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REVIEW ARTICLE

Impact of Dietary Fats on Brain Functions

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Abstract: ***Background*:** Adequate dietary intake and nutritional status have important effects on brain functions and on brain health. Energy intake and specific nutrients excess or deficiency from diet differently affect cognitive processes, emotions, behaviour, neuroendocrine functions and synaptic plasticity with possible protective or detrimental effects on neuronal physiology. Lipids, in particular, play structural and functional roles in neurons. Here the importance of dietary fats and the need to understand the brain mechanisms activated by peripheral and central metabolic sensors. Thus, the manipulation of lifestyle factors such as dietary interventions may represent a successful therapeutic approach to maintain and preserve brain health along lifespan.

***Methods*:** This review aims at summarizing the impact of dietary fats on brain functions.

***Results*:** Starting from fat consumption, nutrient sensing and food-related reward, the impact of gut-brain communications will be discussed in brain health and disease. A specific focus will be on the impact of fats on the molecular pathways within the hypothalamus involved in the control of reproduction *via* the expression and the release of Gonadotropin-Releasing Hormone. Lastly, the effects of specific lipid classes such as polyunsaturated fatty acids and of the "fattest" of all diets, commonly known as "ketogenic diets", on brain functions will also be discussed.

***Conclusion*:** Despite the knowledge of the molecular mechanisms is still a work in progress, the clinical relevance of the manipulation of dietary fats is well acknowledged and such manipulations are in fact currently in use for the treatment of brain diseases.

Keywords: Fat, diet, PUFAs, endocannabinoids, neuroprotection, microbiota, nutrient sensing, hypothalamus, GnRH, reproduction, metabolic sensors, leptin, kisspeptin, ghrelin, neuroprotection, ketogenic diets, epilepsy.

1. INTRODUCTION

The incidence of overweight and obesity in developed and developing countries is rising due to unbalanced diets, the large use of junk food and insufficient physical exercise. According to the World Health Organization (WHO) "*Worldwide obesity has more than doubled since 1980. Most of the world's population live in countries where overweight and obesity kill more people than underweight. 41 million children under the age of 5 were overweight or obese in 2014…. Overall, about 13% of the world's adult population (11% of men and 15% of women) were obese in* 2014 [1].

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The common perception of nutrition and food has usually been linked to the need of energy for cell methabolism homeostasis. In this respect, energy availability and the abundance or the depletion of specific nutrients from diet differently affect the functions of the whole body. In particular, the brain uses more energy than any other human organ and lipids represent about 50% of its dry weight. As a consequence, adequate dietary intake and nutritional status have a recognized impact on brain functions such as cognitive processes, emotions, behaviour, neuroendocrine functions and synaptic plasticity with consequences on health [2].

Food sensing, through the production of autocrine, paracrine and endocrine signals, represents the first step in the modulation of energy homeostasis and brain activity. Several nutrient-sensors released from peripheral tissues (*i.e.* gastrointestinal tract, adipose tissues and skeletal muscle) transmit information concerning the metabolic status and

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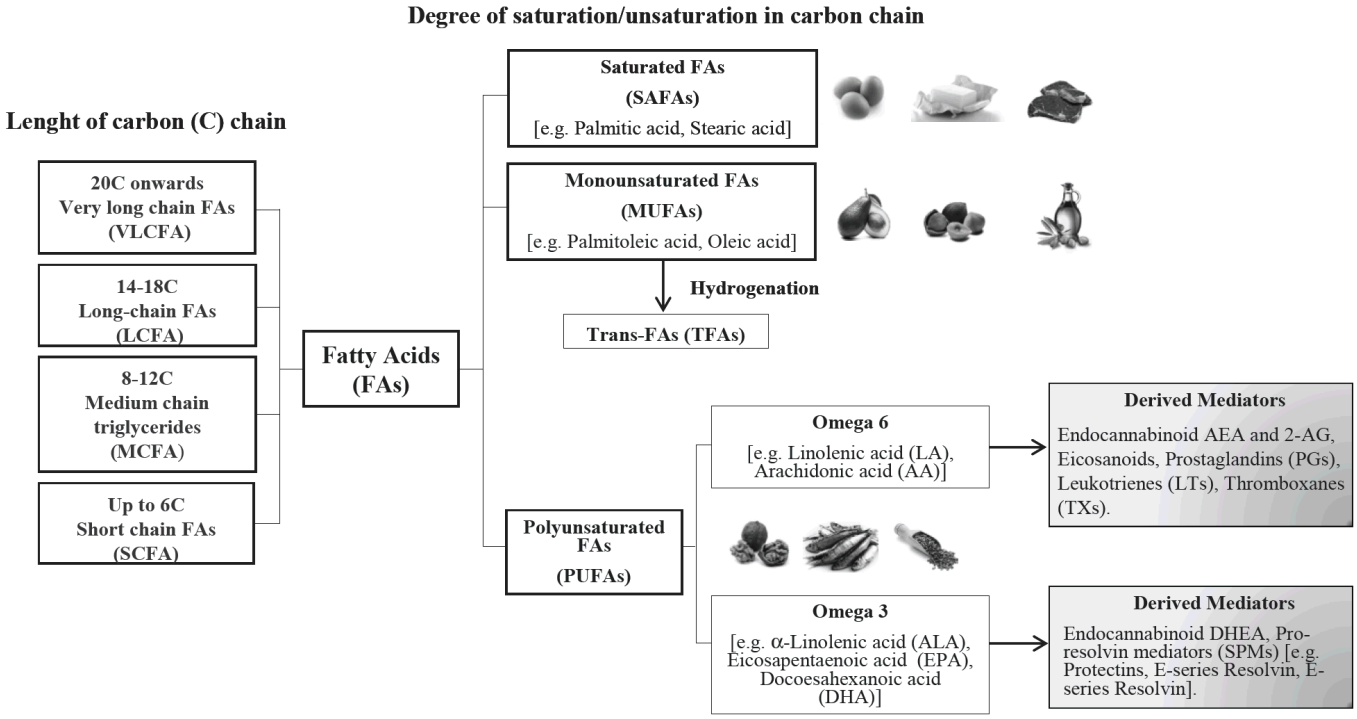

Fig. (1). Schematic representation of fatty acids (FAs). FAs are classified depending on the degree of saturation/unsaturation in the carbon chain and on the lenght of carbon chain. The main source of saturated SAFAs is animal fat; MUFAs and PUFAs mainly derive from vegetables and (fish/vegetable) oils; trans-FAs (TFAs), are mainly formed by the industrial production of hydrogenated fats from vegetable oils.

then enter the brain which in turn produces specific neuropeptides to orchestrate a wide range of biological functions and processes, comprising feeding behavior, energy expenditure and regulation of specific methabolic pathways, mainly through neuroendocrine mechanisms and autonomic terminals [3]. Here the importance and the need to understand the brain mechanisms activated by peripheral and central metabolic sensors.

Foods contain mixture of different types of fatty acids (FAs), which are carboxylic acids with a long aliphatic chain that is either saturated or mono/polyunsaturated (SAFAs, MUFAs/PUFAs respectively). Their impact on health strongly depends on fat types (Fig. **1**) and daily fat intake. Over the last year, dietary lipids have garnered recognition for their direct actions on the brain since they can affect multiple brain processes by regulating synaptic transmission, membrane fluidity and signal-transduction pathways. In this respect, omega-6 and omega-3 long chain (LC) PUFAs, also known as *n-6* or *n-3* PUFAs respectively, are nutrients widely present among dietary lipids with quite different proprieties as their inflammatory potential. In fact, the *n-6* PUFA arachidonic acid (ARA) exerts pro-inflammatory and atherogenic actions *via* its conversion by the cyclooxygenase (COX) and lipooxygenase (LOX) enzymatic pathways to bioactive mediators known as eicosanoids (prostaglandins (PGs), thromboxanes (TXs) and leukotrienes (LTs). However, during the initial (acute) phase of an inflammatory response, the ARA metabolism can also switch to the production of lipoxins (LXs), another eicosanoid class with the capacity to limit the extent and duration of the inflammatory process and promote the resolution of inflammation [4]. LXs are considered the first identified members of the family of specialized pro-resolving mediators (SPMs) [4, 5]. The SPMs family also comprises *n-3* PUFAs eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA)-derived pro-resolving mediators called resolvins (Rvs) and protectins (PDs) [6]. In the brain, the bioavailability of PUFAs and of their bioactive derivatives strongly depends on diet composition with an ideal ratio of 5 (*n-6*): 1 (*n-3*) [7]. Nevertheless, diets are often unbalanced and low *n-3* PUFAs have been associated with neuropsychiatric and neurological disorders with inflammatory outcomes [8].

Among PUFAs derivates, endocannabinoids (eCBs) deserve attention. These are lipid mediators that mainly act *via* type 1 and type 2 cannabinoid receptors (CB1 and CB2 respectively), which are Gi/o protein-coupled receptors. The eCB system is one of the most ancient signaling system of vertebrates [9, 10] with numerous pathways in the brain [11, 12]. The main eCBs are anandamide (AEA) and 2-arachidonoylglycerol (2-AG), which are the *N*-ethanolamide and the glyceryl ester of *n-6* PUFA ARA respectively. Interestingly, eCBs link food lipids to synaptic activity, neuronal plasticity, and to neuroendocrine and reproductive functions [13-21]. This highlights, the importance of dietary lipids to preserve and maintain the specific molecular systems and mechanisms that regulate neuronal functions and the possibility to prevent or to treat brain diseases *via* diet manipulations. For instance, it has been recognized that dietary *n-3* PUFAs have "antiaging" effects that support cognitive processes and maintain synaptic functions and plasticity [8, 22,

23]. In turn, diets that are high in saturated fats negatively impact brain functions and increase the risk of cardiovascular and neurological diseases [24].

Therefore, in this review we report the impact of dietary fats on brain functions. First we describe the gut-brain communications, with focuses on microbiota, dietary fats composition, lipid sensing, satiety and processing of hedonic food. Then we describe the functional interplay between diet and the hypothalamic control of reproduction, through the integrated activity of peripheral and centrally produced metabolic sensors that directly or indirectly convey metabolic cues on the hypothalamus-pituitary-gonad (HPG) axis. Then, we move to the description of the beneficial effect of dietary *n-3* PUFA on the preservation of neuronal function and structure and lastly, we discuss the potential therapeutic effects of ketogenic diets, the "fattest" of all diets.

Taken together, we provide evidence that diet manipulation in fat content can preserve brain health and has a clinical relevance.

2. GUT-BRAIN COMMUNICATION THROUGH MICROBIOTA

There is probably no better expression to define the enteric nervous system (ENS) than the figure of speech of the "second brain" [25]. As far as our knowledge about the ENS extends, the more gaps in the gastrointestinal tract (GIT), neuroendocrine, immune and the central and autonomic nervous systems are reduced. Thus, the notion of "gut-brain axis" is now largely used to explain the close connection and the tight bidirectional communication between the gut and brain and the importance of their cross-talk for brain functions in health and disease [26-29]. Quite surprisingly, the integrity of gut-brain reciprocal signaling appears essential not only for the pathophysiology of GIT disorders such as the irritable bowel syndrome but also for several brain neurological and neuropsychiatric disorders including Parkinson's disease, mood disorders (*e.g*., depression) and autism spectrum disorders (ASDs) [29-32]. The link between gut health and brain disorders can be, nonetheless, elusive as long as we do not consider the extraordinary number of commensal bacteria resident in the human gut, which is estimated to be around 100 trillion [33]. This giant population of symbiotic bacteria, known as microbiota, shapes GIT motility, epithelial barrier function, gut homeostasis and metabolism *via* nutrient processing and affects brain physiology and incidence of disease risk. Within this picture, the gut-brain axis constitutes the bidirectional route by which multiple signals (*e.g*., neural, neurohormonal and immunological) converging to the gut and in the gut re-encoded can access the brain. The microbiota is the living machinery composed of more than one thousand species of microorganisms (basically, *Bacteroidetes* and *Firmicutes*) whose genome outnumbered our genome about 150 times [33, 34].

2.1. Impact of Probiotics and Prebiotics on Brain Functions

The liability to mood disorders (*e.g*., depressive symptoms) is emblematic of the powerful impact that microbiota can exert on brain physiology and the pathogenetic consequences of microbiota dysfunction. Alterations in the microbial composition generate a state of dysbiosis that is a potential pathogenetic environment and a threat for the maintainance of host's health. Dysbiosis of the microbiota is responsible for different pathogenetic events such as changes in the host immunity and intestinal permeability [35]. Dysfunctions of the intestinal barrier increase the risk of endotoxins access to systemic circulation and development of a chronic inflammatory state and higher susceptibility to brain disease [36]. Dysregulated eating produces a dramatic impact on the composition of gut microbial community. The importance of dietary factors may become even more critical than the different genotypic hosts. Indeed, the exposure of different inbred strains of mice to repeated shift between diets with a different nutritional profile demonstrates that gut microbiota can be drastically modeled by dietary factors regardless of the genotype [37]. Prebiotics, probiotics, synbiotics [38] and fecal transplantation are examples of different strategies to reshape the microbial community and counteract neurological and neuropsychiatric diseases. The term probiotic, as opposed to antibiotic, is not recent and can be tracked back in time up to 1965 [39]. According to Food and Agriculture Organization of the United Nations (FAO) and the WHO, we should describe a probiotic as a "live microorganism which when administered in adequate amounts, confers health benefit on the host" [40]. On the other hand, despite several revisions from the original meaning [41], the core concept of prebiotics as a "non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria already resident in the colon" has not radically changed [42]. Probiotics can confer (additional) cytoprotection against a variety of toxins and pathogens, thus reinforcing the epithelial cells of the intestinal wall (*e.g*., tight junction proteins) and the integrity and function of the intestinal mucosal barrier.

Derangement of gut microbiota has been associated with brain disorders and neurodegenerative diseases such as ASDs, depression and Alzheimer's disease (AD). Abnormal increase of *Clostridium* type germs in the GIT [43] and atypical increase of fecal bacteria of *Sutterella* species in ASD children have been reported [44, 45]. A probiotic-based treatment (namely, *Bacteroides fragilis*) was showed to improve gut pearmeability and ASD-like features in mouse model of maternal immune activation [46] and probiotic treatment in ASD children is considered a potential therapeutic option [47].

Depression is known to be associated with dysregulation of the hypothalamic-pituitary-adrenal (HPA) axis and a pivotal study has provided the intriguing evidence for an excessive corticosterone and adrenocorticotrophic hormone response in germ-free stressed (*i.e*., restrained) mice as well as the demonstration that exaggerated stress response can be reverted by recolonization with *Bifidobacterium infantis* [48]. The therapeutic potential of probiotic administration such as *Lactobacillus rhamnosus* has been demonstrated for the modulation of the expression of γ-aminobutyric acid (GABA) receptors in the central nervous system (CNS) and its ability to mitigate stress-induced corticosterone response as well as depression- and anxiety-like behaviors [49]. Simi-

larly, there is evidence that chronic colitis can elicit anxiety-like behavior and that administration of *Bifidobacterium longus* can produce anxiolytic effects *via* the vagal connection between brain and the ENS [50]. Moreover, stress-associated alterations such as memory dysfunctions and altered neurotrophins expression in the hippocampus can be restored by treatment with probiotics [51], thus supporting the idea that changes of microbiota environment can be observed in neuropsychiatric disorders such as schizophrenia and ASDs [32, 52]. The bi-directional relationship throughout the brain-gut axis also implies that prolonged stressors affecting the CNS and the immune system can disrupt the microbiota homeostasis (*i.e*., dysbiosis) and elicit a chronic inflammatory state [53, 54] as for obesity. Interestingly, probiotics may produce similar anti-obesity and anti-inflammatory effects (*i.e*., macrophage infiltration into adipose tissue) through different underlying mechanisms as observed for the administration of *Lactobacillus paracasei*, *Lactobacillus rhamnosus* and *Bifidobacterium animalis subsp. lactis* [55].

Diet and nutrients are among the most relevant environmental stimuli for the enteric ecosystem but also the potential risk factors affecting the microbiota homeostasis. Indeed, dietary habits are critical determinants of microbiota microsystem and health. As a matter of fact, all the different routes by which visceral and interoceptive information can flow through the brain-gut axis can also be affected by dietary nutrients. The neural information generated in the GIT is conveyed in the brain *via* vagal and spinal afferent neurons and, at the same time, the endocrine and the immune information *via* gut hormones and cytokines, respectively. Diet and nutrients can determine microbiota composition and, *via* these signaling pathways, can even influence the metabolic phenotype and liability to develop metabolic dysfunction such as obesity [56-58]. The impact of macronutrients on microbiota composition has received attention with respect to carbohydrate ingestion, specifically dietary fiber. The ingestion of soluble dietary as fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS) produces short chain fatty acids (SCFAs) and improves the microbiota environment by favoring bacteria known to be inversely associated with metabolic dysregulation and chronic inflammation (*e.g*., obesity). The ingestion of prebiotics as non-digestible carbohydrates (CHO) such as cellulose and inulin, fibers and polysaccharides is indeed a strategy known to improve the enteric ecology *via* the increase of beneficial gut bacteria population that may provide resilience against metabolic derangement. SCFAs are organic fatty acids with 2 up to 6 carbon atoms and are the expression of the major part of the metabolites produced by the fermentation of non-digestible CHO, with acetate (C2), propionate (C3) and butyrate (C4) as the main SCFAs present in different proportion in the cecum and colon population [59]. Thus, dietary fibers and derived SCFAs can regulate body weight, food ingestion, glucose homeostasis, and insulin sensitivity. There are several cases in which ingestion of prebiotics such as isolichenan (from the lichen *Cetrariella islandica*) and arabinoxylan from the yeast *Triticumaestivum* has been demonstrated to improve brain functions and elicit the recovery of ethanol-induced or vascular dementia-associated memory deficits in mice [60, 61]. Moreover, as observed for probiotics, also prebiotics can affect brain signaling pathways involved either in the prevention or in the pathophysiology of affective disorders. FOS and GOS can increase the hippocampal expression of brain-derived neurotrophic factor (BDNF) and N-methyl-D-aspartate (NMDAR) subunits that are key factors in memory function and synaptic plasticity [62]. In humans, GOS consumption has been observed to be associated with a reduced secretion of salivary cortisol at awakening, thus suggesting an antidepressant potential for GOS supplementation [63]. Considering that prebiotics supplementation favors the growth of beneficial bacteria (*i.e*., probiotics), there is therefore a virtue circle between probiotics and prebiotics ingestion, both increasing the production of SCFAs.

2.2. SCFAs, Microbiota and Neuroinflammation

Dietary-derived SCFAs are essential substrates for the defence of intestinal epithelial cells and the regulation of lipid metabolism. SCFAs can promote fatty acids oxidation and inhibit their synthesis thus contributing to the decrease of free fatty acids plasma levels and body weight [64, 65]. SCFAs provide beneficial effects for the whole-body energy homeostasis but SCFAs are also signaling molecules whose action is not yet totally understood. SCFAs are indeed ligands for G-protein-coupled receptors such as free fatty acid receptors 2 (FFAR2 or GPR43) and free fatty acid receptors 3 (FFAR3 or GPR41) that have been identified in hematopoietic tissues, in the large intestine, in pancreatic β-cells, in neurons (FFAR3), in leukocytes and in adipocytes (FFAR2) [66]. One key aspect of FFAR2-mediated signaling is the ability, upon their activation, to promote the synthesis of glucagon-like peptide 1 (GLP-1) in enteroendocrine L cells [67]. Remarkably, dietary butyrate supplementation enhances adaptive thermogenesis and fatty acid oxidation in mice [64] and both butyrate and propionate have been shown to inhibit high fat diet (HFD)-induced weight gain and food intake and stimulate glucose-dependent insulinotropic polypeptide (GIP) secretion in a manner independent of FFAR3 [65]. Dietary FOS has a drastic impact on microbiota ecosystem, increasing *Bacteroidetes* and decreasing *Firmicutes* and propionate and butyrate can improve glucose tolerance and insulin sensitivity *via* different but complementary mechanisms leading to the stimulation of intestinal gluconeogenesis (IGN) [68]. Butyrate-generating species are favored by the ingestion of dietary fibers but each macronutrient can modify the microbiota community in a diet-dependent manner [69]. Reminiscent of the alteration of microbiota described in obese individuals show that exposure to Western diet generates an unbalance between *Bacteroidetes* and *Firmicutes* favoring the increase of the latter phyla over the former or, in other words, an increase of the ratio of *Firmicutes* to *Bacteroidetes* [70]. By contrast, in subjects whose diet adheres to Mediterranean diet recommendations, there is an increase of fecal content of SCFA levels (an index of high CHO fermentation) and high prevalence of *Bacteroidetes* phylum [71, 72]. SCFAs have a major impact on enteroendocrine signaling, feeding homeostasis and appetite regulation. Multiple mechanisms can be involved, and appetite can be suppressed by SCFAs-dependent leptin secretion upon FFAR3 activation [73]. In addition to GLP-1 synthesis, SCFAs can influence the secretion of other satiety peptides

such as cholecystokinin (CCK) and peptide YY (PYY) by the epithelial cells, specifically enteroendocrine L cells. The effects of prebiotics supplementation on the increase of plasma PYY and GLP-1 concentrations are paradigmatic of the host-gut microbiota interaction. Oligofructose (OFS) supplementation promotes GLP-1 secretion in proximal colon [74] and colonic infusion of propionate stimulates the release of GLP-1 and PYY [75].

With respect to the deleterious effects of obesity on microbiota ecosystem, the ingestion of dietary fats and in particular of fat-rich diet increases the circulating levels of lipopolysaccharide (LPS). LPS represents the most part of the outer layer of Gram-negative bacteria, an endotoxin originating from gut microbiota with a potent inflammatory action that is believed to underlie the obesity-associated intestinal permeability and increase of LPS plasma levels (*i.e.*, metabolic endotoxaemia) [76]. Even acute high fat meal consumption can elicit a postprandial inflammatory response that is often observed as transitory increase of endotoxaemia [77]. Interestingly, consumption of fat meals enables the intestinal absorption of LPS from the gut and chylomicrons formation has been identified as one factor underlying LPS absorption and chronic inflammatory state [78]. However, different types of dietary fats can elicit different effects on lipaemia (*i.e.*, excessive blood concentrations of lipids), chylomicrons accumulation and postprandial endotoxaemia. For instance, oil emulsification appears much more harmful for postprandial lipaemia than consumption of the same non-emulsified oil (sunflower oil) [79]. This study investigated some possible events linking systemic inflammation, lipid digestion and endotoxin absorption at the light of the large use of oil emulsification in several common industrial foodstuffs. The oral gavage in rats of emulsified sunflower oil produced higher endotoxaemia and hypertriglyceridemia than that caused by the ingestion of non-emulsified sunflower oil. Moreover, healthy humans consuming a mixed meal containing emulsified fat (*e.g.*, margarine, butter) showed transient postprandial endotoxaemia (*i.e.*, plasma endotoxin concentration) and increased plasma levels of the endotoxin soluble receptor sCD14 that is a marker of endotoxin exposure, and a peak of inflammatory cytokine IL-6 two hours after meal ingestion [79]. In contrast to the intake of a rapeseed oil-based diet, the intake of palm oil increases both plasma levels of pro-inflammatory IL-6 and ratio of LPS to the soluble form of binding-protein CD14 (sCD14), which tend to increase as a function of the intensification of the inflammatory response [80]. Thus, fatty acids profile can drastically impact the microbiota-gut-brain function increasing or decreasing chronic inflammation burden by the way of dietary lipid composition. In healthy adults, postprandial endotoxaemia was found maximum after intake of saturated fats (*i.e.*, coconut oil) and reduced after *n*-3 PUFAs (*i.e.*, DHA) ingestion [81].

