a greater presence of IS elements such as immune cells, mucus, immunoglobulin A and some antimicrobial peptides. All of them have an important function in order to maintain a homeostatic relationship between the microbiota and the organism as they prevent microbial translocation. However, the IS also plays an important role in axis communication (13).

The microbiota is able to secrete some molecules such as LPS which are able to get to blood circulation and act as a promoter of innate IS. As a result, inflammatory cytokines, which are able to cross the BBB, are secreted. However, it has been seen that the microbiota is able to promote the secretion of non-inflammatory cytokines with a protective role on the CNS (13,14).

Some animal studies have suggested that an absence of microbiota may result in a lower IS response, so it could be concluded that the presence of microbiota is essential for the proper functioning of the IS (13).

4.6. Short – chain fatty acids

SCFAs are possibly the most studied microbiota metabolites. Acetate, propionate and butyrate make up 95% of the total. These are involved in the regulation of host – homeostasis such as GI function, blood pressure regulation, circadian cycle, neuroimmune function, brain function and behavior, among others. Different studies have shown the great involvement of these compounds in the axis communication (2,26,27).

Although the main source is the microbial fermentation of dietary fiber, there are also endogenous sources such as protein catabolism by the microbiota and the metabolism of long – chain fatty acids and the conversion of pyruvate to acetate by the host. Also, small amounts can be obtained from the consumption of fermented foods (2).

4.6.1. SCFAs receptors

In 2003, two receptors, orphans until then, were identified, whose ligands were the SCFAs. Both belong to the family of GPCRs, which includes many transmembrane proteins where various extracellular molecules can bind. This leads to a large number of

physiological effects that include the regulation of the IS, autonomic NS, sensory function (taste and smell) and the maintenance of energy homeostasis (12).

These two receptors are GPR41 and GPR43, which were later named FFAR3 and FFAR2 respectively. It should be noted that both show a preference for certain ligands depending on his chain length. FFAR2 is more specific for acetate and propionate, unlike FFAR3 which has a higher affinity for butyrate (12). However, some other studies also point to propionate as a FFAR3 ligand (28).

Some studies also include the GPR109A receptor as a target only for butyrate (2,12,25,29).

Related to the location, each receptor is located on the membranes of certain cell types throughout the body. However, although there are some differences between studies, they do agree on the fact that the three receptors are located in the colon, among other cells (2,29,30).

Receptor	**Location**	**Bibliography**
FFAR2	Colon, immune cells, heart, adipose tissue (AT) and skeletal muscle	(2) Cryan JF, O'riordan KJ, Cowan CSM, Sandhu K V., Bastiaanssen TFS, Boehme M, et al. The microbiota-gut-brain axis. Physiol Rev. 2019;99(4):1877-2013.
	Intestinal leukocytes, enteroendocrine cells, intestinal epithelium and white AT.	(29) Sivaprakasam S, Prasad PD, Singh N. Benefits of short-chain fatty acids and their receptors in inflammation and carcinogenesis. Pharmacol Ther. 2016;164:144-51.
	Immune cells (neutrophils, eosinophils, lymphocytes, monocytes), pancreas (β cells), intestinal cells (enteroendocrine L cells and epithelial cells) and white AT.	(30) Grundmann M, Bender E, Schamberger J, Eitner F. Pharmacology of free fatty acid receptors and their allosteric modulators. Int J Mol Sci. 2021;22(4):1-38.

FFAR3	Colon, immune cells, heart, peripheral NS and BBB	(2) Cryan JF, O'riordan KJ, Cowan CSM, Sandhu K V., Bastiaanssen TFS, Boehme M, et al. The microbiota-gut-brain axis. Physiol Rev. 2019;99(4):1877-2013.
	Enteric neurons, enteroendocrine cells and pancreas	(29) Sivaprakasam S, Prasad PD, Singh N. Benefits of short-chain fatty acids and their receptors in inflammation and carcinogenesis. Pharmacol Ther. 2016;164:144-51.
	Peripheral NS, pancreas (β cells), intestinal cells (L enteroendocrine cells, K cells) and immune tissue (dendritic cells and thymus)	(30) Grundmann M, Bender E, Schamberger J, Eitner F. Pharmacology of free fatty acid receptors and their allosteric modulators. Int J Mol Sci. 2021;22(4):1-38.

