The International Journal of Biochemistry & Cell Biology 84 (2017) 40–45

Contents lists available at ScienceDirect

The International Journal of Biochemistry & Cell Biology

journal homepage: www.elsevier.com/locate/biocel

Medicine in focus

Fats for thoughts: An update on brain fatty acid metabolism

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ARTICLE INFO

Article history:
Received 15 October 2016
Received in revised form
22 December 2016
Accepted 28 December 2016
Available online 5 January 2017

Keywords:
Ketone bodies
Medium-chain fatty acids
Short-chain fatty acids
Polyunsaturated fatty acids

ABSTRACT

Brain fatty acid (FA) metabolism deserves a close attention not only for its energetic aspects but also because FAs and their metabolites/derivatives are able to influence many neural functions, contributing to brain pathologies or representing potential targets for pharmacological and/or nutritional interventions.

Glucose is the preferred energy substrate for the brain, whereas the role of FAs is more marginal. In conditions of decreased glucose supply, ketone bodies, mainly formed by FA oxidation, are the alternative main energy source. Ketogenic diets or medium-chain fatty acid supplementations were shown to produce therapeutic effects in several brain pathologies.

Moreover, the positive effects exerted on brain functions by short-chain FAs and the consideration that they can be produced by intestinal flora metabolism contributed to the better understanding of the link between "gut-health" and "brain-health".

Finally, attention was paid also to the regulatory role of essential polyunsaturated FAs and their derivatives on brain homeostasis.

1. Introduction

The human brain has a high energy demand that is almost exclusively satisfied metabolizing glucose and, under particular circumstances, also fatty acids (FAs) and ketone bodies (KBs) (Fig. 1) (Belanger et al., 2011). However, the energetic role of FA oxidation in the brain is still matter of debate. In fact, although it is widely accepted that neuronal mitochondria in adult brain do not oxidize FAs (Schönfeld and Reiser, 2016), a number of observations challenge the dogma. A recent study on isolated rat brain mitochondria demonstrated that FAs are utilized as energy source in astrocytes and neurons when furnished in association with other respiratory substrates, a situation that resembles the *in vivo* condition (Panov et al., 2014). Similarly, a study conducted in Drosophila demonstrated that the adult brain is able to catabolize FAs and release KBs (Schulz et al., 2015), while a study in rats showed that octanoate oxidation contributes to total brain oxidative energy production (Ebert et al., 2003).

Beyond energy metabolism, brain FAs themselves or their metabolites play many essential roles as anti-inflammatory and neuroprotective molecules. In the following paragraphs, we summarized most of the metabolic pathways of FAs in the brain, starting from those used for energetic demand; then mentioning their role in several brain functions and in brain health.

2. Mitochondrial and peroxisomal fatty acid metabolism in the brain

FA transport across the blood-brain barrier (BBB, Fig. 1) is a complex process, involving diffusional and protein-mediated transports, predominantly by FA transport protein-1 and -4 (FATP-1

Abbreviations: AD, Alzheimer's Disease; AA, arachidonic acid; BBB, blood-brain barrier; CPT1, carnitine palmitoyltransferase 1; CNS, central nervous system; DHA, docosahexaenoic acid; EPA, eicosapentaenoic acid; FATP-1 and FATP-4, FA transport protein-1 and -4; FAs, fatty acids; GLUT1, glucose transporter1; GPR, G-protein coupled receptors; KBs, ketone bodies; HFDs, high-fat diets; IL-1β and IL-6, interleukin-1β and -6; MCFAs, medium-chain FAs; MCT1, monocarboxylic acid transporter 1; MUFAs, monounsaturated fatty acids; OA, oleic acid; PD, Parkinson's disease; PUFAs, polyunsaturated fatty acids; SCFAs, short-chain FAs; TNF-α, tumor necrosis factor-α.