As described in details in paragraph 4, PUFAs have a key role in inflammation. In fact, among ARA-derived mediators, LXs can participate to "resolve" inflammation as reported for their signaling activity addressing neutrophils to migrate towards the site of inflammation, accelerating neutrophils apoptosis and clearing, and delaying apoptosis of macrophages [82]. Among *n*-3 PUFAs, SPMs exert potent anti-inflammatory and protective actions *via* multiple mechanisms as the blockage of neutrophil and eosinophil infiltration, the activation of macrophage phagocytosis, scavenging of inflammatory chemokines and the stimulation of antimicrobial defense mechanism [83, 84]. Thus, *n*-3 PUFAs may regulate the immune response *via* the action of SPMs. Given the major impact of diet and nutrients on gut microbial composition, the immune function can be deregulated in case of dysbiosis (diet-induced metabolic endotoxaemia) and, on the contrary, protected by the generation of SCFAs. The fact that both SCFAs and *n*-3 PUFAs stimulate the immune function and regulate the inflammatory response is a challenge for our current vision of the interplay between nutrition, immune regulation and pathogenesis of inflammatory-dependent diseases.

2.3. Lipid Sensing, Satiety and Processing of Hedonic Food

An interesting point of convergence between epidemic obesity in Western countries and changes driven by dietary lipids in gut microbiota, dysbiosis and chronic systemic inflammation relies on the notions of "nutrient sensing" and metabolic-sensing neurons. Nutrients are indeed signaling molecules conveying information about whole-body energy status and microbiota changes to the brain and the immune system. In turn, the brain is the most powerful unit for the processing of nutrient-associated information, including food-associated reward. Neurons sensitive to metabolic and nutrient information are distributed in the ventromedial and arcuate nuclei (ARC) of the hypothalamus in which fuels, gut-derived signals and macronutrients can be detected [85, 86]. However, in extra-hypothalamic areas, metabolic sensing neurons have been identified in the nucleus of the solitary tract (NST) and in the midbrain ventral tegmental area. In particular, the NST emerges as an integrative structure for descending hypothalamic melanocortin inputs and ascending gut-derived satiety signals. Recently, the existence of aminoacid (L-leucine)-dependent satiety signaling detected by NST neurons [87] has been described, which can curb food intake unless animals are fed with HFD [88]. This desensitization of anorexiant signals transmitted through the gut-brain communication occurs as consequence of HFD intake, and is emblematic of the vulnerability of the homeostatic regulation of food-derived energy intake. For an efficient system of homeostatic control, we can predict that energy intake and time intervals between the meals generate molecular signals that are orchestrated with those generated by the energy reservoir (*i.e.*, adipose tissue stores), as for instance by the leptin-dependent satiety signals. Interestingly, the satiety and satiation signaling system is organized redundantly and a plethora of signals are generated through the gut-brain axis. Without considering pancreatic and stomach hormones, in the proximal and distal intestine as well as in the duodenum, we can at least enumerate CCK, neurotensin, GLP-1, PYY, oxyntomodulin, serotonin, obestatin and nesfatin as satiation-triggering signals. In the last years, there has been an intense debate about the pressure exerted by our affluent environment and the prevailing model of food consumption where easily accessible energy-dense and high palatable food can hijack the homeostatic control of food ingestion. This obesogenic food environment is charac-

terized by highly hedonic foods whose signals are processed by separate, though partly overlapping with the homeostatic system, neural circuitries. Hedonic eating involves cognitive, rewarding and emotional aspects (e.g., food seeking) that are processed by corticolimbic structures, including orbitofrontal cortex, ventral tegmental area (VTA), ventral striatum and amygdala [89]. As "canonical" satiety hormone leptin is a powerful example of the multiple homeostatic and non-homeostatic mechanisms underlying its anorexiant action. Indeed, leptin acts on hypothalamic ARC and dorsomedial nuclei to reduce food intake and increase thermogenesis but also on lateral hypothalamus to control mesolimbic dopaminergic (DA-ergic) transmission within VTA and projecting DA-ergic neurons to the ventral striatum. Fat consumption is highly attractive and pleasurable for humans as well as for rodents, and high palatability intensifies the consumption of larger meals and, consequently, the risk to develop brain insensitivity to leptin signaling. Nevertheless, there are dietary fats that can help in the fight against the obesogenic effects of hedonic eating and the potential derangement of leptin signaling system. On one side, eCBs are a special class of ARA derivatives that play a critical role in energy balance and feeding regulation. The best-known and described eCBs, AEA and 2-AG produce robust effects in terms of energy preservation, increasing energy intake and lipid storage, also contributing to the consumption of hedonic food *via* the increase of DA release in mesolimbic structures [90, 91]. Moreover, while the content of eCBs in the food is negligible to mimick eCB-mediated physiological effects [92], the eCBs levels can be modulated by dietary fatty acids intake, and in particular, by the ingestion of linoleic acid, the precursor of ARA [93]. The oral administration of the probiotic *Lactobacillus acidophilus* demonstrated to induce the expression of CB2 receptors in intestinal epithelial cells [94], providing a seminal evidence for the existence of a communication system between microbiota, probiotics and modulation of the eCB function.

On the other hand, the direct infusion of fat into the duodenum is a signal that can elicit satiety or reduce meal size (*i.e*., satiation), in both cases eliciting feeding inhibition and anorexigenic responses. The release of CCK from enteroendocrine cells is one of the mechanisms by which dietary fats such as PUFAs can produce inhibition of feeding responses [95]. There are lipid mediators such as oleoylethanolamide (OEA), palmitoylethanolamide (PEA) and linoleoylethanolamide (LEA) that are members of the family of fatty acids ethanolamide (namely *N*-acylethanolamines, NAEs) except they do not bind CB1 and CB2. For its nature of bioactive lipid mediator and the physiological role of satiety factor able to increase intervals between meals, OEA has been strongly investigated in the last years. OEA is synthesized in the upper intestine by duodenal and jejunal enterocytes that internalize dietary triacylglycerols-derived oleic acid as substrate and generate OEA [96]. OEA production in the jejunal and duodenal enterocytes upon intake of dietary fat-derived oleic acid is a well-characterized mechanism and site of OEA synthesis [96]. Nevertheless, depending on the nutritional status, different levels of OEA are found also in duodenum, stomach, colon, adipocytes, liver, kidney, lung, pancreas, heart and muscle [97-99]. The mechanisms underlying the action of OEA as satiety factor is paradigmatic of the role of post ingestive processes and fat sensing for the control of dietary fats intake. Several studies have contributed to reveal that OEA binds with high affinity the subtype alpha of the peroxisome proliferator-activated receptors (PPAR-alpha) producing satiety responses that are not observed in mice lacking PPAR-alpha [97]. Interestingly, it has been reported that OEA can also evoke the secretion of GLP-1 and produce anorexic effects by engaging the G protein-coupled receptor 119 (GPR119) [100]. The mode of action of OEA illustrates a case of lipid-derived sensor of dietary fats connecting food intake and fatty acids sensing in the gut to hypothalamic fatty acids sensing. Although controversial as for the subdiaphragmatic vagal deafferentation [101], OEA-induced hypophagia is abolished in case vagal sensory afferents are lost as for pharmacological treatment or surgical resection [97, 102]. Next, intraperitoneal OEA administration increases transcription of the early gene c-Fos in the NST [102], and protein expression in oxytocin-immunoreactive neurons in hypothalamic paraventricular (PVN) and supraoptic nuclei (SON) and in the histaminergic tuberomammillary nucleus [103]. Thus, at least two neurotransmitter systems appear involved in the brain control of OEA-induced anorexigenic effects. First, PVN and SON activation increases oxytocin mRNA levels and neurosecretion whereas blockade of oxytocin receptors suppresses OEA-induced hypophagia [103, 104]. Secondly, the hypophagic effects of OEA are abolished in case brain histaminergic system is not fully functional and the integrity of histamine transmission is also required for the OEA-dependent increase of c-Fos expression in oxytocin neurons of the PVN [103]. This is the first demonstration that an intestinal lipid formed upon dietary fats ingestion generates a satiety signal that is decoded by the brain histaminergic system [103]. In spite of its selectivity, this mechanism may contribute to explain several physiological pathways linking intestinal fat sensing to brain circuits involved in energy intake but also in reward assignment to palatable food. Indeed, OEA activity can also help to disclose some mechanisms underlying the obesogenic effects triggered by the overconsumption of palatable energy-dense food, linking fat sensing within the gut-brain axis to homeostatic and hedonic processing of food intake. Prolonged intake of high fat food reduces the intestinal levels of NAEs [105] and also deregulates the nigrostriatal DA release evoked by intragastric lipid infusion [106]. Remarkably, intestinal OEA infusion can revert and normalize DA signaling, and exogenous OEA infusion also appears to reestablish the OEA-mediated anorexigenic effects but only in mice fed with a low-fat diet [106] that increased the intake of a lipid emulsion in parallel with the increase of striatal DA signaling of rewarding food. The link between the homeostatic control of energy intake and brain reward circuits is demonstrated by the increased intake of a non-palatable low fat emulsion following OEA administration in HFD-fed animals. Thus, prolonged intake of HFD may lead to overconsumption of dietary fats because of the lower intestinal OEA levels and reduced brain DA signaling. OEA links fatty acids sensing in the gut to central processing of hedonic hunger and its ability to affect brain DA signaling might contribute to reassign a reward value to foods normally considered as non-palatable or barely hedonic.

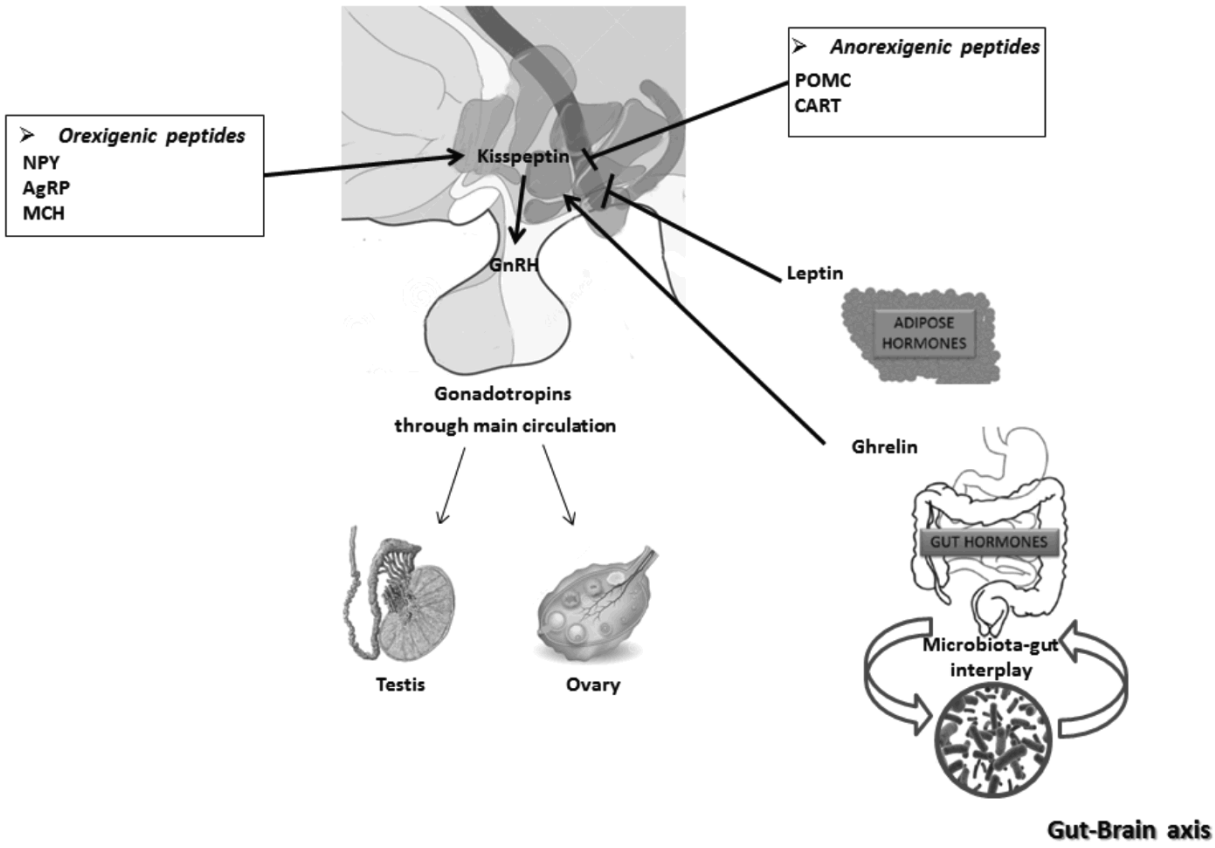

Fig. (2). A schematic view of the interplay between the HPG and gut-brain axis. Kisspeptin neurons convey to GnRH neurons a plethora of central and peripheral metabolic signals. Orexigenic and anorexigenic peptides influence kisspeptin neurons with stimulatory or inhibitory effects, respectively. In addition, peripheral hormones such as leptin and ghrelin, coming from adipose tissue and gut, respectively, *via* kisspeptin neurons, inform the HPG axis of metabolic reserves of the body. As final effect, in both sexes, the reproductive activity may be stimulated or inhibited.

In this view, OEA is a member of a family of lipids that is worth investigating for a better understanding of the lipid-sensing gut-brain pathways and detection of effective drug targets for the treatment of obesity and eating disorders.

3. THE IMPACT OF DIET ON THE HYPOTHALAMIC CONTROL OF REPRODUCTION

The survival and perpetuation of species are preserved through reproduction. This process requires adequate energy resources, likewise indispensable to support the biosynthesis of sex steroids, the production of high quality gametes, pregnancy and lactation in mammals. In conditions which cannot ensure the correct use of the metabolic resources, the body needs to define priorities to preserve physiological processes essential for survival. In this sense, puberty onset, fertility rate and successful pregnancy all depend on diet and energy homeostasis, as excellently reviewed elsewhere [107]. Nevertheless, it is interesting to note that the increase of metabolic disorders matches with increased rates of infertility in developed and developing countries, as a consequence of environmental factors such as over-nutrition and sedentary lifestyle [108]. Furthermore, nutritional status of parents may impact gamete epigenome with effects on metabolic and reproductive health of the offspring [109]. As described in the previous paragraph, several metabolic sensors from adipose tissues and gut sense the availability or the lack of nutritional resources and, *via* specific receptors located in peripheral tissues or in the brain, exert local activities on gonads or integrate the gut-brain communication to the HPG axis (Fig. **2**) with outcomes depending on species, sex and life stages [110]. Therefore, in the next paragraphs, we provide a survey on the centrally mediated effects of diet on reproduction *via* the capturing peripheral signals in the brain (*i.e*. leptin, ghrelin) and *in situ* production of orexigenic and anorexigenic peptides that directly or indirectly convey dietary cues on HPG axis. Possible interplay with lipid mediators such as eCBs is lastly discussed.

3.1. Role of Orexigenic and Anorexigenic Peptides in Reproduction

A complicated network of neuronal circuits supervises reproductive functions, attempting to coordinate and converge towards the HPG axis environmental, hormonal and metabolic conditions (Table **1**). A hierarchical actor in HPG axis is the decapeptide Gonadotropin-Releasing Hormone (GnRH), with its well-known role in the stimulation of pituitary gonadotropins and downstream of gonadal functions [140-144]. Due to their excellent position in the hypothalamus, GnRH neurons are the best candidate to relay metabolic information to the HPG axis, thus they start a dynamic inter-

Table 1. Peripherally and centrally produced metabolic sensors that link metabolism and reproduction.

		Main Site of Synthesis	Metabolic Effects	Reproductive Effects	Refs.
Peripheral hormones	**Adiponectin**	Adipose tissue	Anorexigenic	Acts on the late stages of folliculogenesis and on the development of a functional placenta	[111]
	CCK	Gastrointestinal tract	Anorexigenic	Regulates sperm capacitation and fertilization	[112-114]
	Ghrelin	Gastrointestinal tract	Orexigenic	Downregulates *kiss1* expression	[115-118]
	GLP-1	L-cells in the small intestine and colon	Anorexigenic	Stimulates the HPG axis, in cell lines augments GnRH secretion	[119, 120]
	Insulin	Pancreas	Anorexigenic	Controls pulsatile GnRH secretion	[116, 121]
	Irisin	Skeletal muscle cells	Regulator of body fat and muscle mass	Suggested role as trigger for the activation of the hypothalamic neuronal network monitoring the onset of puberty	[122]
	Leptin	White adipose tissue	Anorexigenic	Puberty onset	[116, 118, 123, 124]
	Obestatin	Gastrointestinal tract and testis	Anorexigenic	Modulates GnRH secretion and regulates testosterone secretion	[125, 126]
	PYY	Entero-endocrine L-cells of the distal ileum and colon	Anorexigenic	Increases gonadotrophin secretion	[127]
Neuropeptides	**AgRP**	ARC	Orexigenic	Mediates the orexigenic action of testosterone	[116, 128, 129]
	CART	ARC	Anorexigenic	Has a stimulatory effect on kisspeptin neurons	[130, 131]
	GALP	ARC	Anorexigenic	Increases serum levels of LH and testosterone	[132]
	Kisspeptin	Hypothalamus	Anorexigenic	Regulates GnRH secretion	[124, 133]
	MCH	Hypothalamus	Orexigenic	Regulates LH release; stimulates hypothalamic GnRH	[116, 134-136]
	NPY	ARC	Orexigenic	Regulates GnRH neurons influencing LH release	[116, 128, 137]
	Orexin	Hypothalamus	Orexigenic	Has direct input to GnRH neurons in the human.	[138, 139]
	POMC	ARC	Anorexigenic	Contacts GnRH neurons	[116, 128, 133]

play with the wide range of the signals involved in the metabolic control of reproduction [145, 146].

The relationship between metabolism and reproduction is centrally orchestrated by orexigenic and anorexigenic neuropeptides produced in the ARC [147] (Table **1**). First class includes peptides able to stimulate the appetite, such as neuropeptide Y (NPY), agouti related protein (AgRP), melanin-concentrating hormone (MCH); the second one includes appetite inhibiting neuropeptides such as proopiomelanocortin (POMC) precursor and cocaine- and amphetamine-related transcript (CART) [116]. Strong evidence confers important roles in reproduction to these metabolic neuropeptides, through their ability to directly contact GnRH neurons [148-152], thus influencing gonadotropin discharge [108].

One of the major peripheral indicators of body metabolic reserves is leptin, a peptide hormone produced by white adipose tissue [123]. Leptin is an essential threshold factor in the control of puberty onset by food intake [118] and such an action has GnRH neurons as potential targets. Many data demonstrate that GnRH neurons are devoid of functional leptin receptors, thus intermediate neuronal pathways convey HPG nutritional cues [153]. In such a context, kisspeptins - *kiss1* gene produced peptides [154] - have an important role through the activation of kisspeptin receptor GPR54 [155]. In fact, the kisspeptin system has a prominent role in the central and local regulation of reproduction as upstream modulators of GnRH [144, 156-160].

Kisspeptin system deeply responds to gonadal and metabolic factors [161-163], including leptin. In fact, ~40% of kisspeptin neurons located in the ARC express leptin receptor [124]. Under caloric restriction or fasting, leptin levels in blood dramatically decrease, causing a drop in hypothalamic *kiss1* mRNA expression [164]; thereafter, leptin administration ameliorates *kiss1* levels [124]. Interestingly, *Ob/Ob* mice, lacking *leptin* gene, show increased appetite and are affected by obesity and sterility. Reduced expression of *kiss1* in the ARC, but not in the AVPV, causes hypogonadotropic hypogonadism in this animal model [124]. However, indirect action of leptin through other hypothalamic neurons in tight connection with kisspeptin neurons cannot be ruled-out [165, 166]. In fact, the selective ablation of leptin receptor from hypothalamic kisspeptin neurons does not alter puberty onset [167]. Consistently, functional crosstalk between kisspeptin neurons NPY and POMC has also been unraveled [133, 168].

Diet can affect reproduction through the inhibition of kisspeptin signaling in diabetes mellitus affected rats as well as diet-induced obese (DIO) male rats [169, 170]. Fasting also reduces *kiss1* mRNA expression in the prepubertal rat [164] and adult mice [168] hypothalamus. Accordingly, kisspeptin administration reverses starvation-induced hypogonadotropism [164]. Similar responses in fasting conditions have been observed on *GPR54* mRNA expression [124].

Lastly, under/overnutrition results in a time shift of puberty through kisspeptin system. In rats, maternal food restriction delays the onset of puberty in offspring of both sexes [171], whereas HFD during pregnancy advances puberty onset in female offspring [172]. Accordingly, HFD during lactation alters pubertal development in female offspring only [173]. All the above effects implicate the regulation of kisspeptin expression in the ARC depending on serum leptin levels [173].

Together with leptin, ghrelin also contributes to inform the hypothalamus of changes in peripheral energy balance. Ghrelin is a peptide secreted by the gastrointestinal tract, working as an orexigenic factor [115]; in volunteers, intravenous ghrelin infusion increases appetite and food intake by 28% [174]. Plasma levels of ghrelin rise almost 2-fold immediately due to fasting and fall after the ingestion of food [175]. However, the exact molecular mechanism by which this hormone regulates feeding is poorly understood. As far as the activity on the HPG axis is concerned, ghrelin has an inhibitory effect on both Luteinizing Hormone (LH) and Follicle Stimulating Hormone (FSH) release. This effect is due to the inhibition of hypothalamic GnRH neurons and direct suppressive effects on gonads [176]. In animal models, ghrelin has the ability to delay puberty onset in response to insufficient energy states, *via* the modulation of *kiss1* expression [115, 117, 177].

However, different sensitivity to ghrelin administration during pre-pubertal period has been reported between males and females [178].

Post-pubertally, circulating ghrelin levels drastically increase in case of body weight decrease induced by diet/exercise [179]; similar effects have been observed in young amenorrheic athletes which also show decreased LH and GnRH pulsatility [180]. Consistently, ghrelin administration disrupts fertility in adul female rats [117]. All these observations support the idea that abnormal eating behavior influences ghrelin levels, with possible suppression of the reproductive axis through kisspeptin regulation and GnRH/LH inhibition.

Therefore, a balance between leptin and ghrelin is maintained in the ARC, at the levels of NPY/AgRP and Kisspeptin populations. Leptin inhibits NPY/AgRP and stimulates Kisspeptin circuits, ghrelin does quite the opposite [181].

3.2. The Involvement of eCBs in the Central Pathways Integrating Metabolism and Reproduction

The functional interplay that links the main actors in food intake (*i.e.* peripherally and centrally produced orexigenic and anorexigenic peptides/hormones) to the main gatekeepers of reproduction (*i.e.* Kisspeptin and GnRH) finds in the *n-6* PUFA ARA derived eCBs key signaling intermediates. [10, 13, 16, 17, 18, 141, 143].

Interestingly, during the 20th century, Western diet has been subjected to deep changes, with an enrichment in *n*-6, over *n*-3 PUFA assumption, thus contributing to the onset of overweight and obesity [182, 183]. Diet is an important source of ARA (further details in parapraph 4) and thus, in addition to enzymatic hydrolysis, it is realistic that the tone of eCBs might be modulated by the fatty acid composition of food [184], with different outcomes on health including the centrally orchestrated control of reproduction.

ECBs work as orexigenic factors, stimulating food intake and promoting the accumulation of body fat [13, 185-188]. Elevated circulating AEA and 2-AG levels and a parallel drop in the FAAH activity in obese subjects corroborate the role of the eCB system in human obesity [189]. Accordingly, the activation of CB1 increases food intake [190], while its genetic and pharmacological impairment implicates less food assumption [191, 192]. The reintroduction of *n*-3 PUFA in the Western diet, and so of EPA and DHA, may help to restore eCB tone [193, 194], since experimental data suggest that a dietary treatment with *n*-3 PUFA decreases the concentration of AEA and 2-AG in the visceral adipose tissue and AEA levels in the liver and heart [195].

Therefore, CB1 seems to cooperate with key hypothalamic peptides involved in the regulation of energy homeostasis, like POMC/CART neurons into ARC [131]. In this regard, the orexigenic effect of AEA may be centrally mediated by inactivation of CART immunoreactive fibers [196]. This crosstalk seems to be well demonstrated in male mice chronically exposed to Bisphenol A (BPA) *via* drinking water [197]. In these animals, BPA works as a powerful anorexigenic signal, depressing cannabinoid signalling and upregulating the hypothalamic expression of CART [197].