Table 1. Location of FFAR2 and FFAR3 receptors throughout the body.

4.6.2. Effect of the short – chain fatty acids on the microbiota – gut – brain axis

SCFAs are GPCR ligands leading to many effects such as the promotion of energy and glucose homeostasis due to their use as an energy source, the regulation of the immune and inflammatory system responses, also hormones that control the feeling of satiety and finally the regulation of the central and peripheral NS (16).

By means of the FFAR2, receptor they have a protective and homeostatic effect on the colon as they are able to regulate the colonic regulatory T cell (Treg). As for the FFAR3 receptor, it has been shown to has the ability to promote beneficial metabolic effects including the control of body weight and glucose through the gut – brain axis (25).

➔ **GLP-1 and PYY peptides regulation**

The main stimulus for GLP-1 and PYY secretion is food intake and digestion as an increase in their plasma levels is observed just after and until hours after ingestion takes place (31).

Since SCFAs are ligands of the endogenous FFAR2 and FFAR3 receptors of enteroendocrine L cells, they are involved in the control of the secretion into the bloodstream of anorexigenic intestinal peptides such as GLP-1 and PYY (3,13,15,28).

GLP-1 and PYY are involved in the regulation of appetite through both central and peripheral pathways as they decrease the intestinal motility, regulate glucose homeostasis and energy expenditure and, in addition, decrease appetite and food intake (32). It should be noted that the effect of decreasing appetite and food intake by GLP-1 is through the autonomic NS and the brain (28).

In subjects supplemented with prebiotics, an increase in plasma of both peptides and also the feeling of satiety could be observed. This could contribute to a change in appetite and, therefore, its use as a treatment for obesity is being considered (16).

Also, it has been seen that the SCFAs regulate the production of PYY from EEC by inhibiting the histone deacetylase (2,22). However, this effect is specific to certain species such as humans, but not in mouse cells and, therefore, in this case, mouse is not valid as a study model (22).

Emphasis should be made on the importance of the colon area where the SCFAs act, since it has been seen that the infusion of acetate in the distal colon produce an increase in circulating PYY levels unlike when it is made in the proximal colon (2).

One study showed that acetate plays a role in the central control of appetite by regulating regions such as the hypothalamus. This effect occurs through activation of acetyl-CoA carboxylase which leads to changes in the expression of GLP-1 and PYY. However, it should be noted that this study was performed on a mouse model (13).

Also, there has been seen an increase of GLP-1 and PYY in the plasma due to an increase in the propionate levels. In addition, an increase in propionate production has been seen to lead to lower subjective appeal by individuals to high calorie foods and also low energy intake during an ad libitum[5] meal (13).

[5] ad libitum: without restrictions.

➔ **Effect on hormones: insulin, glucagon, leptin and ghrelin.**

Another effect of the SCFAs is its impact on other hormones such as insulin, glucagon, leptin and ghrelin (15). However, many more studies are still needed, especially in humans, in order to obtain stronger evidence.

- **Insulin and glucagon**

The GLP-1 increases insulin secretion from the beta – pancreatic cell and decreases glucagon secretion. This effect leads to a lower blood glucose levels as it results in lower liver glucose production and an increased uptake by tissues (28).

In a study done on overweight adults was administered 10 grams of inulin – propionate ester for 24 weeks. The results directed to a reduction of weight gain, intra – abdominal AT distribution and intra – hepatocellular lipid content and also improved insulin resistance compared to the control group who only consumed inulin (17,33).

- **Leptin**

Leptin is a peptide secreted by adipocytes and to a minor degree from gastric parietal cells. This has several functions such as to decrease appetite, weight gain and adiposity. Its receptors are found in different areas of the brain which are involved in controlling appetite and also in the afferent nerves of the VN (34). Leptin provides the brain with information about energy storage. By inhibiting orexigenic AgRP neurons and activation of anorexigenic POMC neurons, leptin is able to decrease the intake and increase energy expenditure (35).