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http://dx.doi.org/10.1016/j.biocel.2016.12.015
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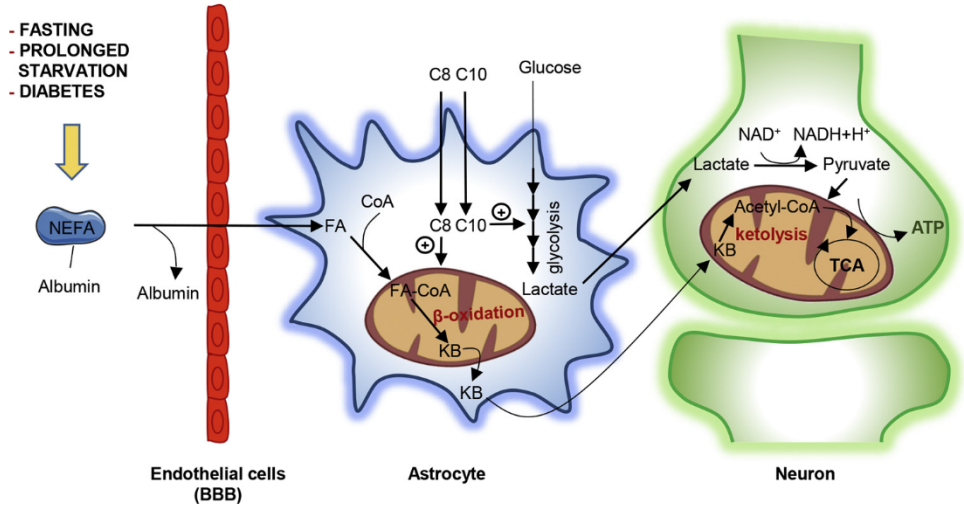

Fig. 1. Role of fatty acids in brain energy metabolism.
During conditions of fasting, prolonged starvation or diabetes the brain can use fatty acid (FA) oxidation to support its energetic demand. The main source of FAs crossing the blood-brain-barrier (BBB) likely derives from nonesterified long-chain FA/albumin complexes, after their dissociation from albumin and, to a lesser extent, from circulating lipoproteins. Once entered into cells, the conversion to acyl-CoA by acyl-CoA synthetases allows their intracellular entrapment.
Once FAs enter into astrocytes, they are translocated into mitochondrial matrix for β-oxidation and ketone body (KB) production. Branched- and very long-chain FAs can be also metabolized by peroxisomal α- and β-oxidation.
KBs (acetoacetate, beta-hydroxybutyrate, and their spontaneous breakdown metabolite, acetone) are produced (mainly by the liver) from two acetyl-CoA units when glucose is less available. These KBs are readily used by extra-hepatic tissues that convert them into acetyl-CoA, which then enters the citric acid cycle to produce energy. Glucose is anyway necessary to provide Krebs cycle substrates (i.e. succinyl-CoA) for the complete oxidation of KBs.
Medium chain FAs (MCFAs), such as octanoic acid (C8:0) and decanoic acid (C10:0) can modulate astrocyte metabolism, by promoting ketogenesis and glycolysis, respectively.

and FATP-4) in humans and mouse (Mitchell et al., 2011). Except for specific hypothalamic neurons (see below), brain FA oxidation for energetic purposes occurs almost exclusively in glial cells (Panov et al., 2014), although with a low efficiency as compared to other tissues with high energy turnover (Schönfeld and Reiser, 2013). This feature seems to reflect both a slow FA translocation across the inner mitochondrial membrane, which is mediated by long-chain carnitine palmitoyltransferase 1 (CPT1), and a low enzymatic capacity of the β-oxidation pathway, mostly due to a low activity of 3-ketoacyl-coenzyme A (Schönfeld and Reiser, 2013). Neurons keep the acyl-CoA concentration low thanks to the abundant expression and high activity of the cytoplasmic acyl-CoA thioesterase 7, whose loss results in multiple defects in neural metabolism (Ellis et al., 2013). According to the most accepted evolutionary hypothesis, such low FA oxidation capacity might be due to the higher oxygen consumption and superoxide generation associated to FA β-oxidation, with respect to glucose degradation, thereby enhancing the hypoxic risk and oxidative stress (Schönfeld and Reiser, 2013).

Whereas the bulk of dietary long-chain FAs are oxidized in mitochondria, branched- and very long-chain FAs undergo peroxisomal α- or β-oxidation (Wanders et al., 2003). Peroxisomes can only shorten but not fully degrade FAs into acetyl-CoA. Carnitine does not participate in the FA uptake by peroxisomes but rather in the export of chain-shortened FAs delivered to mitochondria. Defects of brain peroxisomal α-oxidation are linked to cerebellar defects and demyelinating neuropathy (De Munter et al., 2015), while disorders of peroxisomal β-oxidation can induce different type of neurological diseases depending on the type of enzyme affected (Clayton, 2001).