However, some evidence support the hypothesis that the regulation of food intake by eCBs within the hypothalamus might be more complex with a bimodal orexigenic and anorexigenic action, depending on whether CB1 is activated in glutamatergic or GABAergic terminals, respectively [198].

A strong interaction has also been suggested between eCB system and leptin, the latter producing its anorexigenic effects through the inhibition of hypothalamic eCB levels [199]; accordingly, in *Ob/Ob* mice, there is an overactivation of the hypothalamic eCB signalling [199]. Similarly, a functional synergic overlap in promoting food intake has been demonstrated between ghrelin and eCBs, at both central and peripheral levels [200]. Ghrelin positively regulates the tone of eCBs and hypothalamic 2-AG levels increase after food deprivation and decrease after food consumption in parallel to ghrelin [201]. Thus, both leptin and ghrelin require a functional CB1 signalling to exert their respective anorexigenic and orexigenic effects, since in the hypothalamus of CB1 knockout mice, these effects are abolished [202].

An eCB system has been detected in GnRH secreting neurons, in hypothalamic cell lines, both in *in vitro* and in *in vivo* models and either in mammalian and non-mammalian vertebrates [203-205]. AEA can modulate GnRH biosynthesis, release or signaling *via* CB1 both centrally and peripherally [14, 17, 18, 204, 206-210]. Outcomes on steroid biosynthesis, gametogenesis, gamete quality and fertility rate have been reported [16-18, 142, 211, 212, 213]. Consistently, the characterization of the reproductive phenotype in CB1 knockout mice revealed impairment of HPG axis at multiple levels [214, 215]. At molecular levels, several mechanisms have been reported. Classically, eCBs act as retrograde signals to reduce GABAergic synaptic transmission to GnRH secreting neurons, but involvement of glial cells and the direct activity on subsets of GnRH secreting neurons that express CB1 have been reported [17, 18].

Lastly, updates in the modulation of GnRH *via* eCBs recently come from a non-mammalian vertebrate model, the anuran amphibian *Pelophylax esculentus* and address kisspeptin secreting neurons as a new target for eCBs in the modulation of HPG axis [207, 210]. Interestingly, in male rats exposed to immobilization stress, *kiss1* mRNA decreases in the medial preoptic area rather than in the ARC and serum LH concentrations reduce as a consequence of the HPG axis suppression [216]. Thus, despite the fact that the involvement of eCBs in the functional interplay between kisspeptin and GnRH-secreting neurons in physiological conditions has never been investigated so far in mammals, data in amphians deserve attention since most master regulatory systems are evolutionarily conserved [143].

4. NEUROPROTECTIVE EFFECTS OF *n-3* PUFAS

The main *n-6* and *n-3* LC PUFAs found in the brain are the ARA (20:4 *n-6*) and DHA (22:6 *n-3*) respectively. Both these LC PUFAs have pivotal roles in brain physiology as they regulate fundamental neurobiological processes, in particular those involved in cognition [8, 217]. Neuroprotective activities of LC *n-3* PUFAs DHA and EPA are believed to be potent for protection and/or treatment of cognitive decline and dementia [218-223]. We refer to recent seminal reviews reporting on the mechanisms potentially involved in the neuroprotective activities of LC *n-3* PUFA [8, 223-227]. Here, we briefly discuss recent findings on LC *n-3* PUFAs role in neuroinflammatory pathways and eCB system regulation.

4.1. Dietary PUFAs and Brain PUFAs Metabolism

In the brain, LC-PUFAs are largely esterified to the phospholipid cell membrane of neurons and glial cells (astrocytes, microglia and oligodendrocytes). ARA represents 5 to 11% of total brain phospholipids while DHA represents 13 to 22% [228]. Brain phospholipids enriched with DHA are especially present in grey matter and synapses. Due to the limited capacity of the brain to synthesize LC PUFAs [229, 230], they have to be provided through the diet either as precursors [*n-6* linoleic acid (LA) and *n-3* αlinolenic acid (ALA) found in vegetable oils and grain products] or as preformed ARA and DHA (found in meat products and fish, respectively) [231, 232]. Hence, increased consumption of *n-3* PUFAs rich products results in a partial replacement of ARA by DHA in brain cell membrane [228]. Conversely, a lower *n-3* PUFAs intake leads to lower brain levels of DHA with increased ARA levels. LA and ALA are metabolized into ARA and DHA through a series of elongation and desaturation steps. The fatty acid desaturase (ΔD, gene FADS) Δ5D and Δ6D are rate-limiting enzymes. In humans, carriers of specific genetic variants of FADS display higher biological status of LA and ALA (PUFAs precursors) and lower status of LC-PUFA products, ARA and DHA [233].

Of note, observational studies in humans revealed a gender difference in PUFAs levels, with higher ARA and DHA reported in women as compared to men [233, 234]. These differences could be linked to sex hormones as they influence PUFAs metabolism with estrogen stimulating, and testosterone inhibiting the conversion of both *n-3* and *n-6* precursors into their respective long chain metabolites [235]. However, whether these differences in PUFAs have a role in specific brain diseases with a gender component has been poorly questioned and requires further investigations.

As the endogenous synthesis of DHA from ALA is extremely inefficient, the consumption of preformed DHA from fish sources is recommended. DHA is likely to enter in the brain from the blood, but the mechanisms involved are still a matter of debate [8, 236]. While numerous data show that non-esterified DHA freely enters the brain [8], an orphan receptor, the major facilitator superfamily domain-containing protein 2a (Mfsd2a) has been described as important to transport DHA in the form of lysophosphatidylcholine (LPC) through the blood brain barrier (BBB) [237]. In retinal cells, adiponectin receptor 1 has been recently identified as a key factor for DHA uptake and retention [238].

4.2. Role of PUFAs in the Regulation of Neuroinflammatory Processes

DHA, ARA and their mediators regulate several processes within the brain, such as neurotransmission and neuroinflammation, which are key processes in cognition [8, 216, 239]. Upon activation of phospholipase A2 (PLA2), unesterified ARA and DHA are released from cell membrane and exert their effects directly or upon conversion to a series of bioactive mediators [240]. The major enzymes involved in the synthesis of ARA and DHA bioactive mediators are COX, LOX and cytochrome P450 [241].

Neuroinflammatory pathways are involved in cognitive impairment and neurodegenerative diseases such as Alzheimer's disease. Neuroinflammation involves the brain innate immune system, mainly microglial cells [242, 243]. It is now well accepted that in the healthy brain, these cells modulate synaptic functions, in particular through the phagocytosis of unnecessary synapses [244] and protect neurons from infection or damage [245, 246]. Indeed, microglia deregulation due to aging or neurodegenerative processes participates to synaptic loss observed not only in Alzheimer's disease [247] but also in chronic stress conditions [248] or dietary lipid unbalance [249, 250]. In addition, aging and neurodegenerative diseases are accompanied by increased proinflammatory factors such as cytokines and reactive oxygen species (ROS) production, which participate to neuronal death, neuropathological processes and promote cognitive deficit [23, 251].

COX and LOX enzymes facilitate the conversion of ARA into several prostanoids including PG, LT, TX and LX. These enzymes play a crucial role in the progression of inflammation, either within the brain [8]. COX2 expression is particularly high in neurons. Among ARA/COX2 derived prostanoids, PGE2 is a potent signaling molecule, which regulates neurotransmitter release, neuroinflammation and cerebral blood flow. COX2 expression is upregulated during inflammatory processes in neurons and microglia and its role, together with PGE2, has been consistently reported in inflammation-associated memory impairment [252, 253]. Interestingly, several studies report that blocking COX1/2 with non-steroidal anti-inflammatory drugs (NSAIDs) protects against cognitive impairments in animal model of Alzheimer's disease suggesting a role for PGE2 and COX2 in memory impairment [254]. This is consistent with the observation that in normal population, NSAIDs assumption prevents Alzheimer's disease [255]. Such a protective effect of COX inhibition relies on the prevention of neuroinflammatory processes and the promotion of adequate microglia activity. Indeed, in animal models of Alzheimer's disease, PGE2/EP2 blockade in microglia potently reverses the Aβ42 driven pathogenicity and memory loss [256]. However, no beneficial effects of NSAIDs treatment in Alzheimer's disease patients have been reported, suggesting that preventing COX activation is efficient before the establishment of the disease. LOX-derived ARA prostanoids are also incriminated in neuroinflammatory processes and memory loss. 5-LOX expression is increased in the brain of patients with degenerative diseases, including Alzheimer's disease [257] and the role of ARA-derived LOX bioactive mediators in neuroinflammatory processes is well established [258]. Indeed, a dual COX/5-LOX inhibition to reduce production of PG and LT with proinflammatory activities is proposed as a new therapeutic approach for neurodegenerative diseases [259]. In this context, it would be of high interest to consider *n-6* and *n-3* PUFAs status, as both fatty acids are metabolized through the COX/LOX pathways into derivatives with opposite properties in inflammation [8, 23]. While it has long been recognized that bioactive metabolites of ARA are responsible for many of the actions of ARA, bioactive metabolites of DHA have been identified and characterized more recently [241]. In the brain, several DHA-derived mediators are detected, like, in particular, the LOX-derived SPMs neuroprotectin D1 (NPD1), resolvin D5 (RvD5) and maresin 1 (MaR1) [241, 260]. Both DHA and derived SPMs display potent anti-inflammatory activities *in vivo* and target microglia [252, 261-264]. DHA and SPMs are impaired at the periphery and within the brain of Alzheimer's disease patients [265, 266] and in accelerated aging mice model [267]. Interestingly, decreased DHA distribution in Alzheimer's disease patient's brains correlates with synaptic loss than Aβ42 deposition [268]. In addition, DHA or SPMs promote phagocytosis of Aβ42 by microglia [269] and modulate the number and activation of microglial cells *in vivo* [270]. Whether SPMs play a role in the protective activity of long chain *n-3* PUFAs on neurological disorders remains to be established.

4.3. Role of PUFAs in the Regulation of Brain eCB System

As previously mentioned, eCBs are important PUFAs-derived lipid mediators within the brain and are produced by both neurons and glial cells [271]. The main brain ARA-derived eCBs are AEA and 2-AG, while docosahexaenoylethanolamide (DHEA or synaptamide) is an eCB-like molecule derived from DHA [194]. ECBs' half-life within the brain is regulated by specific catabolizing enzymes like fatty acid amide hydrolase (FAAH) for AEA and DHEA and monoacylglycerol lipase (MAGL) for 2-AG. Importantly, COX and LOX oxidize ARA-derived eCBs into bioactive PG, which promotes inflammation [272]. DHEA has a lower binding affinity for CB1 and CB2 as compared to AEA and 2-AG and binds GPR receptors, in particular GPR110 within the brain [273, 274]. Dietary *n-3*/*n-6* PUFAs ratio directly influences the proportion of ethanolamides derived from ARA and DHA [193]. Importantly, these changes in eCBs are accompanied by impairment of CB1 activity in the brain, leading to synaptic activity impairment in several brain structures [20, 21, 275]. 2-AG and AEA regulate synaptic functions suppressing excitatory and inhibitory synapse neurotransmitter release by acting as retrograde messengers at presynaptic CB1 [276]. Recent studies show that ARA-derived eCBs also modulate synaptic transmission through post-synaptic receptor TRPV1 or through CB receptors expressed on astrocytes [271, 277]. The importance of brain eCB signalling in the understanding of how altered dietary intake of PUFAs correlates with a range of neurological disorders is of high interest. However, further studies are necessary to demonstrate these links [278]. A schematic representation of PUFAs synthesis from food, PUFAs entry across the BBB and production of PUFAs bioactive derivates in neuronal cells are provided in Fig. (**3**).

4.4. Clinical Trials with Dietary n-3 PUFAs

Several correlative epidemiological studies highlight that the consumption of *n*-3 PUFAs-rich food has potential neuroprotective effects through their anti-inflammatoy activities within the brain [239]. In particular, these studies revealed the positive association between *n-3* PUFAs and cognitive performances in elderly and/or patients with neurodegenerative diseases such as Alzheimer's disease [8, 279]. These observations led to a number of clinical trials

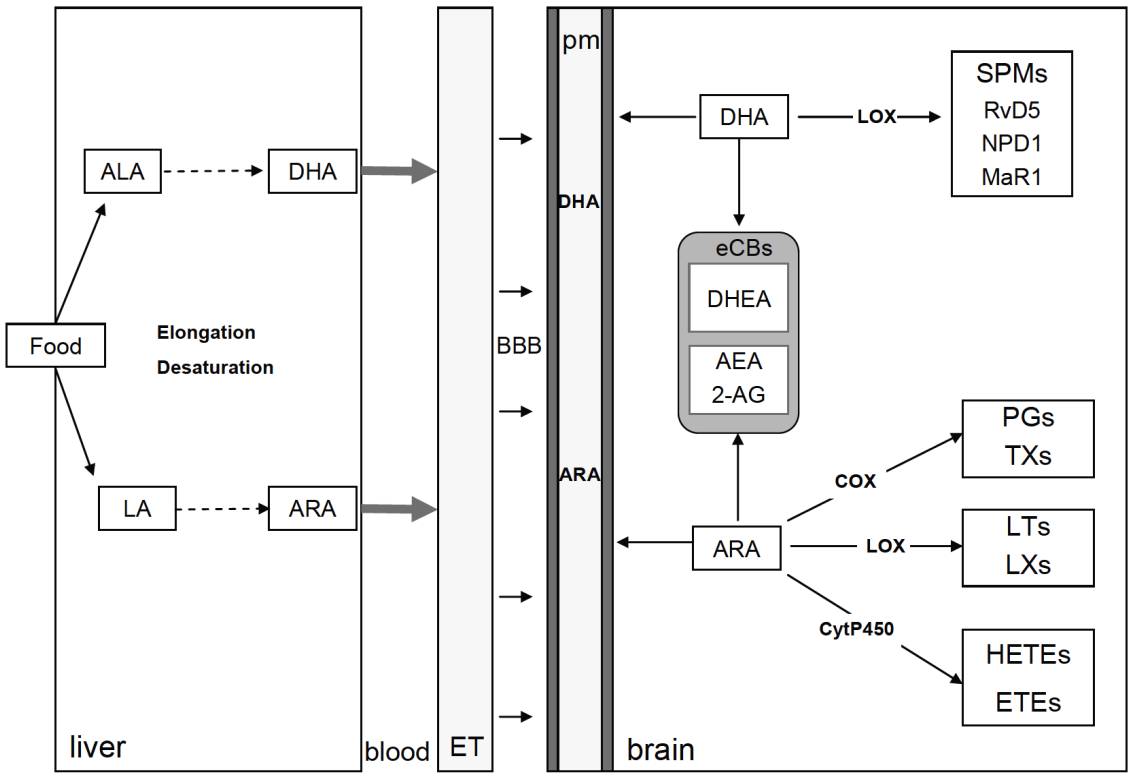

Fig. (3). Schematic representation of PUFAs synthesis from food, PUFAs entry across the BBB and production of PUFAs bioactive derivates in neuronal cells. ET, endothelial cell; pm, plasma membrane of brain cells, HETE, hydroxyeicosatetraenoic acid; ETE, ecosatetraenoic acid.

aimed at assessing whether dietary supplementation with LC *n-3* PUFAs, mainly EPA and DHA, can restore cognitive function in elderly, patients suffering of Alzheimer's disease or at risks of cognitive decline, psychosis or mood disorders [217, 280, 281]. Some of the clinical trials studying the impact of LC *n-3* PUFAs on cognition in healthy or unhealthy subjects are presented in Table **2**. Overall, the results are mitigated. In particular, several trials reveal no improvement of cognitive decline in Alzheimer's disease patients (Table **2**). Of note, some clinical trials report an improvement in cognition in subjects with mild cognitive decline (MCI). Interestingly, a randomized control trial (Multidomain Alzheimer Preventive Trial, MAPT) reported that elderly with the lowest quartile of DHA in erythrocytes get benefit from the LC *n-3* PUFAs supplementation with regard to cognitive improvement [292]. This promising study further highlights the importance of assessing dietary intake of *n-3* PUFAs and/or biological index of these FA to supplement subjects at risk of cognitive decline.

5. THE THERAPEUTIC "FAT DIETS": THE KETOGENIC DIETS

After so many observations about the detrimental effects of the excess of dietary fats on health, it could seem a paradox that a diet composed of fat by more than 90% is currently used as a therapeutic resource. These kinds of therapeutic diets are nearly free of sugar, contain an adequate amount of proteins, vitamins and minerals, and are calorie restricted by roughly 10-25%. They are commonly named "ketogenic diets" (KDs). In fact, there is a lack of glucose from the diet and from neoglucogenesis, given the poor amount of aminoacids assumed in the diet, thus the liver produces ketone bodies: acetoacetate, beta-hydroxybutyrate and acetone [303].

KDs have an anti-epileptic effect and are currently used to treat drug-resistant epilepsies in children [304] even in less restrictive and more palatable forms such as the low-glycemic index diet and the modified Atkins diet [305]. The use of KDs in adults is limited due to poor compliance to the treatment, but recent studies suggest that KDs can be effective in adults as well [306, 307]. The use of KDs as a treatment for epilepsy originated from the very ancient observations about the beneficial effects of fasting, since the times of Hyppocrates. After understanding metabolic pathways in modern era, the attention was focused on the ketogenic effects of fasting, so a ketogenic diet was proposed for the treatment of epilepsy since 1921 [308, 309].

The mechanism for such anti-epileptic effect is actually unknown. Because one of the most evident metabolic effects of KDs is the elevation in blood levels of ketone bodies, many studies have searched for possible anti-epileptic effects of ketone bodies [303], but the results of these studies fail to ultimately confirm that this is the main mechanism of action of KDs.

Simple clinical observations, for example, give somewhat strange data. In fact, while the elevation of blood ketones can be simply obtained by fasting for 12-24 hours, an effective anti-epileptic effect is only observed several weeks

Table 2. Clinical trials assessing the effect of long chain *n-3* PUFAs dietary supplementation on cognition in healthy and unhealthy adult and aged subjects.

Subjects	Treatment/day and Duration	Primary Outcome	Results	Refs.
Healthy adult subjects				
Healthy adults 18–35 years	1 g EPA+DHA 12 weeks	Cognition and mood	No improvement of memory or mood Improvement of cognitive fatigue	[282]
Young adult females	400 mg of DHA 50 days	Memory, mood, reaction times, vigilance or visual acuity	Improvement of memory	[283]
Healthy aged subjects with cognitive complaint or deficit				
Subjects at risk for developing late age-related macular degeneration	1 g LC PUFAs and/or 10 mg lutein/2 mg zeaxanthin 5 years	Cognitive function	No effect	[284]
Healthy subjects 50-75 years	2.2 g/d of n-3 PUFA	Executive function MRI	Improvement of executive function and gray matter volume	[285]
Subjects with subjective memory impairment aged 62-80 years	Fish oil (EPA+DHA: 2.4 g/d) 24 weeks	Erythrocyte membrane EPA+DHA fMRI posterior cingulate cortex working memory task	Positive effect on all parameters	[286]
Healthy adults 50-70 years	240 mg EPA + 240 mg DHA or 480 mg EPA + 480 mg DHA with a multivitamin or 480 mg EPA + 480 mg DHA 6 weeks and 16 weeks	Cognitive and cardiovascular function Erythrocyte n-3 PUFAs	Increased n-3 PUFAs No effect on primary cognitive outcome Improvement in spatial memory	[287]
Postmenopausal women 60-84 years	1g DHA, 160 mg EPA, 240 mg Ginkgo biloba, 60 mg phosphatidylserine, 20mg d-α tocopherol, 1mg folic acid and 20 µg vitamin B12 6 months	Mobility Cognition	Partial improvement	[288]
Cognitively healthy individuals aged 50-75 years	*n-3* LC-PUFAs 2,200mg/day 26 weeks	Object location memory	Improvement of recall of object locations	[289]
Healthy older adults aged 50-70 years with subjective memory deficits	DHA or DHA plus Gingko biloba, phosphatidylserine and vitamins B6 and B12 6 months	Cerebral hemodynamics and cognitive functions	No improvement	[290]
Healthy middle aged to elderly subjects	3g Fish oil *n-3* PUFA 5 weeks	Working memory	Improvement	[291]
Healthy elderly >55 years with subjective memory complaint	900 mg of algal DHA 24 weeks	Paired Associate Learning	Improvement	[292]
Non demented patients with cognitive complaints 70 years	800 mg DHA and 225 mg EPA and/or cognitive training and physical activity 36 months	Cognition	No improvement In a subset of patients with high EPA+DHA in erythrocytes, less cognitive decline	[293]
Unhealthy subjects with cognitive impairment				
Elderly people (average 83 yr) with moderately severe dementia from thrombotic cerebrovascular disorder	4.32 g/day of DHA 3, 6, and 12 months	Cognition (MMSE) Erythrocyte *n-3* PUFAs	Improvement of the dementia score Increase in DHA erythrocyte content	[294]

(Table 2) contd….

Subjects	Treatment/day and Duration	Primary Outcome	Results	Refs.
Unhealthy subjects with cognitive impairment				
Patients with coronary artery disease	1.9 g/d *n-3* PUFA 12 weeks	Vascular cognitive impairment	No effect on cognitive performance Verbal memory impairment in a sub-group of nondepressed patients	[295]
Individuals with cognitive impairment no dementia or Alzheimer's disease	600 mg EPA and 625 mg DHA 4 months	Cognitive functions Mood	No improvement	[296]
Subjects with diagnosis of probable Alzheimer's disease > 55 years	675 mg DHA and 975 mg EPA/day or 675 mg DHA and 975 mg EPA plus 600 mg lipoic acid (LA)/day 12 months	Urine lipid oxidation (F2-isoprostane) Cognition Functional impairment	No significant change of F2-is prostane Improvement of the cognitive decline in the DHA+EPA+LA group Improvement of functional impairment in all groups	[297]
Elderly patients with MCI	1.74 g/d of EPA/DHA 12 months	Memory, psychomotor speed, executive function and attention, and visual-constructive skills	Improvement in memory	[298]
Alzheimer's disease patients				
Drug-naıve patients with mild Alzheimer's disease	DHA, EPA, phospholipids, choline, UMP, vitamin B12, B6, and folate, vitamins C and E, and selenium 24 weeks	Memory performance EEG	Improvement	[299]
Individuals with mild to moderate Alzheimer's disease	2 g of algal DHA/d 18 months	Alzheimer's disease assessment and dementia	No improvement of cognitive and functional decline	[280]
Alzheimer's disease patients	2.3 g *n-3* PUFAs 6 months	Cognitive performance	Positive correlation between n-3 PUFA rize and cognitive performance	[300]
Alzheimer's disease patients, Vascular dementia, Dementia with Lewis Bodies, Parkinson disease dementia, Frontotemporal dementia	*n-3* LC-PUFAs 6, 12 and 18 months	Mental health Dementia	No positive effects Moderate effect on instrumental activity	[301]
Alzheimer's disease patients	1.7 g DHA and 0.6 g of EPA 6 months	Cognition (MMSE)	No improvement of cognition Positive effect in a small group of patients with very mild Alzheimer's disease	[302]

after the initiation of a KD. This observation suggests that ketone bodies should not have a direct, clinically relevant, anti-epileptic effect. On the other hand, the acute assumption of a small amount of sugar is able to abruptly abolish the anti-epileptic effect of KDs, with even possible immediate induction of seizures [310]. This would suggest an important role for low glicaemia or high blood ketones.