Some studies mention that leptin is secreted due to the binding of SCFAs to the FFAR3 receptor which is in adipocytes resulting in a decreased appetite. Therefore, this effect goes alongside GLP-1 and PYY (28).

In some in vitro studies, it has been shown that activation of FFAR3 by SCFAs on the AT resulted in an increased leptin expression (15,35). In the same way, oral propionate administration has been shown to increase circulating leptin levels. It should be noted, that these studies are done in rodents (35,36).

Another study showed an increased leptin expression after administering an ex vivo treatment on human AT with propionic acid[6]. Specifically, showed that the 1 and 3 mM doses increased their expression by 65 and 100% respectively. On the contrary, the 10 mM concentration resulted in no significant changes (37,38).

In a study done on rodents it was seen that both acetate and propionate[7] resulted in an increase in leptin gene transcription. However, more in vivo studies are required in order to study this relationship (39).

It should be noted that some of these studies refer to the FFAR3 receptor when the articles detailing the location of these receptors do not indicate that this receptor is located in AT. However, it cannot be ruled out and more studies should be done.

- **Ghrelin**

The ghrelin is secreted primarily in the stomach. This one is involved in regulating the intake, body weight, adiposity, insulin secretion, glucose metabolism, stomach acid secretion and stimulation of intestinal motility (34).

Among other receptors, ghrelin – secreting cells have on their surface the FFAR2 receptor which has SCFAs as a ligand. Their binding results in an inhibition of ghrelin secretion (31).

Ghrelin response differs from the other gut hormones since it shows an opposite fluctuation in plasma (32). Higher levels are obtained between meals and decrease post-intake (31). In addition, compared to the others hormones, ghrelin has opposite effects: stimulation of gastric emptying, hunger, glucagon secretion and inhibition of insulin secretion and thermogenesis (32).

[6] Concentrations of 0, 0.01, 0.1, 1, 3 and 10 mM (38)
[7] 860 µmol/L of acetate and 78 µmol/L of propionate (39)

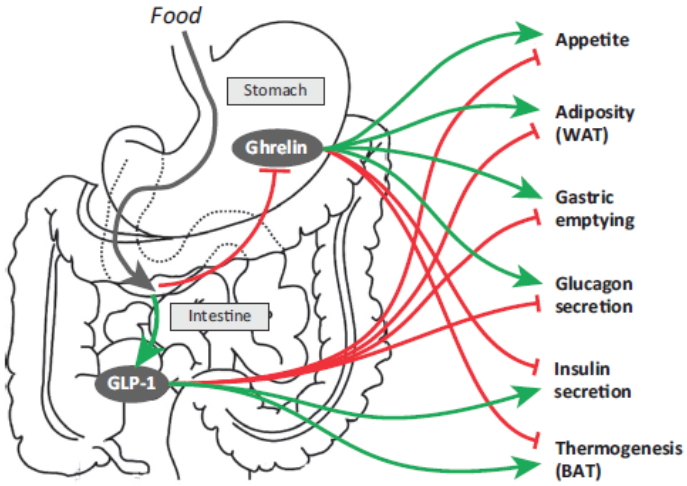

Figure 4. Scheme about the opposite endocrine and metabolic effects of ghrelin and GLP-1 from Engelstoft MS. et al. (31)

In addition, ghrelin crosses the BBB where is able to activate AgRP neurons and inhibit POMC neurons leading to an overall appetite – boosting effect (37).

In regard to the control of ghrelin and GLP-1 secretion, GPCR ligands cause an inhibitory and stimulatory effect respectively. This fact offers the research for possible strategies in order to obtain both effects through the same mechanism (31).

➔ **Effects on serotonin**

Serotonin has several functions such as regulating satiety, anxiety, mood, stimulation of peristalsis, secretion and vasodilation. In addition, there is also some evidence of its role in relation to lipid and glucose metabolism (37).