In hypothalamic neurons of the arcuate nucleus, the mitochondrial CPT1C plays an important role by interacting with malonyl-Coenzyme A (malonyl-CoA), the product of acetyl-CoA carboxylase that starts FA *de novo* synthesis. In particular, an increase of malonyl-CoA generates a signal of energy surplus that regulates orexigenic and anorexigenic neuropeptide release to suppress food intake and increase energy expenditure (Wolfgang et al., 2008); an opposite regulation is set-up by decreased levels of malonyl-CoA. In keeping with this finding, mice genetically lacking CPT1C exhibit decreased food intake and lower body weight than wild-type littermates, but gain excessive body weight and body fat when fed a high-fat diet, while maintaining lower or equivalent food intake (Wolfgang et al., 2008).

3. Neuroprotection of ketogenic diets: role of medium chain fatty acids (MCFAs)

"Ketogenic diets", based on the drastic reduction of carbohydrate assumption, represent a nutritional approach stimulating the brain to use KBs as main energetic fuel. KBs, which can cross the BBB through the monocarboxylic acid transporter 1 (MCT1), represent an important energy source for the brain when glucose is less available (e.g., during fasting, strenuous exercise, diabetes, ketogenic diet, in early life, or in neuropathological conditions) (Fig. 1) (Robinson and Williamson, 1980; Gnoni et al., 2010). Several observations, both in humans and in animal models, suggested that KBs can exert important neuroprotective effects, thus being useful in a number of neurological disorders (Stafstrom and Rho, 2012). Moreover, a very recent finding by Marosi et al. (2016) demonstrated that exercise decreases plasma glucose levels, increases the levels of one of the main KBs, 3-hydroxybutyrate, and induces the expression of the brain-derived neurotrophic factor, an effect of great interest for the treatment of many neurodegenerative disorders. One of the possible neuroprotective mechanisms of ketones is linked to their ability to up-regulate mitochondrial biogenesis in the central nervous system (CNS) (Bough et al., 2006), and to increase mitochondrial glutathione levels (Jarrett et al., 2008) and glutathione peroxidase activity (Ziegler et al., 2003). In agreement with such observations, animals fed with a ketogenic diet showed a reduced production of mitochondrial free radicals (Sullivan et al., 2004).

Similarly, the increased ketogenesis observed during the exposure to high altitudes, rather than simply being a pathophysiological dysregulation, seems to be neuroptotective from reduced oxygen availability through different mechanisms that reduce the

generation of reactive oxygen species (Murray and Montgomery, 2014).

A ketogenic diet may confer cognitive benefit also by increasing brain GABA levels, which, in turn, can counteract the neurotoxic effect of excessive glutamate (Wang et al., 2003). The mechanism has been associated to the induction of glutamate decarboxylase, an enzyme that facilitates the conversion of glutamate into GABA (Cheng et al., 2004). Moreover, KBs were suggested to improve the neuropathological hallmarks of Alzheimer's disease (AD), by both providing an excellent energetic source for the brain, where a dysfunction of glucose transporter1 (GLUT1) decreases neuronal glucose availability, and by reducing amyloid β production and deposition, potentially through the rescue of astroglial cells (Stafstrom and Rho, 2012).

An important source for ketogenesis derives from the catabolism of medium-chain fatty acids (MCFAs, Fig. 2A). The majority of MCFAs ingested are rapidly converted into ketones by hepatocytes. Therefore, MCFAs can induce ketogenesis without the need for a ketogentic diet and have the potential to provide an alternative energy source to prevent neuronal cell death due to lack of glucose (Lei et al., 2016). Different studies demonstrated that MCFAs modulate carbohydrate and lipid metabolism, as well as mitochondrial energy production (Schönfeld and Wojtczak, 2016). MCFAs activate free FAs sensing G-protein coupled receptors (GPR) such as GPR40 and GPR84, which regulate glucose metabolism and inflammation (Yonezawa et al., 2013). Moreover, many studies have shown that MCFAs themselves can have several effects on neural functions. Preclinical observations suggest that MCFAs can readily cross the BBB and can enter neurons via MCT1, a process driven by the electrochemical Na^+ gradient (Martin et al., 2006). Inside neural cells they can cross the double mitochondrial membrane without requiring the carnitine transport system (Schönfeld and Reiser, 2013).