In rat models, some studies have shown that ketone bodies can have acute anti-seizure effects [311, 312] and that an acute administration of a synthetic ketone ester can have a small anti-seizure effect [313]. *In vitro* studies have also suggested that acetoacetate and beta-hydroxybutyrate can decrease the activity of neurons within the substantia nigra, which is an important center for the propagation of seizures [314] and that acetoacetate inhibits vesicular glutamate transporters [315]. However, it has not been proven that a prolonged administration of a synthetic ketone precursor produces a significant anti-epileptic effect. Actually, calorie restriction is believed to have an important role for the effects of KDs [316, 317]. In fact, even fasting is known to have anti-epileptic effects since the beginning of the 20th century [309]. It has been argued that the energy metabolism could be involved in the anticonvulsant mechanism of KDs [318] and that some of the biochemical effects induced and maintained by KDs could have anti-seizure properties. The biochemical pathways evaluated until now include ketone bodies production, GABA and glutamate synthesis and recycling, adenosine production, mitochondrial oxidative me-

tabolism, tricarboxylic acid cycle refueling and fatty acids oxidation [319]. It is supposed that such metabolic effects act on brain neurotransmitter production or on ion channel functioning [320] and that the substantia nigra could be particularly involved in these effects [314, 321].

Surprisingly, despite KD is a high-fat diet, few studies have assessed the effects of KD on lipid levels or proportion within the central nervous system. Two recent studies reported an increase in the content of unsaturated fatty acids within the hippocampus [322, 323], but this topic certainly deserves to be further investigated.

Taken together the above data indicate that blood levels of ketone bodies have not a direct, clinically relevant, antiepileptic effect, but they should be considered an index of the compliance of patients to the diet regimen.

Interestingly, KDs have been proposed to treat many other neurological diseases, like brain trauma, Alzheimer's disease, Parkinson's disease, Amyotrophic Lateral Sclerosis, mitochondriopathies, alternating hemiplegia of childhood, brain tumors, migraine and autism spectrum disorders [324, 325]. Again, the mechanism for the beneficial effects of KDs in these pathologies is unknown, but it is supposed to involve an amelioration of the metabolic pathways for energy utilization in the cells of the nervous system.

KDs also have other interesting therapeutic effects. In fact, it has been acknowledged that KDs produce weight loss and ameliorate glycaemic control and blood lipid profile in metabolic syndrome, insulin resistance and type 2 diabetes [324]. These effects are probably due to the low carbohydrate intake which obviously ameliorates the glycaemic control and promotes lipid catabolism.

There are also some studies reporting possible beneficial effects of KDs on tumor progression [326, 327]. It can be argued that such effects could be ascribed to the restricted availability of nutrients from the diet, particularly aminoacids, which are obviously a limiting factor for cellular growth and, thus, for tumor growth. Another possibility is that KDs could enhance the oxidative stress in cancer cells resulting in a greater vulnerability of these cells to radiation therapies [328].

KDs can have transient adverse effects, like gastrointestinal distress, acidosis, hypoglycaemia, dehydration, hyperlipidaemia, and lethargy. Long treatment with KDs is a risk for vitamin and mineral deficiency which can produce easy bruising, impairment of growth and bone fractures. Hyperuricaemia and kidney stones have also been described [329, 330]. KDs are generally considered safe treatments and most of the side effects can be prevented or treated. One of the greatest problems with KDs is the poor palatability and the difficulty for patients to follow severe dietary restrictions. This is why some less restrictive kinds of KDs are currently proposed to patients [305]. However, the greatest challenge for present research is to understand the true mechanisms of KDs and to find a pharmacological alternative, thus realizing a sort of "KD in a pill", with the same or greater efficacy of a KD but without its dietary limitations [331]; to this aim, the anti-seizure efficacy of a synthetic ketone was tested in animal models and some acute effects have been described [313, 317, 332], but much work is still needed to find an effective drug substitute for KDs.

CONCLUSION

Due to the above observation, we can conclude that dietary fats are both friends and foes for brain functions. Lipids have a structural role in brain and are key factors in neuron activity and health, as for *n-3* PUFAs and their bioactive derivates. By contrast, disorders in energy homeostasis have been linked to several neurological and neuropsychiatric diseases pointing out the importance of the microbiota-gut-brain communication for brain health. As a consequence, the manipulation of lifestyle factors, such as dietary interventions is a recognized approach to maintain and preserve brain health along lifespan. The identification of all the molecular mechanisms is far away to be completed, of course, and further work is necessary in the future. Many efforts are required to assess the optimal conditions for therapeutic use in humans. However, dietary manipulation for the treatment of brain disorders is not just a promise for the future, but yet a reality. In fact, the clinical relevance of the manipulation of dietary lipids, as for KDs, is well-known and a currently in use for the treatment of brain diseases.

LIST OF ABBREVIATIONS

AEA	=	Anandamide
2-AG	=	Arachidonoylglycerol
AgRP	=	Agouti related protein
ALA	=	*n-3* α-linolenic acid
ARA	=	Arachidonic acid
ARC	=	Arcuate nucleus
ASDs	=	Autism spectrum disorders
BBB	=	Blood brain barrier
BDNF	=	Brain-derived neurotrophic factor
BPA	=	Bisphenol A
CART	=	Cocaine- and amphetamine-related transcript
CB1	=	Type 1 cannabinoid receptor
CB2	=	Type 2 cannabinoid receptor
CCK	=	Cholecystokinin
CHO	=	Carbohydrates
COX	=	Cyclooxygenase
CNS	=	Central nervous system
ΔD	=	Fatty acid desaturase
DA-ergic	=	Dopaminergic
DHA	=	Docosahexaenoic acid
DHEA	=	Docosahexaenoylethanolamide or synaptamide
DIO	=	Diet-induced obese

eCBs = Endocannabinoids
ENS = Enteric nervous system
EPA = Eicosapentaenoic acid
FAAH = Fatty acid amide hydrolase
FAs = Fatty acids
FSH = Follicle stimulating hormone
FFAR = Free fatty acid receptors
FOS = Fructo-oligosaccharides
GABA = γ-aminobutyric acid
GALP = Galanin like peptide;
GIP = Glucose-dependent insulinotropic polypeptide
GIT = Gastrointestinal tract
GLP-1 = Glucagon-like peptide 1
GnRH = Gonadotropin-releasing hormone
GOS = Galacto-oligosaccharides
GPR = G protein-coupled receptor
HFD = High fat diet
HPA = Hypothalamic-pituitary-adrenal
HPG = Hypothalamus-pityitary-godad
IGN = Intestinal gluconeogenesis
KDs = Ketogenic diets
LA = *n-6* linoleic acid
LC-PUFAs = Long chain polyunsaturated fatty acids
LEA = Linoleoylethanolamide
LH = Luteinizing hormone
LOX = Lipoxygenases
LPC = Lysophosphatidylcholine
LPS = Lipopolysaccharide
LTs = Leukotrienes
LXs = Lipoxins
MAGL = Monoacylglycerol lipase
MaR1 = Maresin 1
MCH = Melanin-concentrating hormone
Mfsd2a = Major facilitator superfamily domain-containing protein 2a
MUFAs = Monounsaturated FAs
NAEs = *N*-acylethanolamines
NMDAR = *N*-methyl-d-aspartate receptor
NPD1 = Neuroprotectin D1
NPY = Neuropeptide Y
NSAIDs = Non-steroidal anti-inflammatory drugs
NST = Nucleus of the solitary tract
OEA = Oleoylethanolamide
OFS = Oligofructose
PEA = Palmitoylethanolamide
PGs = Prostaglandins
POMC = Proopiomelanocortin precursor
PLA2 = Phospholipase A2
PPAR-alpha = Peroxisome proliferator-activated receptors alpha
PVN = Paraventricular nucleus
PYY = Peptide YY
ROS = Oxygen species
RvD5 = Resolvin D5
sCD14 = Soluble form of binding-protein CD14
SCFAs = Short chain fatty acids
SAFAs = Saturated FAs
SON = Supraoptic nucleus
SPMs = Specialized pro-resolving mediators
TFAs = Trans-FAs
TX = Thromboxanes
VTA = Ventral tegmental area
WHO = World Health Organization

CONSENT FOR PUBLICATION

Not applicable.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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REFERENCES

[1] Obesity and overweight *Fact sheet 311,* **2016**.http://www.who.int/mediacentre/factsheets/fs311/en/
[2] Gómez-Pinilla, F. Brain foods: the effects of nutrients on brain function. *Nat. Rev. Neurosci.,* **2008**, *9*(7), 568-578. [http://dx.doi.org/10.1038/nrn2421] [PMID: 18568016]
[3] Yi, C.X.; Tschöp, M.H. Brain-gut-adipose-tissue communication pathways at a glance. *Dis. Model. Mech.,* **2012**, *5*(5), 583-587. [http://dx.doi.org/10.1242/dmm.009902] [PMID: 22915019]

[4] Serhan, C.N. Lipoxins and aspirin-triggered 15-epi-lipoxins are the first lipid mediators of endogenous anti-inflammation and resolution. *Prostaglandins Leukot. Essent. Fatty Acids,* **2005**, *73*(3-4), 141-162. [http://dx.doi.org/10.1016/j.plefa.2005.05.002] [PMID: 16005201]

[5] Serhan, C.N. Lipoxin biosynthesis and its impact in inflammatory and vascular events. *Biochim. Biophys. Acta,* **1994**, *1212*(1), 1-25. [http://dx.doi.org/10.1016/0005-2760(94)90185-6] [PMID: 8155718]

[6] Serhan, C.N.; Petasis, N.A. Resolvins and protectins in inflammation resolution. *Chem. Rev.,* **2011**, *111*(10), 5922-5943. [http://dx.doi.org/10.1021/cr100396c] [PMID: 21766791]

[7] Simopoulos, A.P. Essential fatty acids in health and chronic diseases. *Forum Nutr.,* **2003**, *56*, 67-70. [PMID: 15806801]

[8] Bazinet, R.P.; Layé, S. Polyunsaturated fatty acids and their metabolites in brain function and disease. *Nat. Rev. Neurosci.,* **2014**, *15*(12), 771-785. [http://dx.doi.org/10.1038/nrn3820] [PMID: 25387473]

[9] Elphick, M.R. The evolution and comparative neurobiology of endocannabinoid signalling. *Philos. Trans. R. Soc. Lond. B Biol. Sci.,* **2012**, *367*(1607), 3201-3215. [http://dx.doi.org/10.1098/rstb.2011.0394] [PMID: 23108540]

[10] Fasano, S.; Meccariello, R.; Cobellis, G.; Chianese, R.; Cacciola, G.; Chioccarelli, T.; Pierantoni, R. The endocannabinoid system: an ancient signaling involved in the control of male fertility. *Ann. N. Y. Acad. Sci.,* **2009**, *1163*, 112-124. [http://dx.doi.org/10.1111/j.1749-6632.2009.04437.x] [PMID: 19456333]

[11] Marsicano, G.; Lutz, B. Neuromodulatory functions of the endocannabinoid system. *J. Endocrinol. Invest.,* **2006**, *29*(3)(Suppl.), 27-46. [PMID: 16751707]

[12] Stella, N. Cannabinoid and cannabinoid-like receptors in microglia, astrocytes, and astrocytomas. *Glia,* **2010**, *58*(9), 1017-1030. [http://dx.doi.org/10.1002/glia.20983] [PMID: 20468046]

[13] Pagotto, U.; Marsicano, G.; Cota, D.; Lutz, B.; Pasquali, R. The emerging role of the endocannabinoid system in endocrine regulation and energy balance. *Endocr. Rev.,* **2006**, *27*(1), 73-100. [http://dx.doi.org/10.1210/er.2005-0009] [PMID: 16306385]

[14] Chianese, R.; Cobellis, G.; Pierantoni, R.; Fasano, S.; Meccariello, R. Non-mammalian vertebrate models and the endocannabinoid system: relationships with gonadotropin-releasing hormone. *Mol. Cell. Endocrinol.,* **2008**, *286*(1-2)(Suppl. 1), S46-S51. [http://dx.doi.org/10.1016/j.mce.2008.01.009] [PMID: 18325658]

[15] Cacciola, G.; Chianese, R.; Chioccarelli, T.; Ciaramella, V.; Fasano, S.; Pierantoni, R.; Meccariello, R.; Cobellis, G. Cannabinoids and reproduction: A lasting and intriguing history. *Pharmac.,* **2010**, *3*, 3275-3323. [http://dx.doi.org/10.3390/ph3103275]

[16] Battista, N.; Meccariello, R.; Cobellis, G.; Fasano, S.; Di Tommaso, M.; Pirazzi, V.; Konje, J.C.; Pierantoni, R.; Maccarrone, M. The role of endocannabinoids in gonadal function and fertility along the evolutionary axis. *Mol. Cell. Endocrinol.,* **2012**, *355*(1), 1-14. [http://dx.doi.org/10.1016/j.mce.2012.01.014] [PMID: 22305972]

[17] Bovolin, P.; Cottone, E.; Pomatto, V.; Fasano, S.; Pierantoni, R.; Cobellis, G.; Meccariello, R. Endocannabinoids are involved in male vertebrate reproduction: regulatory mechanisms at central and gonadal level. *Front. Endocrinol.,* **2014**, *5*, 54. [http://dx.doi.org/10.3389/fendo.2014.00054] [PMID: 24782832]

[18] Cobellis, G.; Meccariello, R.; Chianese, R.; Chioccarelli, T.; Fasano, S.; Pierantoni, R. Effects of neuroendocrine CB1 activity on adult Leydig cells. *Front. Endocrinol. (Lausanne),* **2016**, *7*, 47. [http://dx.doi.org/10.3389/fendo.2016.00047] [PMID: 27375550]

[19] Meccariello, R.; Battista, N.; Bradshaw, HB.; Wang, H. Updates in reproduction coming from the endocannabinoid system. *Int. J. Endocrinol.,* **2014**, *2014*, 412354. [http://dx.doi.org/10.1155/2014/412354]

[20] Lafourcade, M.; Larrieu, T.; Mato, S.; Duffaud, A.; Sepers, M.; Matias, I.; De Smedt-Peyrusse, V.; Labrousse, V.F.; Bretillon, L.; Matute, C.; Rodríguez-Puertas, R.; Layé, S.; Manzoni, O.J. Nutritional omega-3 deficiency abolishes endocannabinoid-mediated neuronal functions. *Nat. Neurosci.,* **2011**, *14*(3), 345-350. [http://dx.doi.org/10.1038/nn.2736] [PMID: 21278728]

[21] Thomazeau, A.; Bosch-Bouju, C.; Manzoni, O.; Layé, S. Nutritional n-3 PUFA deficiency abolishes endocannabinoid gating of hippocampal long-term potentiation. *Cereb. Cortex,* **2016**, *27*(4), 2571-2579. [http://dx.doi.org/10.1093/cercor/bhw052] [PMID: 26946127]

[22] Cederholm, T.; Salem, N., Jr; Palmblad, J. ω-3 fatty acids in the prevention of cognitive decline in humans. *Adv. Nutr.,* **2013**, *4*(6), 672-676. [http://dx.doi.org/10.3945/an.113.004556] [PMID: 24228198]

[23] Layé, S. Polyunsaturated fatty acids, neuroinflammation and well being. *Prostaglandins Leukot. Essent. Fatty Acids,* **2010**, *82*(4-6), 295-303. [http://dx.doi.org/10.1016/j.plefa.2010.02.006] [PMID: 20227866]

[24] Barnard, N.D.; Bunner, A.E.; Agarwal, U. Saturated and trans fats and dementia: a systematic review. *Neurobiol. Aging,* **2014**, *35*(Suppl. 2), S65-S73. [http://dx.doi.org/10.1016/j.neurobiolaging.2014.02.030] [PMID: 24916582]

[25] Gershon, M.D. The Second Brain. *Harper Collins*, **1998**. (**ISBN:** 9780060930721; **ISBN 10:** 0060930721).

[26] Rhee, S.H.; Pothoulakis, C.; Mayer, E.A. Principles and clinical implications of the brain-gut-enteric microbiota axis. *Nat. Rev. Gastroenterol. Hepatol.,* **2009**, *6*(5), 306-314. [http://dx.doi.org/10.1038/nrgastro.2009.35] [PMID: 19404271]

[27] Mayer, E.A. Gut feelings: the emerging biology of gut-brain communication. *Nat. Rev. Neurosci.,* **2011**, *12*(8), 453-466. [http://dx.doi.org/10.1038/nrn3071] [PMID: 21750565]

[28] Collins, S.M.; Surette, M.; Bercik, P. The interplay between the intestinal microbiota and the brain. *Nat. Rev. Microbiol.,* **2012**, *10*(11), 735-742. [http://dx.doi.org/10.1038/nrmicro2876] [PMID: 23000955]

[29] Cryan, J.F.; Dinan, T.G. Mind-altering microorganisms: the impact of the gut microbiota on brain and behaviour. *Nat. Rev. Neurosci.,* **2012**, *13*(10), 701-712. [http://dx.doi.org/10.1038/nrn3346] [PMID: 22968153]

[30] Evrensel, A.; Ceylan, M.E. The gut-brain axis: The missing link in depression. *Clin. Psychopharmacol. Neurosci.,* **2015**, *13*(3), 239-244. [http://dx.doi.org/10.9758/cpn.2015.13.3.239] [PMID: 26598580]

[31] Klingelhoefer, L.; Reichmann, H. Pathogenesis of Parkinson disease--the gut-brain axis and environmental factors. *Nat. Rev. Neurol.,* **2015**, *11*(11), 625-636. [http://dx.doi.org/10.1038/nrneurol.2015.197] [PMID: 26503923]

[32] Vuong, H.E.; Hsiao, E. Y. Emerging Roles for the Gut Microbiome in Autism Spectrum Disorder. *Biol. Psychiatry,* **2016**. S0006-3223(16)32724-X.

[33] Gill, S.R.; Pop, M.; Deboy, R.T.; Eckburg, P.B.; Turnbaugh, P.J.; Samuel, B.S.; Gordon, J.I.; Relman, D.A.; Fraser-Liggett, C.M.; Nelson, K.E. Metagenomic analysis of the human distal gut microbiome. *Science,* **2006**, *312*(5778), 1355-1359. [http://dx.doi.org/10.1126/science.1124234] [PMID: 16741115]

[34] Qin, J.; Li, R.; Raes, J.; Arumugam, M.; Burgdorf, K.S.; Manichanh, C.; Nielsen, T.; Pons, N.; Levenez, F.; Yamada, T.; Mende, D.R.; Li, J.; Xu, J.; Li, S.; Li, D.; Cao, J.; Wang, B.; Liang, H.; Zheng, H.; Xie, Y.; Tap, J.; Lepage, P.; Bertalan, M.; Batto, J.M.; Hansen, T.; Le Paslier, D.; Linneberg, A.; Nielsen, H.B.; Pelletier, E.; Renault, P.; Sicheritz-Ponten, T.; Turner, K.; Zhu, H.; Yu, C.; Li, S.; Jian, M.; Zhou, Y.; Li, Y.; Zhang, X.; Li, S.; Qin, N.; Yang, H.; Wang, J.; Brunak, S.; Doré, J.; Guarner, F.; Kristiansen, K.; Pedersen, O.; Parkhill, J.; Weissenbach, J.; Bork, P.; Ehrlich, S.D.; Wang, J. A human gut microbial gene catalogue established by metagenomic sequencing. *Nature,* **2010**, *464*(7285), 59-65. [http://dx.doi.org/10.1038/nature08821] [PMID: 20203603]

[35] Noble, E.E.; Hsu, T.M.; Kanoski, S.E. Gut to brain dysbiosis: Mechanisms linking western diet consumption, the microbiome, and cognitive impairment. *Front. Behav. Neurosci.,* **2017**, *11*, 9. [http://dx.doi.org/10.3389/fnbeh.2017.00009] [PMID: 28194099]

[36] Kelly, J.R.; Kennedy, P.J.; Cryan, J.F.; Dinan, T.G.; Clarke, G.; Hyland, N.P. Breaking down the barriers: the gut microbiome, intestinal permeability and stress-related psychiatric disorders. *Front. Cell. Neurosci.,* **2015**, *9*, 392. [http://dx.doi.org/10.3389/fncel.2015.00392] [PMID: 26528128]

[37] Carmody, R.N.; Gerber, G.K.; Luevano, J.M., Jr; Gatti, D.M.; Somes, L.; Svenson, K.L.; Turnbaugh, P.J. Diet dominates host genotype in shaping the murine gut microbiota. *Cell Host Microbe,* **2015**, *17*(1), 72-84. [http://dx.doi.org/10.1016/j.chom.2014.11.010] [PMID: 25532804]

[38] de Vrese, M.; Schrezenmeir, J. Probiotics, prebiotics, and synbiotics. *Adv. Biochem. Eng. Biotechnol.,* **2008**, *111*, 1-66. [http://dx.doi.org/10.1007/10_2008_097] [PMID: 18461293]

[39] Lilly, D.M.; Stillwell, R.H. Probiotics: Growth-promoting factors produced by microorganisms. *Science,* **1965**, *147*(3659), 747-748. [http://dx.doi.org/10.1126/science.147.3659.747] [PMID: 14242024]

[40] Hill, C.; Guarner, F.; Reid, G.; Gibson, G.R.; Merenstein, D.J.; Pot, B.; Morelli, L.; Canani, R.B.; Flint, H.J.; Salminen, S.; Calder, P.C.; Sanders, M.E. Expert consensus document. The International Scientific Association for Probiotics and Prebiotics consensus statement on the scope and appropriate use of the term probiotic. *Nat. Rev. Gastroenterol. Hepatol.,* **2014**, *11*(8), 506-514. [http://dx.doi.org/10.1038/nrgastro.2014.66] [PMID: 24912386]

[41] Gibson, G.R.; Roberfroid, M.B. Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. *J. Nutr.,* **1995**, *125*(6), 1401-1412. [PMID: 7782892]

[42] Gibson, G.R.; Scott, K.P.; Rastall, R.A.; Tuohy, K.M.; Hotchkiss, A.; Dubert-Ferrandon, A.; Garau, M.; Murphy, E.F.; Saulnier, D.; Loh, G.; Macfarlane, S.; Delzenne, N.; Ringel, Y.; Kozianowski, G.; Dickmann, R.; Lenoir-Wijnkook, I.; Walker, C.; Buddington, R. Dietary prebiotics: current status and new definition. *Food Sci. Technol. Bull: Funct. Foods.,* **2010**, *7*, 1-19.