On the hypothalamus, it is able to regulate food intake decreasing it by inhibiting AgRP neurons and activating POMCs (37).

In regard to the SCFAs, it has been seen that are able to increase the synthesis and secretion of serotonin (15,18). However, it should be noted that it is not able to cross the BBB (37).

More than 90% of the serotonin we produce comes from the enterochromaffin cells of the intestine where it regulates peristalsis, among other functions. From EEC human treated with acetate and butyrate, it was observed that there was a concentration –

dependent increase in mRNA expression of the Tph1 gene. Tph1 is a limiting enzyme in the serotonin synthesis. Then, is stored in granules before being released (35,40).

In addition, serotonin participates in fasting – induced adaptation as it is able to promote lipolysis in AT and gluconeogenesis in liver. Thus, energy availability increases (35).

Also, propionate has been shown to be able to modulate serotonin secretion in the gut and decrease its levels in the brain. This can lead to an excess of serotonin in plasma that has been observed in children with ASD (41).

Peptides/ Hormones / NT	**SCFAs effect**	**Main physiological effects**
GLP-1	↑	- ↓ Intestinal motility - Glucose homeostasis and energy expenditure regulation - ↓ Appetite and food intake
PYY	↑	
Insulin	↑ (Indirect effect)	- ↓ Glycemia - Improving of insulin resistance
Glucagon	↓ (Indirect effect)	
Leptin	↑	- ↓ Appetite and food intake - ↓ Weight gain and adiposity - ↑ Energy expenditure
Ghrelin	↓	- ↓ Appetite - Body weight, adiposity and glucose metabolism regulation - ↓ Stomach acid secretion, gastric emptying and intestinal motility - ↓ Glucagon secretion - ↑ Insulin secretion - ↑ Thermogenesis
Serotonin	↑	- ↑ Lipolysis in AT and gluconeogenesis in liver → ↑ energy availability - Regulation of satiety, anxiety, mood, stimulation of peristalsis, secretion and vasodilation

Table 2. Main effects of the SCFAs on peptides (GLP-1 and PYY), hormones (insulin, glucagon, leptin and ghrelin) and NT (serotonin) and their resulting physiological effect

➔ **Effects on the nervous system**

Finally, one of the effects that SCFAs develop on the body is on the NS.

Butyrate has been shown to be able to increase the proportion of cholinergic neurons by epigenetic mechanisms. Therefore, the effects on NS by SCFAs are not limited to neuronal activation (15).

The FFAR3 receptor is also expressed in the ENS. When SCFAs cross the intestinal epithelium and reach the portal vein, signaling through the FFAR3 receptors of the portal nerves by propionate takes place. This fact leads to an increase in the activity of the dorsal vagal complex that receives signals from the VN and the hypothalamus, which participates in the control of appetite and metabolism (3,15).

In addition, through FFAR3 receptors located in sympathetic ganglionic neurons, SCFAs can directly activate the sympathetic NS (42).

Also, SCFAs can cross the BBB and help maintain their integrity. SCFAs influence neuronal signaling and NT production as they increase the expression of anorexigenic peptides in the hypothalamus and regulate the levels of GABA, glutamate and glutamine. Thus, they may have an impact on behavior (14,42).