A recent work (Thevenet et al., 2016) reported that some MCFAs may have brain health benefits (Fig. 2A) by modulating astrocyte metabolism. In this regard, decanoic acid (C10:0) promoted glycolysis and lactate formation, whereas octanoic acid (C8:0) increased the rates of astrocyte ketogenesis. These effects may activate shuttle systems that provide nutrients to neighboring neurons in the form of lactate and KBs (Fig. 1). These observations make MCFAs an attractive and novel target for neurodegenerative pathologies. In accordance with such hypothesis, a small number of clinical trials and animal studies showed that ketones derived from MCFAs improve cognition in patients with AD and attenuate neurodegeneration in a mouse model of amyotrophic lateral sclerosis (Zhao et al., 2012). A role of MCFAs on cognition and synaptic stability, not related to the production of KBs, has also been demonstrated in aged rats (Wang and Mitchell, 2016).

Among MCFAs, beneficial effects have also been reported by those with an odd number of carbon atoms. These FAs are metabolized by β-oxidation to provide propionyl-CoA, which is further carboxylated to produce succinyl-CoA, an intermediate of the tricarboxylic cycle. Oral administration of triheptanoin, a glycerol bound to three molecules of heptanoic acid (C7:0), has been demonstrated to be anticonvulsant in acute and chronic murine seizure models (Borges and Sonnewald, 2012). Moreover, a triheptanoin-enriched diet ameliorated mitochondrial functions in the infarcted area of stroked mice, thus improving their neurological outcome (Schwarzkopf et al., 2015).

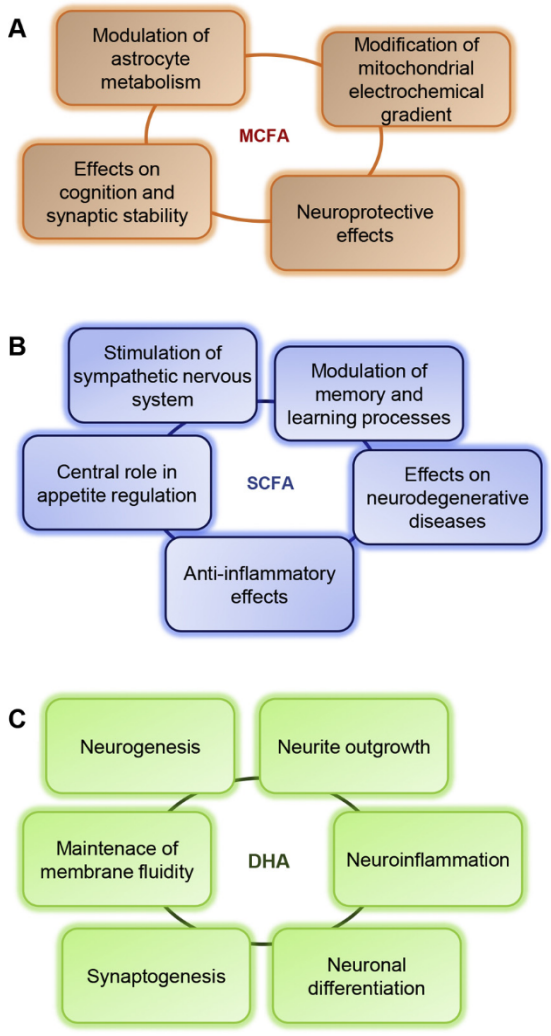

Fig. 2. Role of medium-chain, short-chain and polyunsaturated fatty acids on brain health and brain homeostasis.
Medium-chain FAs (MCFAs, panel A) are FAs with 6 to12 carbon atoms and are found as triacylglycerols in food-staff such as coconut oil and goat milk. Triacylglycerols containing MCFAs are broken down almost immediately by enzymes in the saliva and gastric juices, without using pancreatic fat-digesting enzymes and are absorbed more efficiently than long-chain FAs, without being incorporated into chylomicrons and transported through the lymphatic system.
Short-chain fatty acids (SCFAs, panel B) are molecules containing 2–5 carbon units and are the natural end-product of non-digestible carbohydrate (e.g. dietary fibers) fermentation by the gut flora. SCFAs enter the circulation via monocarboxylate transporters, as well as by diffusion. SCFAs can also be transported through the BBB into the brain and used for energy production by short-chain L-3-hydroxyacyl-CoA dehydrogenase.
Polyunsaturated FAs (PUFAs, panel C) are FAs that present two or more double bonds within the hydrocarbon chain. Depending on the position of the double bonds closest to the methyl side, PUFAs are divided in three classes: ω-3, ω-6, and ω-9.
Linoleic acid (a C18:2 ω-6 PUFA) and α-linolenic acid (a C18:3 ω-3 PUFA) can be the precursors for other PUFAs such as arachidonic acid (AA, C20:4 ω-6 PUFA), eicosapentaenoic acid (EPA C20:5 ω-3 PUFA) and docosahexaenoic acid (DHA, C22:6 ω-3 PUFA). All of them constitute a group of essential PUFAs of high physiological significance and the brain relies on their constant supply from the blood stream, thanks to the activity of transport proteins on the BBB, such as FATP-1/4 and FAT/CD36.