[43] Finegold, S.M.; Molitoris, D.; Song, Y.; Liu, C.; Vaisanen, M.L.; Bolte, E.; McTeague, M.; Sandler, R.; Wexler, H.; Marlowe, E.M.; Collins, M.D.; Lawson, P.A.; Summanen, P.; Baysallar, M.; Tomzynski, T.J.; Read, E.; Johnson, E.; Rolfe, R.; Nasir, P.; Shah, H.; Haake, D.A.; Manning, P.; Kaul, A. Gastrointestinal microflora studies in late-onset autism. *Clin. Infect. Dis.,* **2002**, *35*(Suppl. 1), S6-S16. [http://dx.doi.org/10.1086/341914] [PMID: 12173102]

[44] Williams, B.L.; Hornig, M.; Parekh, T.; Lipkin, W.I. Application of novel PCR-based methods for detection, quantitation, and phylogenetic characterization of Sutterella species in intestinal biopsy samples from children with autism and gastrointestinal disturbances. *MBio,* **2012**, *3*(1), 1-11. [http://dx.doi.org/10.1128/mBio.00261-11] [PMID: 22233678]

[45] Wang, L.; Christophersen, C.T.; Sorich, M.J.; Gerber, J.P.; Angley, M.T.; Conlon, M.A. Increased abundance of Sutterella spp. and *Ruminococcus torques* in feces of children with autism spectrum disorder. *Mol. Autism,* **2013**, *4*(1), 42. [http://dx.doi.org/10.1186/2040-2392-4-42] [PMID: 24188502]

[46] Hsiao, E.Y.; McBride, S.W.; Hsien, S.; Sharon, G.; Hyde, E.R.; McCue, T.; Codelli, J.A.; Chow, J.; Reisman, S.E.; Petrosino, J.F.; Patterson, P.H.; Mazmanian, S.K. Microbiota modulate behavioral and physiological abnormalities associated with neurodevelopmental disorders. *Cell,* **2013**, *155*(7), 1451-1463. [http://dx.doi.org/10.1016/j.cell.2013.11.024] [PMID: 24315484]

[47] Navarro, F.; Liu, Y.; Rhoads, J.M. Can probiotics benefit children with autism spectrum disorders? *World J. Gastroenterol.,* **2016**, *22*(46), 10093-10102. [http://dx.doi.org/10.3748/wjg.v22.i46.10093] [PMID: 28028357]

[48] Sudo, N.; Chida, Y.; Aiba, Y.; Sonoda, J.; Oyama, N.; Yu, X-N.; Kubo, C.; Koga, Y. Postnatal microbial colonization programs the hypothalamic-pituitary-adrenal system for stress response in mice. *J. Physiol.,* **2004**, *558*(Pt 1), 263-275. [http://dx.doi.org/10.1113/jphysiol.2004.063388] [PMID: 15133062]

[49] Bravo, J.A.; Forsythe, P.; Chew, M.V.; Escaravage, E.; Savignac, H.M.; Dinan, T.G.; Bienenstock, J.; Cryan, J.F. Ingestion of Lactobacillus strain regulates emotional behavior and central GABA receptor expression in a mouse *in vivo*the vagus nerve. *Proc. Natl. Acad. Sci. USA,* **2011**, *108*(38), 16050-16055. [http://dx.doi.org/10.1073/pnas.1102999108] [PMID: 21876150]

[50] Bercik, P.; Park, A.J.; Sinclair, D.; Khoshdel, A.; Lu, J.; Huang, X.; Deng, Y.; Blennerhassett, P.A.; Fahnestock, M.; Moine, D.; Berger, B.; Huizinga, J.D.; Kunze, W.; McLean, P.G.; Bergonzelli, G.E.; Collins, S.M.; Verdu, E.F. The anxiolytic effect of *Bifidobacterium longum* NCC3001 involves vagal pathways for gut-brain communication. *Neurogastroenterol. Motil.,* **2011**, *23*(12), 1132-1139. [http://dx.doi.org/10.1111/j.1365-2982.2011.01796.x] [PMID: 21988661]

[51] Gareau, M.G.; Wine, E.; Rodrigues, D.M.; Cho, J.H.; Whary, M.T.; Philpott, D.J.; Macqueen, G.; Sherman, P.M. Bacterial infection causes stress-induced memory dysfunction in mice. *Gut,* **2011**, *60*(3), 307-317. [http://dx.doi.org/10.1136/gut.2009.202515] [PMID: 20966022]

[52] Nemani, K.; Hosseini Ghomi, R.; McCormick, B.; Fan, X. Schizophrenia and the gut-brain axis. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2015**, *56*, 155-160. [http://dx.doi.org/10.1016/j.pnpbp.2014.08.018] [PMID: 25240858]

[53] Bailey, M.T.; Dowd, S.E.; Galley, J.D.; Hufnagle, A.R.; Allen, R.G.; Lyte, M. Exposure to a social stressor alters the structure of the intestinal microbiota: implications for stressor-induced immunomodulation. *Brain Behav. Immun.,* **2011**, *25*(3), 397-407. [http://dx.doi.org/10.1016/j.bbi.2010.10.023] [PMID: 21040780]

[54] Galley, J.D.; Nelson, M.C.; Yu, Z.; Dowd, S.E.; Walter, J.; Kumar, P.S.; Lyte, M.; Bailey, M.T. Exposure to a social stressor disrupts the community structure of the colonic mucosa-associated microbiota. *BMC Microbiol.,* **2014**, *14*, 189. [http://dx.doi.org/10.1186/1471-2180-14-189] [PMID: 25028050]

[55] Wang, J.; Tang, H.; Zhang, C.; Zhao, Y.; Derrien, M.; Rocher, E.; van-Hylckama, V.J.E.; Strissel, K.; Zhao, L.; Obin, M.; Shen, J. Modulation of gut microbiota during probiotic-mediated attenuation of metabolic syndrome in high fat diet-fed mice. *ISME J.,* **2015**, *9*(1), 1-15. [http://dx.doi.org/10.1038/ismej.2014.99] [PMID: 24936764]

[56] Serino, M.; Luche, E.; Gres, S.; Baylac, A.; Bergé, M.; Cenac, C.; Waget, A.; Klopp, P.; Iacovoni, J.; Klopp, C.; Mariette, J.; Bouchez, O.; Lluch, J.; Ouarné, F.; Monsan, P.; Valet, P.; Roques, C.; Amar, J.; Bouloumié, A.; Théodorou, V.; Burcelin, R. Metabolic adaptation to a high-fat diet is associated with a change in the gut microbiota. *Gut,* **2012**, *61*(4), 543-553. [http://dx.doi.org/10.1136/gutjnl-2011-301012] [PMID: 22110050]

[57] Cano, P.G.; Santacruz, A.; Trejo, F.M.; Sanz, Y. Bifidobacterium CECT 7765 improves metabolic and immunological alterations associated with obesity in high-fat diet-fed mice. *Obesity (Silver Spring),* **2013**, *21*(11), 2310-2321. [http://dx.doi.org/10.1002/oby.20330] [PMID: 23418126]

[58] Verdam, F.J.; Fuentes, S.; de Jonge, C.; Zoetendal, E.G.; Erbil, R.; Greve, J.W.; Buurman, W.A.; de Vos, W.M.; Rensen, S.S. Human intestinal microbiota composition is associated with local and systemic inflammation in obesity. *Obesity (Silver Spring),* **2013**, *21*(12), E607-E615. [http://dx.doi.org/10.1002/oby.20466] [PMID: 23526699]

[59] Wong, J.M.; de Souza, R.; Kendall, C.W.; Emam, A.; Jenkins, D.J. Colonic health: fermentation and short chain fatty acids. *J. Clin. Gastroenterol.,* **2006**, *40*(3), 235-243. [http://dx.doi.org/10.1097/00004836-200603000-00015] [PMID: 16633129]

[60] Smriga, M.; Chen, J.; Zhang, J.T.; Narui, T.; Shibata, S.; Hirano, E.; Saito, H. Isolichenan, an alpha-glucan isolated from lichen cetrariella islandica, repairs impaired learning behaviors and facilitates hippocampal synaptic plasticity. *Proc. Jpn. Acad. B, Phys. Biol. Sci.,* **1999**, *75*, 219-223.

[61] Han, H.S.; Jang, J-H.; Jang, J.H.; Choi, J.S.; Kim, Y.J.; Lee, C.; Lim, S.H.; Lee, H-K.; Lee, J. Water extract of *Triticum aestivum* L. and its components demonstrate protective effect in a model of vascular dementia. *J. Med. Food,* **2010**, *13*(3), 572-578. [http://dx.doi.org/10.1089/jmf.2009.1242] [PMID: 20521983]

[62] Savignac, H.M.; Corona, G.; Mills, H.; Chen, L.; Spencer, J.P.; Tzortzis, G.; Burnet, P.W. Prebiotic feeding elevates central brain derived neurotrophic factor, N-methyl-D-aspartate receptor subunits and D-serine. *Neurochem. Int.,* **2013**, *63*(8), 756-764. [http://dx.doi.org/10.1016/j.neuint.2013.10.006] [PMID: 24140431]

[63] Schmidt, K.; Cowen, P.J.; Harmer, C.J.; Tzortzis, G.; Errington, S.; Burnet, P.W. Prebiotic intake reduces the waking cortisol response and alters emotional bias in healthy volunteers. *Psychopharmacology (Berl.),* **2015**, *232*(10), 1793-1801. [http://dx.doi.org/10.1007/s00213-014-3810-0] [PMID: 25449699]

[64] Gao, Z.; Yin, J.; Zhang, J.; Ward, R.E.; Martin, R.J.; Lefevre, M.; Cefalu, W.T.; Ye, J. Butyrate improves insulin sensitivity and increases energy expenditure in mice. *Diabetes,* **2009**, *58*(7), 1509-1517. [http://dx.doi.org/10.2337/db08-1637] [PMID: 19366864]

[65] Lin, H.V.; Frassetto, A.; Kowalik, E.J., Jr; Nawrocki, A.R.; Lu, M.M.; Kosinski, J.R.; Hubert, J.A.; Szeto, D.; Yao, X.; Forrest, G.; Marsh, D.J. Butyrate and propionate protect against diet-induced obesity and regulate gut hormones *in vivo* free fatty acid receptor 3-independent mechanisms. *PLoS One,* **2012**, *7*(4), e35240. [http://dx.doi.org/10.1371/journal.pone.0035240] [PMID: 22506074]

[66] Bolognini, D.; Tobin, A.B.; Milligan, G.; Moss, C.E. The pharmacology and function of short chain fatty acid receptors. *Mol. Pharmacol.,* **2016**, *89*, 388-398. [http://dx.doi.org/10.1124/mol.115.102301] [PMID: 26719580]

[67] Tolhurst, G.; Heffron, H.; Lam, Y.S.; Parker, H.E.; Habib, A.M.; Diakogiannaki, E.; Cameron, J.; Grosse, J.; Reimann, F.; Gribble, F.M. Short-chain fatty acids stimulate glucagon-like peptide-1 se-

cretion *in vivo*the G-protein-coupled receptor FFAR2. *Diabetes,* **2012**, *61*(2), 364-371. [http://dx.doi.org/10.2337/db11-1019] [PMID: 22190648]

[68] De Vadder, F.; Kovatcheva-Datchary, P.; Goncalves, D.; Vinera, J.; Zitoun, C.; Duchampt, A.; Bäckhed, F.; Mithieux, G. Microbiota-generated metabolites promote metabolic benefits *in vivo*gut-brain neural circuits. *Cell,* **2014**, *156*(1-2), 84-96. [http://dx.doi.org/10.1016/j.cell.2013.12.016] [PMID: 24412651]

[69] Graf, D.; Di Cagno, R.; Fåk, F.; Flint, H.J.; Nyman, M.; Saarela, M.; Watzl, B. Contribution of diet to the composition of the human gut microbiota. *Microb. Ecol. Health Dis.,* **2015**, *26*, 26164. [PMID: 25656825]

[70] Ley, R.E.; Turnbaugh, P.J.; Klein, S.; Gordon, J.I. Microbial ecology: human gut microbes associated with obesity. *Nature,* **2006**, *444*(7122), 1022-1023. [http://dx.doi.org/10.1038/4441022a] [PMID: 17183309]

[71] De Filippis, F.; Pellegrini, N.; Vannini, L.; Jeffery, I. B.; La Storia, A.; Laghi, L.; Serrazanetti, D. I.; Di Cagno, R.; Ferrocino, I.; Lazzi, C.; Turroni, S.; Cocolin, L.; Brigidi, P.; Neviani, E.; Gobbetti, M.; O'Toole, P.W.; Ercolini, D. High-level adherence to a mediterranean diet beneficially impacts the gut microbiota and associated metabolome. *Gut,* **2016**, *65*(11), 1812-1821. [PMID: 26416813].

[72] Gutiérrez-Díaz, I.; Fernández-Navarro, T.; Sánchez, B.; Margolles, A.; González, S. Mediterranean diet and faecal microbiota: a transversal study. *Food Funct.,* **2016**, *7*(5), 2347-2356. [http://dx.doi.org/10.1039/C6FO00105J] [PMID: 27137178]

[73] Xiong, Y.; Miyamoto, N.; Shibata, K.; Valasek, M.A.; Motoike, T.; Kedzierski, R.M.; Yanagisawa, M. Short-chain fatty acids stimulate leptin production in adipocytes through the G protein-coupled receptor GPR41. *Proc. Natl. Acad. Sci. USA,* **2004**, *101*(4), 1045-1050. [http://dx.doi.org/10.1073/pnas.2637002100] [PMID: 14722361]

[74] Cani, P.D.; Neyrinck, A.M.; Maton, N.; Delzenne, N.M. Oligofructose promotes satiety in rats fed a high-fat diet: involvement of glucagon-like Peptide-1. *Obes. Res.,* **2005**, *13*(6), 1000-1007. [http://dx.doi.org/10.1038/oby.2005.117] [PMID: 15976142]

[75] Psichas, A.; Sleeth, M.L.; Murphy, K.G.; Brooks, L.; Bewick, G.A.; Hanyaloglu, A.C.; Ghatei, M.A.; Bloom, S.R.; Frost, G. The short chain fatty acid propionate stimulates GLP-1 and PYY secretion *in vivo*free fatty acid receptor 2 in rodents. *Int. J. Obes.,* **2015**, *39*(3), 424-429. [http://dx.doi.org/10.1038/ijo.2014.153] [PMID: 25109781]

[76] Cani, P.D.; Amar, J.; Iglesias, M.A.; Poggi, M.; Knauf, C.; Bastelica, D.; Neyrinck, A.M.; Fava, F.; Tuohy, K.M.; Chabo, C.; Waget, A.; Delmée, E.; Cousin, B.; Sulpice, T.; Chamontin, B.; Ferrières, J.; Tanti, J.F.; Gibson, G.R.; Casteilla, L.; Delzenne, N.M.; Alessi, M.C.; Burcelin, R. Metabolic endotoxemia initiates obesity and insulin resistance. *Diabetes,* **2007**, *56*(7), 1761-1772. [http://dx.doi.org/10.2337/db06-1491] [PMID: 17456850]

[77] Erridge, C.; Attina, T.; Spickett, C.M.; Webb, D.J. A high-fat meal induces low-grade endotoxemia: evidence of a novel mechanism of postprandial inflammation. *Am. J. Clin. Nutr.,* **2007**, *86*(5), 1286-1292. [PMID: 17991637]

[78] Ghoshal, S.; Witta, J.; Zhong, J.; de Villiers, W.; Eckhardt, E. Chylomicrons promote intestinal absorption of lipopolysaccharides. *J. Lipid Res.,* **2009**, *50*(1), 90-97. [http://dx.doi.org/10.1194/jlr.M800156-JLR200] [PMID: 18815435]

[79] Laugerette, F.; Vors, C.; Géloën, A.; Chauvin, M.A.; Soulage, C.; Lambert-Porcheron, S.; Peretti, N.; Alligier, M.; Burcelin, R.; Laville, M.; Vidal, H.; Michalski, M.C. Emulsified lipids increase endotoxemia: possible role in early postprandial low-grade inflammation. *J. Nutr. Biochem.,* **2011**, *22*(1), 53-59. [http://dx.doi.org/10.1016/j.jnutbio.2009.11.011] [PMID: 20303729]

[80] Laugerette, F.; Furet, J.P.; Debard, C.; Daira, P.; Loizon, E.; Géloën, A.; Soulage, C.O.; Simonet, C.; Lefils-Lacourtablaise, J.; Bernoud-Hubac, N.; Bodennec, J.; Peretti, N.; Vidal, H.; Michalski, M.C. Oil composition of high-fat diet affects metabolic inflammation differently in connection with endotoxin receptors in mice. *Am. J. Physiol. Endocrinol. Metab.,* **2012**, *302*(3), E374-E386. [http://dx.doi.org/10.1152/ajpendo.00314.2011] [PMID: 22094473]

[81] Lyte, J.M.; Gabler, N.K.; Hollis, J.H. Postprandial serum endotoxin in healthy humans is modulated by dietary fat in a randomized, controlled, cross-over study. *Lipids Health Dis.,* **2016**, *15*(1), 186. [http://dx.doi.org/10.1186/s12944-016-0357-6] [PMID: 27816052]

[82] Chandrasekharan, J.A.; Sharma-Walia, N. Lipoxins: nature's way to resolve inflammation. *J. Inflamm. Res.,* **2015**, *8*, 181-192. [PMID: 26457057]

[83] Serhan, C.N.; Hong, S.; Gronert, K.; Colgan, S.P.; Devchand, P.R.; Mirick, G.; Moussignac, R.L. Resolvins: a family of bioactive products of omega-3 fatty acid transformation circuits initiated by aspirin treatment that counter proinflammation signals. *J. Exp. Med.,* **2002**, *196*(8), 1025-1037. [http://dx.doi.org/10.1084/jem.20020760] [PMID: 12391014]

[84] Serhan, C.N.; Chiang, N.; Van Dyke, T.E. Resolving inflammation: dual anti-inflammatory and pro-resolution lipid mediators. *Nat. Rev. Immunol.,* **2008**, *8*(5), 349-361. [http://dx.doi.org/10.1038/nri2294] [PMID: 18437155]

[85] Jo, Y.H.; Su, Y.; Gutierrez-Juarez, R.; Chua, S., Jr. Oleic acid directly regulates POMC neuron excitability in the hypothalamus. *J. Neurophysiol.,* **2009**, *101*(5), 2305-2316. [http://dx.doi.org/10.1152/jn.91294.2008] [PMID: 19261705]

[86] Levin, B.E.; Magnan, C.; Dunn-Meynell, A.; Le Foll, C. Metabolic sensing and the brain: who, what, where, and how? *Endocrinology,* **2011**, *152*(7), 2552-2557. [http://dx.doi.org/10.1210/en.2011-0194] [PMID: 21521751]

[87] Blouet, C.; Schwartz, G.J. Brainstem nutrient sensing in the nucleus of the solitary tract inhibits feeding. *Cell Metab.,* **2012**, *16*(5), 579-587. [http://dx.doi.org/10.1016/j.cmet.2012.10.003] [PMID: 23123165]

[88] Cavanaugh, A.R.; Schwartz, G.J.; Blouet, C. High-fat feeding impairs nutrient sensing and gut brain integration in the caudomedial nucleus of the solitary tract in mice. *PLoS One,* **2015**, *10*(3), e0118888. [http://dx.doi.org/10.1371/journal.pone.0118888] [PMID: 25774780]

[89] Zheng, H.; Lenard, N.R.; Shin, A.C.; Berthoud, H.R. Appetite control and energy balance regulation in the modern world: reward-driven brain overrides repletion signals. *Int. J. Obes.,* **2009**, *33*(Suppl. 2), S8-S13. [http://dx.doi.org/10.1038/ijo.2009.65] [PMID: 19528982]

[90] Mahler, S.V.; Smith, K.S.; Berridge, K.C. Endocannabinoid hedonic hotspot for sensory pleasure: anandamide in nucleus accumbens shell enhances 'liking' of a sweet reward. *Neuropsychopharmacology,* **2007**, *32*(11), 2267-2278. [http://dx.doi.org/10.1038/sj.npp.1301376] [PMID: 17406653]

[91] Melis, T.; Succu, S.; Sanna, F.; Boi, A.; Argiolas, A.; Melis, M.R. The cannabinoid antagonist SR 141716A (Rimonabant) reduces the increase of extra-cellular dopamine release in the rat nucleus accumbens induced by a novel high palatable food. *Neurosci. Lett.,* **2007**, *419*(3), 231-235. [http://dx.doi.org/10.1016/j.neulet.2007.04.012] [PMID: 17462824]

[92] Di Marzo, V.; Sepe, N.; De Petrocellis, L.; Berger, A.; Crozier, G.; Fride, E.; Mechoulam, R. Trick or treat from food endocannabinoids? *Nature,* **1998**, *396*(6712), 636-637. [http://dx.doi.org/10.1038/25267] [PMID: 9872309]

[93] Alvheim, A.R.; Malde, M.K.; Osei-Hyiaman, D.; Lin, Y.H.; Pawlosky, R.J.; Madsen, L.; Kristiansen, K.; Frøyland, L.; Hibbeln, J.R. Dietary linoleic acid elevates endogenous 2-AG and anandamide and induces obesity. *Obesity (Silver Spring),* **2012**, *20*(10), 1984-1994. [http://dx.doi.org/10.1038/oby.2012.38] [PMID: 22334255]

[94] Rousseaux, C.; Thuru, X.; Gelot, A.; Barnich, N.; Neut, C.; Dubuquoy, L.; Dubuquoy, C.; Merour, E.; Geboes, K.; Chamaillard, M.; Ouwehand, A.; Leyer, G.; Carcano, D.; Colombel, J.F.; Ardid, D.; Desreumaux, P. Lactobacillus acidophilus modulates intestinal pain and induces opioid and cannabinoid receptors. *Nat. Med.,* **2007**, *13*(1), 35-37. [http://dx.doi.org/10.1038/nm1521] [PMID: 17159985]

[95] Motter, A.L.; Ahern, G.P. TRPA1 is a polyunsaturated fatty acid sensor in mammals. *PLoS One,* **2012**, *7*(6), e38439. [http://dx.doi.org/10.1371/journal.pone.0038439] [PMID: 22723860]

[96] Piomelli, D. A fatty gut feeling. *Trends Endocrinol. Metab.,* **2013**, *24*(7), 332-341. [http://dx.doi.org/10.1016/j.tem.2013.03.001] [PMID: 23567058]

[97] Fu, J.; Gaetani, S.; Oveisi, F.; Lo Verme, J.; Serrano, A.; Rodríguez De Fonseca, F.; Rosengarth, A.; Luecke, H.; Di Giacomo, B.; Tarzia, G.; Piomelli, D. Oleylethanolamide regulates feeding and body weight through activation of the nuclear receptor PPAR-alpha. *Nature,* **2003**, *425*(6953), 90-93. [http://dx.doi.org/10.1038/nature01921] [PMID: 12955147]

[98] Izzo, A.A.; Piscitelli, F.; Capasso, R.; Marini, P.; Cristino, L.; Petrosino, S.; Di Marzo, V. Basal and fasting/refeeding-regulated tissue levels of endogenous PPAR-alpha ligands in Zucker rats. *Obesity (Silver Spring),* **2010**, *18*(1), 55-62. [http://dx.doi.org/10.1038/oby.2009.186] [PMID: 19521349]

[99] Gonthier, M.P.; Hoareau, L.; Festy, F.; Matias, I.; Valenti, M.; Bès-Houtmann, S.; Rouch, C.; Robert-Da Silva, C.; Chesne, S.; Lefebvre d'Hellencourt, C.; Césari, M.; Di Marzo, V.; Roche, R. Identification of endocannabinoids and related compounds in human fat cells. *Obesity (Silver Spring),* **2007**, *15*(4), 837-845. [http://dx.doi.org/10.1038/oby.2007.581] [PMID: 17426318]

[100] Hansen, K.B.; Rosenkilde, M.M.; Knop, F.K.; Wellner, N.; Diep, T.A.; Rehfeld, J.F.; Andersen, U.B.; Holst, J.J.; Hansen, H.S. 2-Oleoyl glycerol is a GPR119 agonist and signals GLP-1 release in humans. *J. Clin. Endocrinol. Metab.,* **2011**, *96*(9), E1409-E1417. [http://dx.doi.org/10.1210/jc.2011-0647] [PMID: 21778222]

[101] Azari, E.K.; Ramachandran, D.; Weibel, S.; Arnold, M.; Romano, A.; Gaetani, S.; Langhans, W.; Mansouri, A. Vagal afferents are not necessary for the satiety effect of the gut lipid messenger oleoylethanolamide. *Am. J. Physiol. Regul. Integr. Comp. Physiol.,* **2014**, *307*(2), R167-R178. [http://dx.doi.org/10.1152/ajpregu.00067.2014] [PMID: 24829501]

[102] Rodríguez de Fonseca, F.; Navarro, M.; Gómez, R.; Escuredo, L.; Nava, F.; Fu, J.; Murillo-Rodríguez, E.; Giuffrida, A.; LoVerme, J.; Gaetani, S.; Kathuria, S.; Gall, C.; Piomelli, D. An anorexic lipid mediator regulated by feeding. *Nature,* **2001**, *414*(6860), 209-212. [http://dx.doi.org/10.1038/35102582] [PMID: 11700558]

[103] Provensi, G.; Coccurello, R.; Umehara, H.; Munari, L.; Giacovazzo, G.; Galeotti, N.; Nosi, D.; Gaetani, S.; Romano, A.; Moles, A.; Blandina, P.; Passani, M.B. Satiety factor oleoylethanolamide recruits the brain histaminergic system to inhibit food intake. *Proc. Natl. Acad. Sci. USA,* **2014**, *111*(31), 11527-11532. [http://dx.doi.org/10.1073/pnas.1322016111] [PMID: 25049422]

[104] Gaetani, S.; Fu, J.; Cassano, T.; Dipasquale, P.; Romano, A.; Righetti, L.; Cianci, S.; Laconca, L.; Giannini, E.; Scaccianoce, S.; Mairesse, J.; Cuomo, V.; Piomelli, D. The fat-induced satiety factor oleoylethanolamide suppresses feeding through central release of oxytocin. *J. Neurosci.,* **2010**, *30*(24), 8096-8101. [http://dx.doi.org/10.1523/JNEUROSCI.0036-10.2010] [PMID: 20554860]