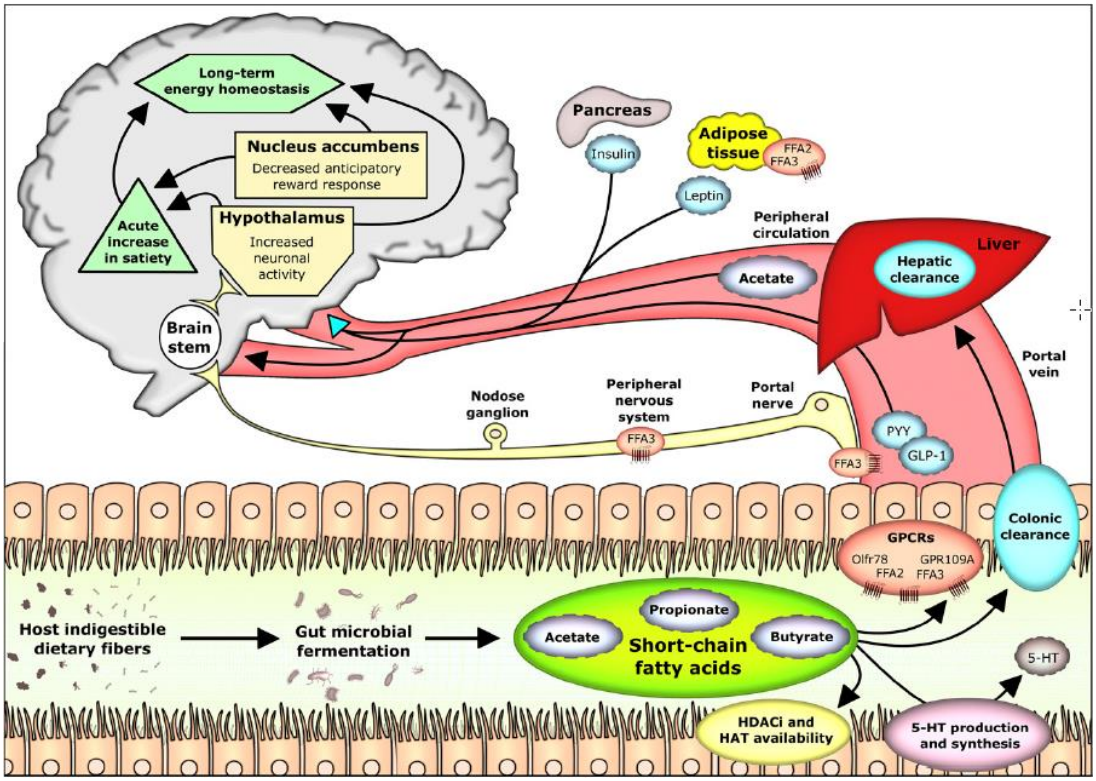

Figure 5. SCFAs involvement in the regulation of appetite and metabolism from van de Wouw M. et al. (15).

4.7. Involvement of SCFAs in some neurological disorders

There is an increasing evidence about the relationship between microbiota and different neurological disorders such as ASD, Parkinson, Alzheimer, and so on (4,17–21). However, the evidence of the SCFAs in relation to these disorders is not so clear.

Some compounds produced by the microbiota such as LPS, bacterial lipoproteins, flagellin, and CpG islands of unmethylated DNA are capable of stimulate cytokine secretion by IS innate cells. These cytokines are able to cross the BBB and activate microglia and certain neurons resulting in altered neuronal function that can affect mood and behavior. Based on this fact, it is important to have in mind the role that SCFAs play in the integrity of BBB through the production of the tight junction proteins that limit the access of certain molecules through it (16).

GPCRs are also found in the CNS where they are involved in the regulation of metabolism, inflammation, neurological disorders and other diseases (25). SCFAs can cross the BBB and participate in neuronal signaling, NT production, and behavior (42).

Moreover, SCFAs are able to induce the Treg proliferation by histone modifications, increasing acetylation and decreasing deacetylation at Foxp3+ promoter region (24,43). Also, they have been shown to stimulate the production of retinoic acid in the intestine, which inhibits Th17 cell differentiation and promotes the proliferation of Treg leading to beneficial effects on neuroinflammation (12,24,30). Therefore, all these actions go in the direction of controlling inflammation and improving the IS functioning.

Another important concept to consider is the intestinal permeability. Some products of the microbiota have been shown to be involved in the maintenance of the intestinal barrier. For example, SCFAs have been shown to act as trophic factors of the mucosa and epithelial layer (3,42). Moreover, butyrate has effects on mucin production, anti – inflammatory effects, and increase tight junction proteins leading to a better maintenance of the intestinal barrier and reduced permeability (44).