4. Short-chain fatty acids (SCFAs): the gut-brain axis

It is clear the existence of a bidirectional signaling between the gastrointestinal tract and the brain that can be involved in the etiology of several metabolic and mental dysfunctions (Braniste et al., 2014). Moreover, it has recently become evident that intestinal microbiota can be part of this signaling greatly influencing many brain functions (Braniste et al., 2014). The main products of intestinal bacterial metabolism are short-chain FAs (SCFAs, Fig. 2B), such as butyric acid, propionic acid and acetic acid, which are able to produce different effects at the central and peripheral nervous system (Fig. 2B). For example, a study conducted in mice by Frost and

colleagues (Frost et al., 2014) demonstrated that acetic acid has a direct central effect on the hypothalamic control of appetite, as suggested by the increase of pro-opiomelanocortin expression and by the concomitant reduction of agouti-related protein levels following peripheral acetate administration. This observation expands the broad spectrum of actions of SCFAs on appetite regulation and energy homeostasis by the modulation of several metabolic pathways at peripheral levels (reviewed by Byrne et al., 2015).

Diet can impact the composition and activity of the gut microbiota and, as a result, the production of intestinal SCFAs. Butyrate has received particular attention in this scenario: its production is dependent on diet and intestinal microflora composition, and it is able to exert many beneficial extra-intestinal effects through epigenetic mechanisms. In fact, butyrate is part of a class of epigenetic modulators known as histone deacetylase inhibitors and was preclinically tested as possible treatment for neurodegenerative diseases with aberrant histone acetylation. In a transgenic mouse model of AD, sodium butyrate administration was able to reinstate learning and memory (Fischer et al., 2007), decrease tau phosphorylation and restore dendritic spine density in hippocampal neurons (Ricobaraza et al., 2010). Such memory enhancing effects of butyrate have been associated to its ability to facilitate neuronal plasticity, long-term memory formation or LTP (Lattal et al., 2007; Vecsey et al., 2007). Furthermore, a prolonged treatment with sodium butyrate improved associative memory in a transgenic murine model for amyloid deposition (APP/PS1 mice) by increasing both hippocampal histone acetylation and the expression of genes implicated in associative learning (Govindarajan et al., 2011). Sodium butyrate was also demonstrated to prevent the induced-apoptotic cell death of two dopaminergic cell lines (human neuroblastoma-derived SK-N-SH and rat mesencephalic-derived MES 23.5) (Kidd and Schneider, 2010), thus suggesting a potential beneficial effect in Parkinson's disease (PD). Moreover, a very recent study showed that treatment with sodium butyrate could decrease the BBB permeability in mice, by increasing the expression of occludin, a major transmembrane protein of the tight junction (Braniste et al., 2014).

5. Role of essential polyunsaturated fatty acids (PUFAs) in the brain

In the brain, polyunsatured FAs (PUFAs) are mostly incorporated into neural membrane glycerophospholipids, with a proportion of ω-6 and ω-3 PUFA that varies considerably. Arachinodic acid (AA) is evenly distributed in all types of neural cells, while docosahexaenoic acid (DHA) is mostly concentrated in neuronal (including synaptic) membranes. Membrane glycerophospholipids, in turn, can be metabolized to a very large numbers of lipid mediators with powerful multiple neurochemical effects that could be harmful (pro-inflammatory effects of AA derivatives), beneficial (anti-inflammatory, repairing, neuroprotective, and antioxidant effects of DHA metabolites) or neuromodulatory (AA-derived endocannabinoids) (Schönfeld and Reiser, 2013).

A large body of evidence demonstrates important biological functions of DHA in neuronal homeostasis (Fig. 2C), mostly linked to its role in neurogenesis, synaptogenesis, neuronal differentiation, neurite outgrowth and maintenance of membrane fluidity (Belkouch et al., 2016). Moreover, DHA is able to modulate neuroinflammation, in both *in vivo* and *in vitro* experiments. In particular, DHA decreases the production of proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), interleukin-1β and -6 (IL-1β and IL-6), in cultured microglial cells (Lu et al., 2013) and reduces signs of inflammation in mouse microglia (Chen et al., 2014).