[105] Diep, T.A.; Madsen, A.N.; Holst, B.; Kristiansen, M.M.; Wellner, N.; Hansen, S.H.; Hansen, H.S. Dietary fat decreases intestinal levels of the anorectic lipids through a fat sensor. *FASEB J.,* **2011**, *25*(2), 765-774. [http://dx.doi.org/10.1096/fj.10-166595] [PMID: 20959516]

[106] Tellez, L.A.; Medina, S.; Han, W.; Ferreira, J.G.; Licona-Limón, P.; Ren, X.; Lam, T.T.; Schwartz, G.J.; de Araujo, I.E. A gut lipid messenger links excess dietary fat to dopamine deficiency. *Science,* **2013**, *341*(6147), 800-802. [http://dx.doi.org/10.1126/science.1239275] [PMID: 23950538]

[107] Cheng, G.; Buyken, A.E.; Shi, L.; Karaolis-Danckert, N.; Kroke, A.; Wudy, S.A.; Degen, G.H.; Remer, T. Beyond overweight: nutrition as an important lifestyle factor influencing timing of puberty. *Nutr. Rev.,* **2012**, *70*(3), 133-152. [http://dx.doi.org/10.1111/j.1753-4887.2011.00461.x] [PMID: 22364156]

[108] Wade, G.N.; Jones, J.E. Neuroendocrinology of nutritional infertility. *Am. J. Physiol. Regul. Integr. Comp. Physiol.,* **2004**, *287*(6), R1277-R1296. [http://dx.doi.org/10.1152/ajpregu.00475.2004] [PMID: 15528398]

[109] Yan, M.; Zhai, Q. Sperm tsRNAs and acquired metabolic disorders. *J. Endocrinol.,* **2016**, *230*(3), F13-F18. [http://dx.doi.org/10.1530/JOE-16-0185] [PMID: 27340033]

[110] Comninos, A.N.; Jayasena, C.N.; Dhillo, W.S. The relationship between gut and adipose hormones, and reproduction. *Hum. Reprod. Update,* **2014**, *20*(2), 153-174. [http://dx.doi.org/10.1093/humupd/dmt033] [PMID: 24173881]

[111] Dos Santos, E.; Pecquery, R.; de Mazancourt, P.; Dieudonné, M.N. Adiponectin and reproduction. *Vitam. Horm.,* **2012**, *90*, 187-209. [http://dx.doi.org/10.1016/B978-0-12-398313-8.00008-7] [PMID: 23017717]

[112] Stanley, S.; Wynne, K.; McGowan, B.; Bloom, S. Hormonal regulation of food intake. *Physiol. Rev.,* **2005**, *85*(4), 1131-1158. [http://dx.doi.org/10.1152/physrev.00015.2004] [PMID: 16183909]

[113] Zhou, Y.; Ru, Y.; Shi, H.; Wang, Y.; Wu, B.; Upur, H.; Zhang, Y. Cholecystokinin receptors regulate sperm protein tyrosine phosphorylation *in vivo*uptake of HCO3-. *Reproduction,* **2015**, *150*(4), 257-268. [http://dx.doi.org/10.1530/REP-15-0138] [PMID: 26175429]

[114] Zelezná, B.; Maixnerová, J.; Matysková, R.; Haugvicová, R.; Blokesová, D.; Maletínská, L. Anorexigenic effect of cholecystokinin is lost but that of CART (Cocaine and Amphetamine Regulated Transcript) peptide is preserved in monosodium glutamate obese mice. *Physiol. Res.,* **2009**, *58*(5), 717-723. [PMID: 19093718]

[115] Roa, J.; García-Galiano, D.; Castellano, J.M.; Gaytan, F.; Pinilla, L.; Tena-Sempere, M. Metabolic control of puberty onset: new players, new mechanisms. *Mol. Cell. Endocrinol.,* **2010**, *324*(1-2), 87-94. [http://dx.doi.org/10.1016/j.mce.2009.12.018] [PMID: 20026241]

[116] Wilson, J.L.; Enriori, P.J. A talk between fat tissue, gut, pancreas and brain to control body weight. *Mol. Cell. Endocrinol.,* **2015**, *418*(Pt 2), 108-119. [http://dx.doi.org/10.1016/j.mce.2015.08.022] [PMID: 26316427]

[117] Forbes, S.; Li, X.F.; Kinsey-Jones, J.; O'Byrne, K. Effects of ghrelin on Kisspeptin mRNA expression in the hypothalamic medial preoptic area and pulsatile luteinising hormone secretion in the female rat. *Neurosci. Lett.,* **2009**, *460*(2), 143-147. [http://dx.doi.org/10.1016/j.neulet.2009.05.060] [PMID: 19477231]

[118] Tena-Sempere, M. Roles of ghrelin and leptin in the control of reproductive function. *Neuroendocrinology,* **2007**, *86*(3), 229-241. [http://dx.doi.org/10.1159/000108410] [PMID: 17851226]

[119] Tang-Christensen, M.; Larsen, P.J.; Göke, R.; Fink-Jensen, A.; Jessop, D.S.; Møller, M.; Sheikh, S.P. Central administration of GLP-1-(7-36) amide inhibits food and water intake in rats. *Am. J. Physiol.,* **1996**, *271*(4 Pt 2), R848-R856. [PMID: 8897973]

[120] Beak, S.A.; Heath, M.M.; Small, C.J.; Morgan, D.G.; Ghatei, M.A.; Taylor, A.D.; Buckingham, J.C.; Bloom, S.R.; Smith, D.M. Glucagon-like peptide-1 stimulates luteinizing hormone-releasing hormone secretion in a rodent hypothalamic neuronal cell line. *J. Clin. Invest.,* **1998**, *101*(6), 1334-1341. [http://dx.doi.org/10.1172/JCI610] [PMID: 9502775]

[121] Sliwowska, J.H.; Fergani, C.; Gawałek, M.; Skowronska, B.; Fichna, P.; Lehman, M.N. Insulin: its role in the central control of reproduction. *Physiol. Behav.,* **2014**, *133*, 197-206. [http://dx.doi.org/10.1016/j.physbeh.2014.05.021] [PMID: 24874777]

[122] Wahab, F.; Shahab, M.; Behr, R. Hypothesis: Irisin is a metabolic trigger for the activation of the neurohormonal axis governing puberty onset. *Med. Hypotheses,* **2016**, *95*, 1-4. [http://dx.doi.org/10.1016/j.mehy.2016.08.003] [PMID: 27692156]

[123] Halaas, J.L.; Gajiwala, K.S.; Maffei, M.; Cohen, S.L.; Chait, B.T.; Rabinowitz, D.; Lallone, R.L.; Burley, S.K.; Friedman, J.M. Weight-reducing effects of the plasma protein encoded by the obese gene. *Science,* **1995**, *269*(5223), 543-546. [http://dx.doi.org/10.1126/science.7624777] [PMID: 7624777]

[124] Smith, J.T.; Acohido, B.V.; Clifton, D.K.; Steiner, R.A. KiSS-1 neurones are direct targets for leptin in the ob/ob mouse. *J. Neuroendocrinol.,* **2006**, *18*(4), 298-303. [http://dx.doi.org/10.1111/j.1365-2826.2006.01417.x] [PMID: 16503925]

[125] Sarwat, J.; Shakeel, A.; Nazifa, T. Hizbullah. Possible modulation of testosterone secretion by obestatin in pubertal male rats. *Pak. J. Zool.,* **2011**, *43*, 799-803.

[126] Zhang, J.V.; Ren, P.G.; Avsian-Kretchmer, O.; Luo, C.W.; Rauch, R.; Klein, C.; Hsueh, A.J. Obestatin, a peptide encoded by the ghrelin gene, opposes ghrelin's effects on food intake. *Science,* **2005**, *310*(5750), 996-999. [http://dx.doi.org/10.1126/science.1117255] [PMID: 16284174]

[127] Pinilla, L.; Fernández-Fernández, R.; Roa, J.; Castellano, J.M.; Tena-Sempere, M.; Aguilar, E. Selective role of neuropeptide Y receptor subtype Y2 in the control of gonadotropin secretion in the rat. *Am. J. Physiol. Endocrinol. Metab.,* **2007**, *293*(5), E1385-E1392. [http://dx.doi.org/10.1152/ajpendo.00274.2007] [PMID: 17785504]

[128] Broberger, C.; Johansen, J.; Johansson, C.; Schalling, M.; Hökfelt, T. The neuropeptide Y/agouti gene-related protein (AGRP) brain circuitry in normal, anorectic, and monosodium glutamate-treated mice. *Proc. Natl. Acad. Sci. USA,* **1998**, *95*(25), 15043-15048. [http://dx.doi.org/10.1073/pnas.95.25.15043] [PMID: 9844012]

[129] Nestor, C.C.; Qiu, J.; Padilla, S.L.; Zhang, C.; Bosch, M.A.; Fan, W.; Aicher, S.A.; Palmiter, R.D.; Rønnekleiv, O.K.; Kelly, M.J. Optogenetic Stimulation of arcuate nucleus kiss1 neurons reveals a steroid-dependent glutamatergic input to POMC and AgRP neurons in male mice. *Mol. Endocrinol.,* **2016**, *30*(6), 630-644. [http://dx.doi.org/10.1210/me.2016-1026] [PMID: 27093227]

[130] True, C.; Verma, S.; Grove, K.L.; Smith, M.S. Cocaine- and amphetamine-regulated transcript is a potent stimulator of GnRH and kisspeptin cells and may contribute to negative energy balance-induced reproductive inhibition in females. *Endocrinology,* **2013**, *154*(8), 2821-2832. [http://dx.doi.org/10.1210/en.2013-1156] [PMID: 23736294]

[131] Lindberg, D.; Chen, P.; Li, C. Conditional viral tracing reveals that steroidogenic factor 1-positive neurons of the dorsomedial subdivision of the ventromedial hypothalamus project to autonomic centers of the hypothalamus and hindbrain. *J. Comp. Neurol.,* **2013**, *521*(14), 3167-3190. [http://dx.doi.org/10.1002/cne.23338] [PMID: 23696474]

[132] Krasnow, S.M.; Fraley, G.S.; Schuh, S.M.; Baumgartner, J.W.; Clifton, D.K.; Steiner, R.A. A role for galanin-like peptide in the integration of feeding, body weight regulation, and reproduction in the mouse. *Endocrinology,* **2003**, *144*(3), 813-822. [http://dx.doi.org/10.1210/en.2002-220982] [PMID: 12586757]

[133] Fu, L.Y.; Van den Pol, A.N. Kisspeptin directly excites anorexigenic POMC neurons, but inhibits orexigenic NPY cells by indirect synaptic mechanism. *J. Neurosci.,* **2010**, *30*, 10205-10219. [http://dx.doi.org/10.1523/JNEUROSCI.2098-10.2010] [PMID: 20668204]

[134] Skofitsch, G.; Jacobowitz, D.M.; Zamir, N. Immunohistochemical localization of a melanin concentrating hormone-like peptide in the rat brain. *Brain Res. Bull.,* **1985**, *15*(6), 635-649. [http://dx.doi.org/10.1016/0361-9230(85)90213-8] [PMID: 4084816]

[135] Santollo, J.; Eckel, L.A. The orexigenic effect of melanin-concentrating hormone (MCH) is influenced by sex and stage of the estrous cycle. *Physiol. Behav.,* **2008**, *93*(4-5), 842-850. [http://dx.doi.org/10.1016/j.physbeh.2007.11.050] [PMID: 18191424]

[136] Naufahu, J.; Cunliffe, A.D.; Murray, J.F. The roles of melanin-concentrating hormone in energy balance and reproductive function: Are they connected? *Reproduction,* **2013**, *146*(5), R141-R150. [http://dx.doi.org/10.1530/REP-12-0385] [PMID: 23884861]

[137] Li, C.; Chen, P.; Smith, M.S. Morphological evidence for direct interaction between arcuate nucleus neuropeptide Y (NPY) neurons and gonadotropin-releasing hormone neurons and the possible involvement of NPY Y1 receptors. *Endocrinology,* **1999**, *140*(11), 5382-5390. [http://dx.doi.org/10.1210/endo.140.11.7093] [PMID: 10537170]

[138] Skrapits, K.; Kanti, V.; Savanyú, Z.; Maurnyi, C.; Szenci, O.; Horváth, A.; Borsay, B.Á.; Herczeg, L.; Liposits, Z.; Hrabovszky, E. Lateral hypothalamic orexin and melanin-concentrating hormone neurons provide direct input to gonadotropin-releasing hormone neurons in the human. *Front. Cell. Neurosci.,* **2015**, *9*, 348. [http://dx.doi.org/10.3389/fncel.2015.00348] [PMID: 26388735]

[139] Goforth, P.B; Myers, M.G. Roles for orexin/hypocretin in the control of energy balance and metabolism. *Curr. Top. Behav. Neurosci*., **2017**, *33*, 137-156. [PMID: 27909992].

[140] Pierantoni, R.; Cobellis, G.; Meccariello, R.; Fasano, S. Evolutionary aspects of cellular communication in the vertebrate hypothalamo-hypophysio-gonadal axis. *Int. Rev. Cytol.,* **2002**, *218*, 69-141. [http://dx.doi.org/10.1016/S0074-7696(02)18012-0] [PMID: 12199520]

[141] Pierantoni, R.; Cobellis, G.; Meccariello, R.; Cacciola, G.; Chianese, R.; Chioccarelli, T.; Fasano, S. CB1 activity in male reproduction: mammalian and nonmammalian animal models. *Vitam. Horm.,* **2009**, *81*, 367-387. [http://dx.doi.org/10.1016/S0083-6729(09)81014-5] [PMID: 19647119]

[142] Pierantoni, R.; Cobellis, G.; Meccariello, R.; Cacciola, G.; Chianese, R.; Chioccarelli, T.; Fasano, S. Testicular gonadotropin-releasing hormone activity, progression of spermatogenesis, and sperm transport in vertebrates. *Ann. N. Y. Acad. Sci.,* **2009**, *1163*, 279-291. [http://dx.doi.org/10.1111/j.1749-6632.2008.03617.x] [PMID: 19456349]

[143] Chianese, R.; Chioccarelli, T.; Cacciola, G.; Ciaramella, V.; Fasano, S.; Pierantoni, R.; Meccariello, R.; Cobellis, G. The contribution of lower vertebrate animal models in human reproduction research. *Gen. Comp. Endocrinol.,* **2011**, *171*(1), 17-27. [http://dx.doi.org/10.1016/j.ygcen.2010.12.011] [PMID: 21192939]

[144] Meccariello, R.; Chianese, R.; Chioccarelli, T.; Ciaramella, V.; Fasano, S.; Pierantoni, R.; Cobellis, G. Intra-testicular signals regulate germ cell progression and production of qualitatively mature spermatozoa in vertebrates. *Front. Endocrinol. (Lausanne),* **2014**, *5*, 69. [http://dx.doi.org/10.3389/fendo.2014.00069] [PMID: 24847312]

[145] Cornejo, M.P.; Hentges, S.T.; Maliqueo, M.; Coirini, H.; Becu-Villalobos, D.; Elias, C.F. Neuroendocrine Regulation of Metabolism. *J. Neuroendocrinol.,* **2016**, *28*(7), 12395. [http://dx.doi.org/10.1111/jne.12395] [PMID: 27114114]

[146] Hill, J.W.; Elmquist, J.K.; Elias, C.F. Hypothalamic pathways linking energy balance and reproduction. *Am. J. Physiol. Endocrinol. Metab.,* **2008**, *294*(5), E827-E832. [http://dx.doi.org/10.1152/ajpendo.00670.2007] [PMID: 18285524]

[147] Wynne, K.; Stanley, S.; McGowan, B.; Bloom, S. Appetite control. *J. Endocrinol.,* **2005**, *184*(2), 291-318. [http://dx.doi.org/10.1677/joe.1.05866] [PMID: 15684339]

[148] Qian, S.; Chen, H.; Weingarth, D.; Trumbauer, M.E.; Novi, D.E.; Guan, X.; Yu, H.; Shen, Z.; Feng, Y.; Frazier, E.; Chen, A.; Camacho, R.E.; Shearman, L.P.; Gopal-Truter, S.; MacNeil, D.J.; Van der Ploeg, L.H.; Marsh, D.J. Neither agouti-related protein nor neuropeptide Y is critically required for the regulation of energy homeostasis in mice. *Mol. Cell. Biol.,* **2002**, *22*(14), 5027-5035. [http://dx.doi.org/10.1128/MCB.22.14.5027-5035.2002] [PMID: 12077332]

[149] Gropp, E.; Shanabrough, M.; Borok, E.; Xu, A.W.; Janoschek, R.; Buch, T.; Plum, L.; Balthasar, N.; Hampel, B.; Waisman, A.; Barsh, G.S.; Horvath, T.L.; Brüning, J.C. Agouti-related peptide-expressing neurons are mandatory for feeding. *Nat. Neurosci.,* **2005**, *8*(10), 1289-1291. [http://dx.doi.org/10.1038/nn1548] [PMID: 16158063]

[150] Dicken, M.S.; Hughes, A.R.; Hentges, S.T. Gad1 mRNA as a reliable indicator of altered GABA release from orexigenic neurons in the hypothalamus. *Eur. J. Neurosci.,* **2015**, *42*(9), 2644-2653. [http://dx.doi.org/10.1111/ejn.13076] [PMID: 26370162]

[151] Elias, C.F.; Saper, C.B.; Maratos-Flier, E.; Tritos, N.A.; Lee, C.; Kelly, J.; Tatro, J.B.; Hoffman, G.E.; Ollmann, M.M.; Barsh, G.S.; Sakurai, T.; Yanagisawa, M.; Elmquist, J.K. Chemically defined projections linking the mediobasal hypothalamus and the lateral hypothalamic area. *J. Comp. Neurol.,* **1998**, *402*(4), 442-459. [http://dx.doi.org/10.1002/(SICI)1096-9861(19981228)402:4<442::AID-CNE2>3.0.CO;2-R] [PMID: 9862320]

[152] Jarvie, B.C.; Hentges, S.T. Expression of GABAergic and glutamatergic phenotypic markers in hypothalamic proopiomelanocortin neurons. *J. Comp. Neurol.,* **2012**, *520*(17), 3863-3876. [http://dx.doi.org/10.1002/cne.23127] [PMID: 22522889]

[153] Hausman, G.J.; Barb, C.R.; Lents, C.A. Leptin and reproductive function. *Biochimie,* **2012**, *94*(10), 2075-2081. [http://dx.doi.org/10.1016/j.biochi.2012.02.022] [PMID: 22980196]

[154] Kotani, M.; Detheux, M.; Vandenbogaerde, A.; Communi, D.; Vanderwinden, J.M.; Le Poul, E.; Brézillon, S.; Tyldesley, R.; Suarez-Huerta, N.; Vandeput, F.; Blanpain, C.; Schiffmann, S.N.; Vassart, G.; Parmentier, M. The metastasis suppressor gene KiSS-1 encodes kisspeptins, the natural ligands of the orphan G protein-coupled receptor GPR54. *J. Biol. Chem.,* **2001**, *276*(37), 34631-34636. [http://dx.doi.org/10.1074/jbc.M104847200] [PMID: 11457843]

[155] Thompson, E.L.; Patterson, M.; Murphy, K.G.; Smith, K.L.; Dhillo, W.S.; Todd, J.F.; Ghatei, M.A.; Bloom, S.R. Central and peripheral administration of kisspeptin-10 stimulates the hypothalamic-pituitary-gonadal axis. *J. Neuroendocrinol.,* **2004**, *16*(10), 850-858. [http://dx.doi.org/10.1111/j.1365-2826.2004.01240.x] [PMID: 15500545]

[156] Messager, S.; Chatzidaki, E.E.; Ma, D.; Hendrick, A.G.; Zahn, D.; Dixon, J.; Thresher, R.R.; Malinge, I.; Lomet, D.; Carlton, M.B.; Colledge, W.H.; Caraty, A.; Aparicio, S.A. Kisspeptin directly stimulates gonadotropin-releasing hormone release *in vivo*G protein-coupled receptor 54. *Proc. Natl. Acad. Sci. USA,* **2005**, *102*(5), 1761-1766. [http://dx.doi.org/10.1073/pnas.0409330102] [PMID: 15665093]

[157] Clarkson, J.; Herbison, A.E. Postnatal development of kisspeptin neurons in mouse hypothalamus; sexual dimorphism and projections to gonadotropin-releasing hormone neurons. *Endocrinology,* **2006**, *147*(12), 5817-5825. [http://dx.doi.org/10.1210/en.2006-0787] [PMID: 16959837]

[158] Chianese, R.; Cobellis, G.; Chioccarelli, T.; Ciaramella, V.; Migliaccio, M.; Fasano, S.; Pierantoni, R.; Meccariello, R. Kisspeptins, estrogens and male fertility. *Curr. Med. Chem.,* **2016**, *23*(36), 4070-4091. [http://dx.doi.org/10.2174/0929867323666160902155434] [PMID: 27593959]

[159] Chianese, R.; Ciaramella, V.; Fasano, S.; Pierantoni, R.; Meccariello, R. Kisspeptin receptor, GPR54, as a candidate for the regula-

tion of testicular activity in the frog Rana esculenta. *Biol. Reprod.,* **2013**, *88*(3), 73. [http://dx.doi.org/10.1095/biolreprod.112.103515] [PMID: 23365413]

[160] Chianese, R.; Ciaramella, V.; Fasano, S.; Pierantoni, R.; Meccariello, R. Kisspeptin drives germ cell progression in the anuran amphibian Pelophylax esculentus: a study carried out in ex vivo testes. *Gen. Comp. Endocrinol.,* **2015**, *211*, 81-91. [http://dx.doi.org/10.1016/j.ygcen.2014.11.008] [PMID: 25452028]

[161] Revel, F.G.; Ansel, L.; Klosen, P.; Saboureau, M.; Pévet, P.; Mikkelsen, J.D.; Simonneaux, V. Kisspeptin: a key link to seasonal breeding. *Rev. Endocr. Metab. Disord.,* **2007**, *8*(1), 57-65. [http://dx.doi.org/10.1007/s11154-007-9031-7] [PMID: 17380397]

[162] Fernandez-Fernandez, R.; Martini, A.C.; Navarro, V.M.; Castellano, J.M.; Dieguez, C.; Aguilar, E.; Pinilla, L.; Tena-Sempere, M. Novel signals for the integration of energy balance and reproduction. *Mol. Cell. Endocrinol.,* **2006**, *254-255*, 127-132. [http://dx.doi.org/10.1016/j.mce.2006.04.026] [PMID: 16759792]

[163] Franceschini, I.; Lomet, D.; Cateau, M.; Delsol, G.; Tillet, Y.; Caraty, A. Kisspeptin immunoreactive cells of the ovine preoptic area and arcuate nucleus co-express estrogen receptor alpha. *Neurosci. Lett.,* **2006**, *401*(3), 225-230. [http://dx.doi.org/10.1016/j.neulet.2006.03.039] [PMID: 16621281]

[164] Castellano, J.M.; Navarro, V.M.; Fernández-Fernández, R.; Nogueiras, R.; Tovar, S.; Roa, J.; Vazquez, M.J.; Vigo, E.; Casanueva, F.F.; Aguilar, E.; Pinilla, L.; Dieguez, C.; Tena-Sempere, M. Changes in hypothalamic KiSS-1 system and restoration of pubertal activation of the reproductive axis by kisspeptin in undernutrition. *Endocrinology,* **2005**, *146*(9), 3917-3925. [http://dx.doi.org/10.1210/en.2005-0337] [PMID: 15932928]

[165] Finn, P.D.; Cunningham, M.J.; Pau, K.Y.; Spies, H.G.; Clifton, D.K.; Steiner, R.A. The stimulatory effect of leptin on the neuroendocrine reproductive axis of the monkey. *Endocrinology,* **1998**, *139*(11), 4652-4662. [http://dx.doi.org/10.1210/endo.139.11.6297] [PMID: 9794477]