Increased permeability can lead to translocation of the microbiota or its products such as LPS so, IS is activated and pro – inflammatory cytokines are secreted. These, as already mentioned, have an impact on the CNS and ENS (42).

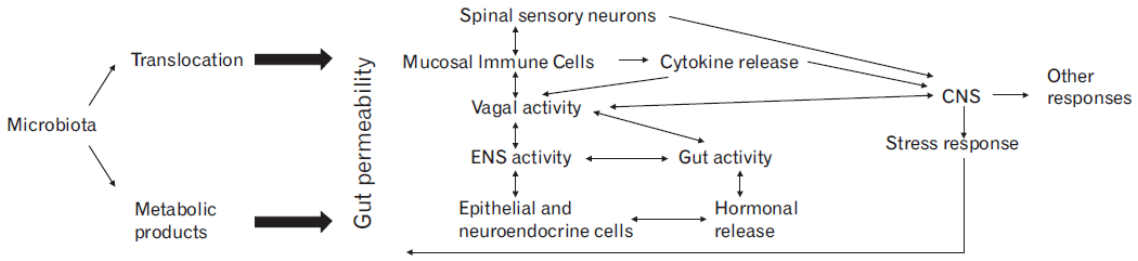

Figure 6. Interaction between microbiota, intestinal permeability and CNS from Yarandi SS. et al. (42)

➔ **Parkinson's disease**

The Parkinson's disease is a neurodegenerative disorder quite common among the population. The main feature that accompanies this disorder is the loss of dopaminergic neurons in substantia nigra and the accumulation of α – synuclein and Lewis bodies. Recent evidence suggests that accumulation of α – synuclein starts in ENS where it is associated to some digestive symptoms (2,24). Due to the implication of SCFAs in the regulation of IS, certain strategies can be contemplated as an effective treatment of the disease (24).

In these patients, a lower amount of Prevotellaceae has been found which is a genus producer of SCFAs (43). In fact, decreased levels of SCFAs have been found in the feces of Parkinson's patients compared with controls (19,43).

➔ **Autism spectrum disorder**

As for ASD, it is a neurodevelopmental disorder that has an important genetic basis (13). Given the neuroactive properties of SCFAs we should not stop studying the relationship with this disorder (2).

It is also important to note that in children with ASD a higher intestinal permeability has been observed which leads to an increase in LPS. This leads to an inflammatory state as a result of the secretion of pro – inflammatory cytokines such as IL-6 (42).

Several preclinical studies in rodents have shown how neurotoxic doses[8] of propionic acid induce a similar behavior in ASD (2,45,46).

[8] Intracerebroventricular administration of 4 µl of a solution that contains 0.26 M of propionic acid (45,46)

Also, some studies show the relationship between certain levels of SCFAs and the pathogenesis of ASD. In children with this disorder, high levels of acetic acid and propionic acid have been found in both feces and serum, as well as increased production by the microbiota. However, the exact mechanisms by which SCFAs are involved are not known yet (41).

So, according to these latest studies, it seems that SCFAs play a negative role in this disorder.

On the other hand, some studies have shown that children with ASD have significantly higher levels of Clostridium and lower levels of healthy bacteria and metabolites such as SCFAs compared to the control group (17). Therefore, because of these contradictory studies, the SCFAs role on this disorder is still unclear (13).

➔ **Multiple Sclerosis**

Multiple sclerosis is an inflammatory disease where there is a demyelination of neuronal axons. It has been seen an abnormal immune response to the secretion of pro-inflammatory cytokines due to an increased activity of Th1 and Th17 cells, which can lead to infiltration of immune cells in the CNS. In these patients, this fact has been accompanied by lower activity of Treg worsening autoimmune reactions (24). Some studies have shown the ability of SCFAs to decrease Th17 cells and increase Treg proliferation (12,24,30).

Also, an experimental model of multiple sclerosis showed that the administration of propionic acid improved the disease course because a lower inflammatory state of the CNS resulted in less neuronal demyelination (43).

Although there is growing evidence that understanding of the microbiota – gut – brain axis could lead to strategies for the prevention and treatment of certain brain disorders, many other studies are still needed (25).