The dietary ω-3/ω-6 PUFA ratio seems to impact FA composition of membrane phospholipids, thus producing functional effects during perinatal and adult periods. The modern western diet is characterized by an AA/DHA ratio of about 15:1. The optimal ratio is still debated; however, dietary supplementations of DHA have been proven efficacious to exert neuroprotective effects *in vitro*, and *in vivo*, both pre-clinically and clinically (Schönfeld and Reiser 2013).

6. Role of monounsaturated fatty acids (MUFAs) in the brain

Monounsaturated FAs (MUFAs) are FAs having only one double bond. Depending on the position of the hydrogen atoms around the double bond it can be distinguished a *cis* or *trans* isomer. Most of the beneficial effects of MUFAs on cardiovascular system are associated to *cis* MUFAs, mostly oleic acid (OA, *cis* C18:1). A diet high in MUFA levels is often referred to as the Mediterranean diet. Some studies report that a high adherence to a traditional Mediterranean diet rich in MUFAs is associated with a slower age-related cognitive decline and reduced risk of developing AD (Morris and Tangney, 2014). Analogously, a canola oil-based diet, rich in OA, was demonstrated to provide beneficial cognitive effects (Arsenault et al., 2012). OA, in association with extra virgin olive oil antioxidants, such as tyrosol, hydroxytyrosol, and oleuropein, decreased chronic inflammation in human glioblastoma cells by preventing TNF-α- induced expression of cyclooxygenase (COX)-2 (Lamy et al., 2015). Moreover, OA was shown to influence lipid metabolism in C6 glioma cells down-regulating the activity and expression of key enzymes of FA and cholesterol synthesis (Natali et al., 2007). Interestingly, albumin-induced stimulation of OA synthesis in astrocytes can furnish neurons of a substrate that promotes axonal growth, neuronal clustering, and expression of the axonal growth-associated protein-43 during the postnatal period (Rodríguez-Rodríguez et al., 2004).

7. Conclusions

The brain requires a constant and substantial energy supply to maintain its main functions. Despite glucose remains its key energetic substrate, growing evidence suggests that the brain is able to adapt to different metabolic conditions, by using other circulating substrates, like FAs and KBs. Considering the importance of energetics in the etiology of several neurodegenerative diseases, this adaptability represents a neuroprotective strategy. From this consideration stems the rationale for the development of ketogenic diets based on the drastic reduction of carbohydrate intake and the consumption of fats as main energetic source. In fact, this dietary condition, which can mimic fasting without severe caloric deprivation, reduces the amount of glucose availability so that FAs are used by the liver to produce KBs. A large body of evidence indicates that KBs exert neuroprotective effects and/or produce beneficial effects on brain functions. However, it has been recognized for a long-time that the consumption of high-fat diets (HFDs), particularly rich of saturated and *trans*-FAs, can lead to metabolic disorders (obesity, diabetes), cardiovascular diseases, and even neurofunctional alterations. Therefore, the positive effects of ketogenic diets on "brain health" should be taken with caution.

Moreover the knowledge on the role of gut microbiota on the circulating levels of SCFAs, such as butyric acid, propionic acid and acetic acid, can explain part of the gut-CNS interactions involved in many pathological states. Disturbances in "gut health" have been linked to multiple sclerosis, autistic spectrum disorders, AD, and PD. On the other hand, beneficial effects of increased SCFAs availability have been observed in many preclinical and clinical studies. Many of these effects are attributed to their ability to regulate epigenetic mechanisms. The most empowering aspect of the role played in the brain by SCFAs produced by intestinal flora is that a simple lifestyle

change, such an increased consumption of fruits and vegetables, can make our brain healthy.

This is also true for essential PUFAs, whose dietary supply (mostly from fish and seeds) is fundamental for brain functioning but, at the same time, whose assortment can provoke beneficial or detrimental effects depending from the balance between ω-3 and ω-6 provisions.

In sum, we are all well aware that our daily dietary choices can influence our overall wellness but we should also take in due consideration that it might influence our brain functioning, such as our cognitive performance, our mood and anxiety, besides setting the metabolic base for the etiology of neuropathological states. In this context, the better understanding on the role played by all the different FAs and their derivatives in the nervous system can contribute to the development of better prevention strategies and also of novel therapeutic/nutritional approaches.

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