[166] Wahab, F.; Shahab, M.; Behr, R. The involvement of gonadotropin inhibitory hormone and kisspeptin in the metabolic regulation of reproduction. *J. Endocrinol.,* **2015**, *225*(2), R49-R66. [http://dx.doi.org/10.1530/JOE-14-0688] [PMID: 25957191]

[167] Donato, J., Jr; Cravo, R.M.; Frazão, R.; Gautron, L.; Scott, M.M.; Lachey, J.; Castro, I.A.; Margatho, L.O.; Lee, S.; Lee, C.; Richardson, J.A.; Friedman, J.; Chua, S., Jr; Coppari, R.; Zigman, J.M.; Elmquist, J.K.; Elias, C.F. Leptin's effect on puberty in mice is relayed by the ventral premammillary nucleus and does not require signaling in Kiss1 neurons. *J. Clin. Invest.,* **2011**, *121*(1), 355-368. [http://dx.doi.org/10.1172/JCI45106] [PMID: 21183787]

[168] Luque, R.M.; Kineman, R.D.; Tena-Sempere, M. Regulation of hypothalamic expression of KiSS-1 and GPR54 genes by metabolic factors: analyses using mouse models and a cell line. *Endocrinology,* **2007**, *148*(10), 4601-4611. [http://dx.doi.org/10.1210/en.2007-0500] [PMID: 17595226]

[169] Castellano, J.M.; Navarro, V.M.; Roa, J.; Pineda, R.; Sánchez-Garrido, M.A.; García-Galiano, D.; Vigo, E.; Dieguez, C.; Aguilar, E.; Pinilla, L.; Tena-Sempere, M. Alterations in hypothalamic KiSS-1 system in experimental diabetes: early changes and functional consequences. *Endocrinology,* **2009**, *150*(2), 784-794. [http://dx.doi.org/10.1210/en.2008-0849] [PMID: 18845637]

[170] Dudek, M.; Kołodziejski, P.A.; Pruszyńska-Oszmałek, E.; Sassek, M.; Ziarniak, K.; Nowak, K.W.; Sliwowska, J.H. Effects of high-fat diet-induced obesity and diabetes on Kiss1 and GPR54 expression in the hypothalamic-pituitary-gonadal (HPG) axis and peripheral organs (fat, pancreas and liver) in male rats. *Neuropeptides,* **2016**, *56*, 41-49. [http://dx.doi.org/10.1016/j.npep.2016.01.005] [PMID: 26853724]

[171] Léonhardt, M.; Lesage, J.; Croix, D.; Dutriez-Casteloot, I.; Beauvillain, J.C.; Dupouy, J.P. Effects of perinatal maternal food restriction on pituitary-gonadal axis and plasma leptin level in rat pup at birth and weaning and on timing of puberty. *Biol. Reprod.,* **2003**, *68*(2), 390-400. [http://dx.doi.org/10.1095/biolreprod.102.003269] [PMID: 12533401]

[172] Connor, K.L.; Vickers, M.H.; Beltrand, J.; Meaney, M.J.; Sloboda, D.M. Nature, nurture or nutrition? Impact of maternal nutrition on maternal care, offspring development and reproductive function. *J. Physiol.,* **2012**, *590*(9), 2167-2180. [http://dx.doi.org/10.1113/jphysiol.2011.223305] [PMID: 22411006]

[173] Takumi, K.; Shimada, K.; Iijima, N.; Ozawa, H. Maternal high-fat diet during lactation increases Kiss1 mRNA expression in the arcuate nucleus at weaning and advances puberty onset in female rats. *Neurosci. Res.,* **2015**, *100*, 21-28. [http://dx.doi.org/10.1016/j.neures.2015.06.004] [PMID: 26094983]

[174] Wren, A.M.; Seal, L.J.; Cohen, M.A.; Brynes, A.E.; Frost, G.S.; Murphy, K.G.; Dhillo, W.S.; Ghatei, M.A.; Bloom, S.R. Ghrelin enhances appetite and increases food intake in humans. *J. Clin. Endocrinol. Metab.,* **2001**, *86*(12), 5992. [http://dx.doi.org/10.1210/jcem.86.12.8111] [PMID: 11739476]

[175] Cummings, D.E. Ghrelin and the short- and long-term regulation of appetite and body weight. *Physiol. Behav.,* **2006**, *89*(1), 71-84. [http://dx.doi.org/10.1016/j.physbeh.2006.05.022] [PMID: 16859720]

[176] Tena-Sempere, M. Ghrelin: novel regulator of gonadal function. *J. Endocrinol. Invest.,* **2005**, *28*(5)(Suppl.), 26-29. [PMID: 16114272]

[177] Martini, A.C.; Fernández-Fernández, R.; Tovar, S.; Navarro, V.M.; Vigo, E.; Vazquez, M.J.; Davies, J.S.; Thompson, N.M.; Aguilar, E.; Pinilla, L.; Wells, T.; Dieguez, C.; Tena-Sempere, M. Comparative analysis of the effects of ghrelin and unacylated ghrelin on luteinizing hormone secretion in male rats. *Endocrinology,* **2006**, *147*(5), 2374-2382. [http://dx.doi.org/10.1210/en.2005-1422] [PMID: 16455774]

[178] Fernández-Fernández, R.; Tena-Sempere, M.; Aguilar, E.; Pinilla, L. Ghrelin effects on gonadotropin secretion in male and female rats. *Neurosci. Lett.,* **2004**, *362*(2), 103-107. [http://dx.doi.org/10.1016/j.neulet.2004.03.003] [PMID: 15193764]

[179] Leidy, H.J.; Gardner, J.K.; Frye, B.R.; Snook, M.L.; Schuchert, M.K.; Richard, E.L.; Williams, N.I. Circulating ghrelin is sensitive to changes in body weight during a diet and exercise program in normal-weight young women. *J. Clin. Endocrinol. Metab.,* **2004**, *89*(6), 2659-2664. [http://dx.doi.org/10.1210/jc.2003-031471] [PMID: 15181038]

[180] Ackerman, K.E.; Slusarz, K.; Guereca, G.; Pierce, L.; Slattery, M.; Mendes, N.; Herzog, D.B.; Misra, M. Higher ghrelin and lower leptin secretion are associated with lower LH secretion in young amenorrheic athletes compared with eumenorrheic athletes and controls. *Am. J. Physiol. Endocrinol. Metab.,* **2012**, *302*(7), E800-E806. [http://dx.doi.org/10.1152/ajpendo.00598.2011] [PMID: 22252944]

[181] Fuqua, J.S.; Rogol, A.D. Neuroendocrine alterations in the exercising human: implications for energy homeostasis. *Metabolism,* **2013**, *62*(7), 911-921. [http://dx.doi.org/10.1016/j.metabol.2013.01.016] [PMID: 23415825]

[182] Blasbalg, T.L.; Hibbeln, J.R.; Ramsden, C.E.; Majchrzak, S.F.; Rawlings, R.R. Changes in consumption of omega-3 and omega-6 fatty acids in the United States during the 20th century. *Am. J. Clin. Nutr.,* **2011**, *93*(5), 950-962. [http://dx.doi.org/10.3945/ajcn.110.006643] [PMID: 21367944]

[183] Cascio, M.G. PUFA-derived endocannabinoids: an overview. *Proc. Nutr. Soc.,* **2013**, *72*(4), 451-459. [http://dx.doi.org/10.1017/S0029665113003418] [PMID: 24020830]

[184] Bisogno, T.; Maccarrone, M. Endocannabinoid signaling and its regulation by nutrients. *Biofactors,* **2014**, *40*(4), 373-380. [http://dx.doi.org/10.1002/biof.1167] [PMID: 24753395]

[185] Matias, I.; Gonthier, M.P.; Orlando, P.; Martiadis, V.; De Petrocellis, L.; Cervino, C.; Petrosino, S.; Hoareau, L.; Festy, F.; Pasquali, R.; Roche, R.; Maj, M.; Pagotto, U.; Monteleone, P.; Di Marzo, V. Regulation, function, and dysregulation of endocannabinoids in models of adipose and beta-pancreatic cells and in obesity and hyperglycemia. *J. Clin. Endocrinol. Metab.,* **2006**, *91*(8), 3171-3180. [http://dx.doi.org/10.1210/jc.2005-2679] [PMID: 16684820]

[186] Côté, M.; Matias, I.; Lemieux, I.; Petrosino, S.; Alméras, N.; Després, J.P.; Di Marzo, V. Circulating endocannabinoid levels, abdominal adiposity and related cardiometabolic risk factors in obese men. *Int. J. Obes.,* **2007**, *31*(4), 692-699. [http://dx.doi.org/10.1038/sj.ijo.0803539] [PMID: 17224929]

[187] Williams, C.M.; Kirkham, T.C. Anandamide induces overeating: mediation by central cannabinoid (CB1) receptors. *Psychopharmacology (Berl.),* **1999**, *143*(3), 315-317. [http://dx.doi.org/10.1007/s002130050953] [PMID: 10353436]

[188] Cristino, L.; Becker, T.; Di Marzo, V. Endocannabinoids and energy homeostasis: an update. *Biofactors,* **2014**, *40*(4), 389-397. [http://dx.doi.org/10.1002/biof.1168] [PMID: 24752980]

[189] Di Marzo, V.; Côté, M.; Matias, I.; Lemieux, I.; Arsenault, B.J.; Cartier, A.; Piscitelli, F.; Petrosino, S.; Alméras, N.; Després, J.P.

Changes in plasma endocannabinoid levels in viscerally obese men following a 1 year lifestyle modification programme and waist circumference reduction: associations with changes in metabolic risk factors. *Diabetologia,* **2009**, *52*(2), 213-217. [http://dx.doi.org/10.1007/s00125-008-1178-6] [PMID: 18972095]

[190] Quarta, C.; Bellocchio, L.; Mancini, G.; Mazza, R.; Cervino, C.; Braulke, L.J.; Fekete, C.; Latorre, R.; Nanni, C.; Bucci, M.; Clemens, L.E.; Heldmaier, G.; Watanabe, M.; Leste-Lassere, T.; Maitre, M.; Tedesco, L.; Fanelli, F.; Reuss, S.; Klaus, S.; Srivastava, R.K.; Monory, K.; Valerio, A.; Grandis, A.; De Giorgio, R.; Pasquali, R.; Nisoli, E.; Cota, D.; Lutz, B.; Marsicano, G.; Pagotto, U. CB(1) signaling in forebrain and sympathetic neurons is a key determinant of endocannabinoid actions on energy balance. *Cell Metab.,* **2010**, *11*(4), 273-285. [http://dx.doi.org/10.1016/j.cmet.2010.02.015] [PMID: 20374960]

[191] Ravinet Trillou, C.; Delgorge, C.; Menet, C.; Arnone, M.; Soubrié, P. CB1 cannabinoid receptor knockout in mice leads to leanness, resistance to diet-induced obesity and enhanced leptin sensitivity. *Int. J. Obes. Relat. Metab. Disord.,* **2004**, *28*(4), 640-648. [http://dx.doi.org/10.1038/sj.ijo.0802583] [PMID: 14770190]

[192] Després, J.P.; Golay, A.; Sjöström, L. Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N. Engl. J. Med.,* **2005**, *353*(20), 2121-2134. [http://dx.doi.org/10.1056/NEJMoa044537] [PMID: 16291982]

[193] Kim, J.; Li, Y.; Watkins, B.A. Fat to treat fat: emerging relationship between dietary PUFA, endocannabinoids, and obesity. *Prostaglandins Other Lipid Mediat.,* **2013**, *104-105*, 32-41. [http://dx.doi.org/10.1016/j.prostaglandins.2012.11.005] [PMID: 23466458]

[194] Kim, H.Y.; Spector, A.A. Synaptamide, endocannabinoid-like derivative of docosahexaenoic acid with cannabinoid-independent function. *Prostaglandins Leukot. Essent. Fatty Acids,* **2013**, *88*(1), 121-125. [http://dx.doi.org/10.1016/j.plefa.2012.08.002] [PMID: 22959887]

[195] Batetta, B.; Griinari, M.; Carta, G.; Murru, E.; Ligresti, A.; Cordeddu, L.; Giordano, E.; Sanna, F.; Bisogno, T.; Uda, S.; Collu, M.; Bruheim, I.; Di Marzo, V.; Banni, S. Endocannabinoids may mediate the ability of (n-3) fatty acids to reduce ectopic fat and inflammatory mediators in obese Zucker rats. *J. Nutr.,* **2009**, *139*(8), 1495-1501. [http://dx.doi.org/10.3945/jn.109.104844] [PMID: 19549757]

[196] Osei-Hyiaman, D.; Depetrillo, M.; Harvey-White, J.; Bannon, A.W.; Cravatt, B.F.; Kuhar, M.J.; Mackie, K.; Palkovits, M.; Kunos, G. Cocaine- and amphetamine-related transcript is involved in the orexigenic effect of endogenous anandamide. *Neuroendocrinology,* **2005**, *81*(4), 273-282. [http://dx.doi.org/10.1159/000087925] [PMID: 16131814]

[197] Suglia, A.; Chianese, R.; Migliaccio, M.; Ambrosino, C.; Fasano, S.; Pierantoni, R.; Cobellis, G.; Chioccarelli, T. Bisphenol A induces hypothalamic down-regulation of the the cannabinoid receptor 1 and anorexigenic effects in male mice. *Pharmacol. Res.,* **2016**, *113*(Pt A), 376-383. [http://dx.doi.org/10.1016/j.phrs.2016.09.005] [PMID: 27641926]

[198] Bellocchio, L.; Lafenêtre, P.; Cannich, A.; Cota, D.; Puente, N.; Grandes, P.; Chaouloff, F.; Piazza, P.V.; Marsicano, G. Bimodal control of stimulated food intake by the endocannabinoid system. *Nat. Neurosci.,* **2010**, *13*(3), 281-283. [http://dx.doi.org/10.1038/nn.2494] [PMID: 20139974]

[199] Di Marzo, V.; Goparaju, S.K.; Wang, L.; Liu, J.; Bátkai, S.; Járai, Z.; Fezza, F.; Miura, G.I.; Palmiter, R.D.; Sugiura, T.; Kunos, G. Leptin-regulated endocannabinoids are involved in maintaining food intake. *Nature,* **2001**, *410*(6830), 822-825. [http://dx.doi.org/10.1038/35071088] [PMID: 11298451]

[200] Cani, P.D.; Montoya, M.L.; Neyrinck, A.M.; Delzenne, N.M.; Lambert, D.M. Potential modulation of plasma ghrelin and glucagon-like peptide-1 by anorexigenic cannabinoid compounds, SR141716A (rimonabant) and oleoylethanolamide. *Br. J. Nutr.,* **2004**, *92*(5), 757-761. [http://dx.doi.org/10.1079/BJN20041256] [PMID: 15533263]

[201] Kirkham, T.C.; Williams, C.M.; Fezza, F.; Di Marzo, V. Endocannabinoid levels in rat limbic forebrain and hypothalamus in relation to fasting, feeding and satiation: stimulation of eating by 2-arachidonoyl glycerol. *Br. J. Pharmacol.,* **2002**, *136*(4), 550-557. [http://dx.doi.org/10.1038/sj.bjp.0704767] [PMID: 12055133]

[202] Kola, B.; Farkas, I.; Christ-Crain, M.; Wittmann, G.; Lolli, F.; Amin, F.; Harvey-White, J.; Liposits, Z.; Kunos, G.; Grossman, A.B.; Fekete, C.; Korbonits, M. The orexigenic effect of ghrelin is mediated through central activation of the endogenous cannabinoid system. *PLoS One,* **2008**, *3*(3), e1797. [http://dx.doi.org/10.1371/journal.pone.0001797] [PMID: 18335063]

[203] Gammon, C.M.; Freeman, G.M., Jr; Xie, W.; Petersen, S.L.; Wetsel, W.C. Regulation of gonadotropin-releasing hormone secretion by cannabinoids. *Endocrinology,* **2005**, *146*(10), 4491-4499. [http:// dx.doi.org/10.1210/en.2004-1672] [PMID: 16020480]

[204] Scorticati, C.; Fernández-Solari, J.; De Laurentiis, A.; Mohn, C.; Prestifilippo, J.P.; Lasaga, M.; Seilicovich, A.; Billi, S.; Franchi, A.; McCann, S.M.; Rettori, V. The inhibitory effect of anandamide on luteinizing hormone-releasing hormone secretion is reversed by estrogen. *Proc. Natl. Acad. Sci. USA,* **2004**, *101*(32), 11891-11896. [http://dx.doi.org/10.1073/pnas.0404366101] [PMID: 15280536]

[205] Meccariello, R.; Chianese, R.; Cacciola, G.; Cobellis, G.; Pierantoni, R.; Fasano, S. Type-1 cannabinoid receptor expression in the frog, Rana esculenta, tissues: a possible involvement in the regulation of testicular activity. *Mol. Reprod. Dev.,* **2006**, *73*(5), 551-558. [http://dx.doi.org/10.1002/mrd.20434] [PMID: 16485273]

[206] Meccariello, R.; Franzoni, M.F.; Chianese, R.; Cottone, E.; Scarpa, D.; Donna, D.; Cobellis, G.; Guastalla, A.; Pierantoni, R.; Fasano, S. Interplay between the endocannabinoid system and GnRH-I in the forebrain of the anuran amphibian *Rana esculenta*. *Endocrinology,* **2008**, *149*(5), 2149-2158. [http://dx.doi.org/10.1210/en.2007-1357] [PMID: 18218699]

[207] Chianese, R.; Ciaramella, V.; Fasano, S.; Pierantoni, R.; Meccariello, R. Anandamide modulates the expression of GnRH-II and GnRHRs in frog, Rana esculenta, diencephalon. *Gen. Comp. Endocrinol.,* **2011**, *173*(3), 389-395. [http://dx.doi.org/10.1016/j.ygcen.2011.07.001] [PMID: 21802420]

[208] Chianese, R.; Ciaramella, V.; Scarpa, D.; Fasano, S.; Pierantoni, R.; Meccariello, R. Anandamide regulates the expression of GnRH1, GnRH2, and GnRH-Rs in frog testis. *Am. J. Physiol. Endocrinol. Metab.,* **2012**, *303*(4), E475-E487. [http://dx.doi.org/10.1152/ajpendo.00086.2012] [PMID: 22669247]

[209] Chianese, R.; Ciaramella, V.; Scarpa, D.; Fasano, S.; Pierantoni, R.; Meccariello, R. Endocannabinoids and endovanilloids: a possible balance in the regulation of the testicular GnRH signalling. *Int. J. Endocrinol.,* **2013**, *2013*, 904748. [http://dx.doi.org/10.1155/2013/904748] [PMID: 24072997]

[210] Ciaramella, V.; Meccariello, R.; Chioccarelli, T.; Sirleto, M.; Fasano, S.; Pierantoni, R.; Chianese, R. Anandamide acts *in vivo*kisspeptin in the regulation of testicular activity of the frog, Pelophylax esculentus. *Mol. Cell. Endocrinol.,* **2016**, *420*, 75-84. [http://dx.doi.org/10.1016/j.mce.2015.11.011] [PMID: 26586207]

[211] Wenger, T.; Ledent, C.; Csernus, V.; Gerendai, I. The central cannabinoid receptor inactivation suppresses endocrine reproductive functions. *Biochem. Biophys. Res. Commun.,* **2001**, *284*(2), 363-368. [http://dx.doi.org/10.1006/bbrc.2001.4977] [PMID: 11394887]

[212] Chianese, R.; Ciaramella, V.; Fasano, S.; Pierantoni, R.; Meccariello, R. Hypothalamus-pituitary axis: an obligatory target for endocannabinoids to inhibit steroidogenesis in frog testis. *Gen. Comp. Endocrinol.,* **2014**, *205*, 88-93. [http://dx.doi.org/10.1016/j.ygcen.2014.02.010] [PMID: 24566122]

[213] Meccariello, R.; Battista, N.; Bradshawa, H.B.; Wang, H. Endocannabinoids and reproduction. *Int. J. Endocrinol.,* **2014**, *2014*, 378069. [http://dx.doi.org/10.1155/2014/378069] [PMID: 24575130]

[214] Cacciola, G.; Chioccarelli, T.; Fasano, S.; Pierantoni, R.; Cobellis, G. Estrogens and spermiogenesis: new insights from type 1 cannabinoid receptor knockout mice. *Int. J. Endocrinol.,* **2013**, *2013*, 501350. [http://dx.doi.org/10.1155/2013/501350] [PMID: 24324492]

[215] Cacciola, G.; Chioccarelli, T.; Altucci, L.; Ledent, C.; Mason, J.I.; Fasano, S.; Pierantoni, R.; Cobellis, G. Low 17beta-estradiol levels in CNR1 knock-out mice affect spermatid chromatin remodeling by interfering with chromatin reorganization. *Biol. Reprod.,* **2013**, *88*(6), 152. [http://dx.doi.org/10.1095/biolreprod.112.105726] [PMID: 23677985]

[216] Karamikheirabad, M.; Behzadi, G.; Faghihi, M.; Raoofian, R.; Ejtemaei Mehr, S.; Zuure, W.A.; Sadeghipour, H.R. A role for endocannabinoids in acute stress-induced suppression of the hypothalamic-pituitary-gonadal axis in male rats. *Clin. Exp. Reprod. Med.,* **2013**, *40*(4), 155-162. [http://dx.doi.org/10.5653/cerm.2013.40.4.155] [PMID: 24505561]

[217] Joffre, C.; Nadjar, A.; Lebbadi, M.; Calon, F.; Layé, S. n-3 LCPUFA improves cognition: the young, the old and the sick.