5. DISCUSSION

Current evidence appears to show a relationship between SCFAs and the microbiota – gut – brain axis through their effect at different levels.

Considering diet as one of the factors that regulates the microbiome, and this one, at the same time, conditions the production of SCFAs, it is necessary to highlight the role of the pattern of eating habits in everything that surrounds the microbiota – gut – brain axis.

Following high – fat and high – sugar diets usually leads to lower fiber intake, which can lead to dysbiosis. At the same time, this results in a decreased synthesis of some beneficial products by the microbiota such as SCFAs (3).

Also, the antibiotics and other drugs intake are other factors that can lead to dysbiosis. It should be noted that a state of dysbiosis can lead to negative consequences on neurological and mental health status (27).

Although studies are still needed to correctly define the impact of SCFAs on the microbiota – gut – brain axis, one of the effects that has been seen more clearly is the GLP-1 increase. However, other effects like the one it has on leptin are not so clear and more studies are needed.

The overall effect, consists in a decrease in appetite and food intake, regulation of glucose homeostasis, energy expenditure and control of body weight.

In relation to GLP-1, currently, there are pharmacological therapies that mimic this peptide and are indicated in people with diabetes and even one of them exclusively in obesity (Saxenda®). Some of these active ingredients are: Dulaglutida (Trulicity®), Exenatida (Bydureon®, Byetta®), Semaglutida (Ozempic®, Rybelsus®), Liraglutida (Victoza®, Saxenda®) i Lixisenatida (Adlyxin®). Even though, Rybelsus ® and Adlyxin ® are not marketed in Spain (47).

These are drugs that, despite their proven effectiveness, are not first – line treatments in type 2 diabetes due to their higher cost and method of administration that, unlike the oral route used in most antidiabetic drugs, these ones, except Rybelsus®, need to be injected (48).

Although SCFAs effect is in the same direction as these drugs by increasing GLP-1, their effect is currently not comparable. Among other reasons, because the production of SCFAs from dietary fiber is highly variable depending on the person. Consumption of the same type and amount of fiber by different subjects does not imply that it results in the production of the same amount of SCFAs. That is because it depends, among other things, on the type of microbiota the subject has. However, if the possibility of consuming SCFAs directly is contemplated, more studies would be needed to analyze the efficacy in relation to increasing GLP-1.

Another study area is their relationship with some neurological diseases like Parkinson, ASD and multiple sclerosis. The involvement of the microbiota in these types of disorders is becoming more important. However, more studies are needed to obtain clear conclusions about SCFAs role.

Within this area, should be emphasized the importance of continuing with the study of possible strategies for future treatments that may be beneficial for individuals suffering from these types of neurological disorders.

On the other hand, it should be considered that one of the limitations of some of the studies is that they are made in animals, mainly rodents. This fact represents an obstacle due to the rodent's diet differs from the human's diet, which makes the comparison between both microbiota problematic (4).

Most reviews show that more studies are still needed in order to define the SCFAs impact on the axis. In relation to this, not all studies have identical results due to the methodology used among other factors. However, they also emphasize the importance of continuing to study this relationship.

6. CONCLUSION

After the research, it can be concluded that the SCFAs produced by the gut microbiota have an involvement in microbiota – gut – brain axis. However, it should be emphasized that while some of the effects are well – proven, others still require more study.

Also, it should be noted that the information collected was different depending on the article consulted creating some contradictions. These, once again, leads to the conclusion that more studies have to be performed.

Currently there is a deficient fiber intake in the population. In a study done in an adult Spanish population between 18 and 64 years old, the fiber consumption was 12.5 ± 5.66 g / day on average. This consumption is below from the European Food Safety Authority (EFSA) recommendation (25 g / day) (49,50).

Finally, considering the results of this research that show the potential beneficial effects of the SCFAs, could be added one more reason why is important to increase the fiber intake. However, as already mentioned, although most prebiotics belong to the fiber category, it should be noted that not all fiber types act as prebiotics.

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