Prostaglandins Leukot. Essent. Fatty Acids, **2014**, *91*(1-2), 1-20. [http://dx.doi.org/10.1016/j.plefa.2014.05.001] [PMID: 24908517]

[218] Bazan, N.G. Cell survival matters: docosahexaenoic acid signaling, neuroprotection and photoreceptors. *Trends Neurosci.,* **2006**, *29*(5), 263-271. [http://dx.doi.org/10.1016/j.tins.2006.03.005] [PMID: 16580739]

[219] Calon, F.; Cole, G. Neuroprotective action of omega-3 polyunsaturated fatty acids against neurodegenerative diseases: evidence from animal studies. *Prostaglandins Leukot. Essent. Fatty Acids,* **2007**, *77*(5-6), 287-293. [http://dx.doi.org/10.1016/j.plefa.2007.10.019] [PMID: 18037281]

[220] Dyall, S.C.; Michael-Titus, A.T. Neurological benefits of omega-3 fatty acids. *Neuromol. Med.,* **2008**, *10*(4), 219-235. [http://dx.doi.org/10.1007/s12017-008-8036-z] [PMID: 18543124]

[221] Carrié, I.; Abellan Van Kan, G.; Rolland, Y.; Gillette-Guyonnet, S.; Vellas, B. PUFA for prevention and treatment of dementia? *Curr. Pharm. Des.,* **2009**, *15*(36), 4173-4185. [http://dx.doi.org/10.2174/138161209789909764] [PMID: 20041819]

[222] Cunnane, S.C.; Chouinard-Watkins, R.; Castellano, C.A.; Barberger-Gateau, P. Docosahexaenoic acid homeostasis, brain aging and Alzheimer's disease: Can we reconcile the evidence? *Prostaglandins Leukot. Essent. Fatty Acids,* **2013**, *88*(1), 61-70. [http://dx.doi.org/10.1016/j.plefa.2012.04.006] [PMID: 22575581]

[223] Salem, N., Jr; Vandal, M.; Calon, F. The benefit of docosahexaenoic acid for the adult brain in aging and dementia. *Prostaglandins Leukot. Essent. Fatty Acids,* **2015**, *92*, 15-22. [http://dx.doi.org/10.1016/j.plefa.2014.10.003] [PMID: 25457546]

[224] Dyall, S.C. Long-chain omega-3 fatty acids and the brain: a review of the independent and shared effects of EPA, DPA and DHA. *Front. Aging Neurosci.,* **2015**, *7*, 52. [http://dx.doi.org/10.3389/fnagi.2015.00052] [PMID: 25954194]

[225] Denis, I.; Potier, B.; Vancassel, S.; Heberden, C.; Lavialle, M. Omega-3 fatty acids and brain resistance to ageing and stress: body of evidence and possible mechanisms. *Ageing Res. Rev.,* **2013**, *12*(2), 579-594. [http://dx.doi.org/10.1016/j.arr.2013.01.007] [PMID: 23395782]

[226] Palacios-Pelaez, R.; Lukiw, W.J.; Bazan, N.G. Omega-3 essential fatty acids modulate initiation and progression of neurodegenerative disease. *Mol. Neurobiol.,* **2010**, *41*(2-3), 367-374. [http://dx.doi.org/10.1007/s12035-010-8139-z] [PMID: 20467837]

[227] Cole, G.M.; Frautschy, S.A. DHA may prevent age-related dementia. *J. Nutr.,* **2010**, *140*(4), 869-874. [http://dx.doi.org/10.3945/jn.109.113910] [PMID: 20181786]

[228] Joffre, C.; Grégoire, S.; De Smedt, V.; Acar, N.; Bretillon, L.; Nadjar, A.; Layé, S. Modulation of brain PUFA content in different experimental models of mice. *Prostaglandins Leukot. Essent. Fatty Acids,* **2016**, *114*, 1-10. [http://dx.doi.org/10.1016/j.plefa.2016.09.003] [PMID: 27926457]

[229] Plourde, M.; Cunnane, S.C. Extremely limited synthesis of long chain polyunsaturates in adults: implications for their dietary essentiality and use as supplements. *Appl. Physiol. Nutr. Metab.,* **2007**, *32*(4), 619-634. [http://dx.doi.org/10.1139/H07-034] [PMID: 17622276]

[230] DeMar, J.C. Jr; Lee, H.J.; Ma, K.; Chang, L.; Bell, J.M.; Rapoport, S.I.; Bazinet, R.P. Brain elongation of linoleic acid is a negligible source of the arachidonate in brain phospholipids of adult rats. *Biochim. Biophys Acta,* **2006**, *1761*, 1050-1059. [PMID: 16920015]

[231] Alashmali, S.M.; Hopperton, K.E.; Bazinet, R.P. Lowering dietary n-6 polyunsaturated fatty acids: interaction with brain arachidonic and docosahexaenoic acids. *Curr. Opin. Lipidol.,* **2016**, *27*(1), 54-66. [http://dx.doi.org/10.1097/MOL.0000000000000255] [PMID: 26709472]

[232] Domenichiello, A.F.; Kitson, A.P.; Chen, C.T.; Trépanier, M.O.; Stavro, P.M.; Bazinet, R.P. The effect of linoleic acid on the whole body synthesis rates of polyunsaturated fatty acids from α-linolenic acid and linoleic acid in free-living rats. *J. Nutr. Biochem.,* **2016**, *30*, 167-176. [http://dx.doi.org/10.1016/j.jnutbio.2015.11.016] [PMID: 27012633]

[233] Minihane, A.M. Impact of genotype on EPA and DHA status and responsiveness to increased intakes. *Nutrients,* **2016**, *8*(3), 123. [http://dx.doi.org/10.3390/nu8030123] [PMID: 26950146]

[234] Kitson, A.P.; Stroud, C.K.; Stark, K.D. Elevated production of docosahexaenoic acid in females: potential molecular mechanisms. *Lipids,* **2010**, *45*(3), 209-224. [http://dx.doi.org/10.1007/s11745-010-3391-6] [PMID: 20151220]

[235] Decsi, T.; Kennedy, K. Sex-specific differences in essential fatty acid metabolism. *Am. J. Clin. Nutr.,* **2011**, *94*(6)(Suppl.), 1914S-1919S. [http://dx.doi.org/10.3945/ajcn.110.000893] [PMID: 22089435]

[236] Song, B.J.; Elbert, A.; Rahman, T.; Orr, S.K.; Chen, C.T.; Febbraio, M.; Bazinet, R.P. Genetic ablation of CD36 does not alter mouse brain polyunsaturated fatty acid concentrations. *Lipids,* **2010**, *45*(4), 291-299. [http://dx.doi.org/10.1007/s11745-010-3398-z] [PMID: 20306148]

[237] Nguyen, L.N.; Ma, D.; Shui, G.; Wong, P.; Cazenave-Gassiot, A.; Zhang, X.; Wenk, M.R.; Goh, E.L.; Silver, D.L. Mfsd2a is a transporter for the essential omega-3 fatty acid docosahexaenoic acid. *Nature,* **2014**, *509*(7501), 503-506. [http://dx.doi.org/10.1038/nature13241] [PMID: 24828044]

[238] Rice, D.S.; Calandria, J.M.; Gordon, W.C.; Jun, B.; Zhou, Y.; Gelfman, C.M.; Li, S.; Jin, M.; Knott, E.J.; Chang, B.; Abuin, A.; Issa, T.; Potter, D.; Platt, K.A.; Bazan, N.G. Adiponectin receptor 1 conserves docosahexaenoic acid and promotes photoreceptor cell survival. *Nat. Commun.,* **2015**, *6*, 6228. [http://dx.doi.org/10.1038/ncomms7228] [PMID: 25736573]

[239] Vauzour, D.; Martinsen, A.; Layé, S. Neuroinflammatory processes in cognitive disorders: Is there a role for flavonoids and n-3 polyunsaturated fatty acids in counteracting their detrimental effects? *Neurochem. Int.,* **2015**, *89*, 63-74. [http://dx.doi.org/10.1016/j.neuint.2015.08.004] [PMID: 26260547]

[240] Burke, J.E.; Dennis, E.A. Phospholipase A2 structure/function, mechanism, and signaling. *J. Lipid Res.,* **2009**, *50*(Suppl.), S237-S242. [http://dx.doi.org/10.1194/jlr.R800033-JLR200] [PMID: 19011112]

[241] Serhan, C.N. Pro-resolving lipid mediators are leads for resolution physiology. *Nature,* **2014**, *510*(7503), 92-101. [http://dx.doi.org/10.1038/nature13479] [PMID: 24899309]

[242] Heneka, M.T.; Golenbock, D.T.; Latz, E. Innate immunity in Alzheimer's disease. *Nat. Immunol.,* **2015**, *16*(3), 229-236. [http://dx.doi.org/10.1038/ni.3102] [PMID: 25689443]

[243] Perry, V.H.; Holmes, C. Microglial priming in neurodegenerative disease. *Nat. Rev. Neurol.,* **2014**, *10*(4), 217-224. [http://dx.doi.org/10.1038/nrneurol.2014.38] [PMID: 24638131]

[244] Hanisch, U.K.; Kettenmann, H. Microglia: active sensor and versatile effector cells in the normal and pathologic brain. *Nat. Neurosci.,* **2007**, *10*(11), 1387-1394. [http://dx.doi.org/10.1038/nn1997] [PMID: 17965659]

[245] Ransohoff, R.M.; Perry, V.H. Microglial physiology: unique stimuli, specialized responses. *Annu. Rev. Immunol.,* **2009**, *27*, 119-145. [http://dx.doi.org/10.1146/annurev.immunol.021908.132528] [PMID: 19302036]

[246] Tremblay, M.È.; Stevens, B.; Sierra, A.; Wake, H.; Bessis, A.; Nimmerjahn, A. The role of microglia in the healthy brain. *J. Neurosci.,* **2011**, *31*(45), 16064-16069. [http://dx.doi.org/10.1523/JNEUROSCI.4158-11.2011] [PMID: 22072657]

[247] Hong, S.; Dissing-Olesen, L.; Stevens, B. New insights on the role of microglia in synaptic pruning in health and disease. *Curr. Opin. Neurobiol.,* **2016**, *36*, 128-134. [http://dx.doi.org/10.1016/j.conb.2015.12.004] [PMID: 26745839]

[248] Delpech, J.C.; Madore, C.; Nadjar, A.; Joffre, C.; Wohleb, E.S.; Layé, S. Microglia in neuronal plasticity: Influence of stress. *Neuropharmacology,* **2015**, *96*(Pt A), 19-28. [http://dx.doi.org/10.1016/j.neuropharm.2014.12.034] [PMID: 25582288]

[249] Nadjar, A.; Leyrolle, Q.; Joffre, C.; Layé, S. Bioactive lipids as new class of microglial modulators: When nutrition meets neuroimunology. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2013**, *104-105*, 32-41. [PMID: 27392882]

[250] Madore, C.; Leyrolle, Q.; Lacabanne, C.; Benmammar-Badel, A.; Joffre, C.; Nadjar, A.; Layé, S. Neuroinflammation in autism: Plausible role of maternal inflammation, dietary omega 3, and microbiota. *Neural. Plast,* **2016**, *2016*, 3597209. [http://dx.doi.org/10.1155/2016/3597209] [PMID: 27840741]

[251] Ransohoff, R.M. How neuroinflammation contributes to neurodegeneration. *Science,* **2016**, *353*(6301), 777-783. [http://dx.doi.org/10.1126/science.aag2590] [PMID: 27540165]

[252] Lukiw, W.J.; Bazan, N.G. Neuroinflammatory signaling upregulation in Alzheimer's disease. *Neurochem. Res.,* **2000**, *25*(9-10), 1173-1184. [http://dx.doi.org/10.1023/A:1007627725251] [PMID: 11059791]

[253] Sil, S.; Ghosh, T. Role of cox-2 mediated neuroinflammation on the neurodegeneration and cognitive impairments in colchicine in-

duced rat model of Alzheimer's Disease. *J. Neuroimmunol.,* **2016**, *291*, 115-124. [http://dx.doi.org/10.1016/j.jneuroim.2015.12.003] [PMID: 26857505]

[254] Cunningham, C.; Skelly, D.T. Non-steroidal anti-inflammatory drugs and cognitive function: are prostaglandins at the heart of cognitive impairment in dementia and delirium? *J. Neuroimmune Pharmacol.,* **2012**, *7*(1), 60-73. [http://dx.doi.org/10.1007/s11481-011-9312-5] [PMID: 21932048]

[255] Etminan, M.; Gill, S.; Samii, A. Effect of non-steroidal anti-inflammatory drugs on risk of Alzheimer's disease: systematic review and meta-analysis of observational studies. *BMJ,* **2003**, *327* (7407), 128. [http://dx.doi.org/10.1136/bmj.327.7407.128] [PMID: 12869452]

[256] Johansson, J.U.; Woodling, N.S.; Wang, Q.; Panchal, M.; Liang, X.; Trueba-Saiz, A.; Brown, H.D.; Mhatre, S.D.; Loui, T.; Andreasson, K.I. Prostaglandin signaling suppresses beneficial microglial function in Alzheimer's disease models. *J. Clin. Invest.,* **2015**, *125*(1), 350-364. [http://dx.doi.org/10.1172/JCI77487] [PMID: 25485684]

[257] Manev, H.; Chen, H.; Dzitoyeva, S.; Manev, R. Cyclooxygenases and 5-lipoxygenase in Alzheimer's disease. *Prog. Neuropsychopharmacol. Biol. Psychiatry,* **2011**, *35*(2), 315-319. [http://dx.doi.org/10.1016/j.pnpbp.2010.07.032] [PMID: 20691748]

[258] Czapski, G.A.; Czubowicz, K.; Strosznajder, J.B.; Strosznajder, R.P. The Lipoxygenases: Their Regulation and Implication in Alzheimer's Disease. *Neurochem. Res.,* **2016**, *41*(1-2), 243-257. [http://dx.doi.org/10.1007/s11064-015-1776-x] [PMID: 26677076]

[259] Kong, W.; Hooper, K.M.; Ganea, D. The natural dual cyclooxygenase and 5-lipoxygenase inhibitor flavocoxid is protective in EAE through effects on Th1/Th17 differentiation and macrophage/microglia activation. *Brain Behav. Immun.,* **2016**, *53*, 59-71. [http://dx.doi.org/10.1016/j.bbi.2015.11.002] [PMID: 26541818]

[260] Bazan, N.G. The docosanoid neuroprotectin D1 induces homeostatic regulation of neuroinflammation and cell survival. *Prostaglandins Leukot. Essent. Fatty Acids,* **2013**, *88*(1), 127-129. [http://dx.doi.org/10.1016/j.plefa.2012.08.008] [PMID: 23022417]

[261] De Smedt-Peyrusse, V.; Sargueil, F.; Moranis, A.; Harizi, H.; Mongrand, S.; Layé, S. Docosahexaenoic acid prevents lipopolysaccharide-induced cytokine production in microglial cells by inhibiting lipopolysaccharide receptor presentation but not its membrane subdomain localization. *J. Neurochem.,* **2008**, *105*(2), 296-307. [http://dx.doi.org/10.1111/j.1471-4159.2007.05129.x] [PMID: 18021297]

[262] Madore, C.; Nadjar, A.; Delpech, J.C.; Sere, A.; Aubert, A.; Portal, C.; Joffre, C.; Layé, S. Nutritional n-3 PUFAs deficiency during perinatal periods alters brain innate immune system and neuronal plasticity-associated genes. *Brain Behav. Immun.*, **2014**, *41*, 22-31. [http://dx.doi.org/10.1016/j.bbi.2014.03.021] [PMID: 24735929]

[263] Rey, C.; Nadjar, A.; Buaud, B.; Vaysse, C.; Aubert, A.; Pallet, V.; Layé, S.; Joffre, C. Resolvin D1 and E1 promote resolution of inflammation in microglial cells *in vitro*. *Brain Behav. Immun.,* **2016**, *55*, 249-259. [http://dx.doi.org/10.1016/j.bbi.2015.12.013] [PMID: 26718448]

[264] Orr, S.K.; Palumbo, S.; Bosetti, F.; Mount, H.T.; Kang, J.X.; Greenwood, C.E.; Ma, D.W.; Serhan, C.N.; Bazinet, R.P. Unesterified docosahexaenoic acid is protective in neuroinflammation. *J. Neurochem.,* **2013**, *127*(3), 378-393. [http://dx.doi.org/10.1111/jnc.12392] [PMID: 23919613]

[265] Zhu, M.; Wang, X.; Hjorth, E.; Colas, R.A.; Schroeder, L.; Granholm, A.C.; Serhan, C.N.; Schultzberg, M. Pro-resolving lipid mediators improve neuronal survival and increase Aβ42 phagocytosis. *Mol. Neurobiol.,* **2016**, *53*(4), 2733-2749. [http://dx.doi.org/10.1007/s12035-015-9544-0] [PMID: 26650044]

[266] Freund-Levi, Y.; Hjorth, E.; Lindberg, C.; Cederholm, T.; Faxen-Irving, G.; Vedin, I.; Palmblad, J.; Wahlund, L.O.; Schultzberg, M.; Basun, H.; Eriksdotter Jönhagen, M. Effects of omega-3 fatty acids on inflammatory markers in cerebrospinal fluid and plasma in Alzheimer's disease: the OmegAD study. *Dement. Geriatr. Cogn. Disord.,* **2009**, *27*(5), 481-490. [http://dx.doi.org/10.1159/000218081] [PMID: 19439966]

[267] Wang, X.; Puerta, E.; Cedazo-Minguez, A.; Hjorth, E.; Schultzberg, M. Insufficient resolution response in the hippocampus of a senescence-accelerated mouse model--SAMP8. *J. Mol. Neurosci.,* **2015**, *55*(2), 396-405. [http://dx.doi.org/10.1007/s12031-014-0346-z] [PMID: 24913689]

[268] Yuki, D.; Sugiura, Y.; Zaima, N.; Akatsu, H.; Takei, S.; Yao, I.; Maesako, M.; Kinoshita, A.; Yamamoto, T.; Kon, R.; Sugiyama, K.; Setou, M. DHA-PC and PSD-95 decrease after loss of synaptophysin and before neuronal loss in patients with Alzheimer's disease. *Sci. Rep.,* **2014**, *4*, 7130. [http://dx.doi.org/10.1038/srep07130] [PMID: 25410733]

[269] Hjorth, E.; Zhu, M.; Toro, V.C.; Vedin, I.; Palmblad, J.; Cederholm, T.; Freund-Levi, Y.; Faxen-Irving, G.; Wahlund, L.O.; Basun, H.; Eriksdotter, M.; Schultzberg, M. Omega-3 fatty acids enhance phagocytosis of Alzheimer's disease-related amyloid-β42 by human microglia and decrease inflammatory markers. *J. Alzheimers Dis.,* **2013**, *35*(4), 697-713. [PMID: 23481688]

[270] Hopperton, K.E.; Trépanier, M.O.; Giuliano, V.; Bazinet, R.P. Brain omega-3 polyunsaturated fatty acids modulate microglia cell number and morphology in response to intracerebroventricular amyloid-β 1-40 in mice. *J. Neuroinflammation,* **2016**, *13*(1), 257. [http://dx.doi.org/10.1186/s12974-016-0721-5] [PMID: 27688126]

[271] Di Marzo, V.; Stella, N.; Zimmer, A. Endocannabinoid signalling and the deteriorating brain. *Nat. Rev. Neurosci.,* **2015**, *16*(1), 30-42. [http://dx.doi.org/10.1038/nrn3876] [PMID: 25524120]

[272] Alhouayek, M.; Muccioli, G.G. COX-2-derived endocannabinoid metabolites as novel inflammatory mediators. *Trends Pharmacol. Sci.,* **2014**, *35*(6), 284-292. [http://dx.doi.org/10.1016/j.tips.2014.03.001] [PMID: 24684963]

[273] Lee, J.W.; Huang, B.X.; Kwon, H.; Rashid, M.A.; Kharebava, G.; Desai, A.; Patnaik, S.; Marugan, J.; Kim, H.Y. Orphan GPR110 (ADGRF1) targeted by N-docosahexaenoylethanolamine in development of neurons and cognitive function. *Nat. Commun.,* **2016**, *7*, 13123. [http://dx.doi.org/10.1038/ncomms13123] [PMID: 27759003]

[274] Maccarrone, M.; Bab, I.; Bíró, T.; Cabral, G.A.; Dey, S.K.; Di Marzo, V.; Konje, J.C.; Kunos, G.; Mechoulam, R.; Pacher, P.; Sharkey, K.A.; Zimmer, A. Endocannabinoid signaling at the periphery: 50 years after THC. *Trends Pharmacol. Sci.,* **2015**, *36*(5), 277-296. [http://dx.doi.org/10.1016/j.tips.2015.02.008] [PMID: 25796370]

[275] Larrieu, T.; Madore, C.; Joffre, C.; Layé, S. Nutritional n-3 polyunsaturated fatty acids deficiency alters cannabinoid receptor signaling pathway in the brain and associated anxiety-like behavior in mice. *J. Physiol. Biochem.,* **2012**, *68*(4), 671-681. [http://dx.doi.org/10.1007/s13105-012-0179-6] [PMID: 22707188]

[276] Castillo, P.E.; Younts, T.J.; Chávez, A.E.; Hashimotodani, Y. Endocannabinoid signaling and synaptic function. *Neuron,* **2012**, *76*(1), 70-81. [http://dx.doi.org/10.1016/j.neuron.2012.09.020] [PMID: 23040807]

[277] Han, J.; Kesner, P.; Metna-Laurent, M.; Duan, T.; Xu, L.; Georges, F.; Koehl, M.; Abrous, D.N.; Mendizabal-Zubiaga, J.; Grandes, P.; Liu, Q.; Bai, G.; Wang, W.; Xiong, L.; Ren, W.; Marsicano, G.; Zhang, X. Acute cannabinoids impair working memory through astroglial CB1 receptor modulation of hippocampal LTD. *Cell,* **2012**, *148*(5), 1039-1050. [http://dx.doi.org/10.1016/j.cell.2012.01.037] [PMID: 22385967]

[278] Bosch-Bouju, C.; Layé, S. Dietary omega-6/omega-3 and endocannabinoids: Implications for brain health and diseases. *Cannabinoids in Health and Disease.,* **2016**, 111-142. [http://dx.doi.org/10.5772/62498]

[279] Yassine, H.N.; Braskie, M.N.; Mack, W.J.; Castor, K.J.; Fonteh, A.N.; Schneider, L.S.; Harrington, M.G.; Chui, H.C. Association of docosahexaenoic acid supplementation with alzheimer disease stage in apolipoprotein E ε4 carriers: A review. *JAMA Neurol.,* **2017**, *74*(3), 339-347. [http://dx.doi.org/10.1001/jamaneurol.2016.4899] [PMID: 28114437]

[280] Quinn, J.F.; Raman, R.; Thomas, R.G.; Yurko-Mauro, K.; Nelson, E.B.; Van Dyck, C.; Galvin, J.E.; Emond, J.; Jack, C.R., Jr; Weiner, M.; Shinto, L.; Aisen, P.S. Docosahexaenoic acid supplementation and cognitive decline in Alzheimer disease: a randomized trial. *JAMA,* **2010**, *304*(17), 1903-1911. [http://dx.doi.org/10.1001/jama.2010.1510] [PMID: 21045096]

[281] Yurko-Mauro, K.; Alexander, D.D.; Van Elswyk, M.E. Docosahexaenoic acid and adult memory: a systematic review and meta-analysis. *PLoS One,* **2015**, *10*(3), e0120391. [http://dx.doi.org/10.1371/journal.pone.0120391] [PMID: 25786262]

[282] Jackson, P.A.; Deary, M.E.; Reay, J.L.; Scholey, A.B.; Kennedy, D.O. No effect of 12 weeks' supplementation with 1 g DHA-rich or EPA-rich fish oil on cognitive function or mood in healthy young adults aged 18-35 years. *Br. J. Nutr.,* **2012**, *107*(8), 1232-

1243. [http://dx.doi.org/10.1017/S000711451100403X] [PMID: 21864417]

[283] Benton, D.; Donohoe, R.T.; Clayton, D.E.; Long, S.J. Supplementation with DHA and the psychological functioning of young adults. *Br. J. Nutr.,* **2013**, *109*(1), 155-161. [http://dx.doi.org/10.1017/S0007114512000566] [PMID: 22715808]

[284] Chew, E.Y.; Clemons, T.E.; Agrón, E.; Launer, L.J.; Grodstein, F.; Bernstein, P.S. Effect of omega-3 fatty acids, lutein/zeaxanthin, or other nutrient supplementation on cognitive function: The AREDS2 randomized clinical trial. *JAMA,* **2015**, *314*(8), 791-801. [http://dx.doi.org/10.1001/jama.2015.9677] [PMID: 26305649]

[285] Witte, A.V.; Kerti, L.; Hermannstädter, H.M.; Fiebach, J.B.; Schreiber, S.J.; Schuchardt, J.P.; Hahn, A.; Flöel, A. Long-chain omega-3 fatty acids improve brain function and structure in older adults. *Cereb. Cortex,* **2014**, *24*(11), 3059-3068. [http://dx.doi.org/10.1093/cercor/bht163] [PMID: 23796946]

[286] Boespflug, E.L.; McNamara, R.K.; Eliassen, J.C.; Schidler, M.D.; Krikorian, R. Fish oil supplementation increases event-related posterior cingulate activation in older adults with subjective memory impairment. *J. Nutr. Health Aging,* **2016**, *20*(2), 161-169. [http://dx.doi.org/10.1007/s12603-015-0609-6] [PMID: 26812512]

[287] Pase, M.P.; Grima, N.; Cockerell, R.; Stough, C.; Scholey, A.; Sali, A.; Pipingas, A. The effects of long-chain omega-3 fish oils and multivitamins on cognitive and cardiovascular function: a randomized, controlled clinical trial. *J. Am. Coll. Nutr.,* **2015**, *34*(1), 21-31. [http://dx.doi.org/10.1080/07315724.2014.880660] [PMID: 25565485]

[288] Strike, S.C.; Carlisle, A.; Gibson, E.L.; Dyall, S.C. A high omega-3 fatty acid multinutrient supplement benefits cognition and mobility in older women: A randomized, double-blind, placebo-controlled pilot study. *J. Gerontol. A Biol. Sci. Med. Sci.,* **2016**, *71*(2), 236-242. [http://dx.doi.org/10.1093/gerona/glv109] [PMID: 26265727]

[289] Külzow, N.; Witte, A.V.; Kerti, L.; Grittner, U.; Schuchardt, J.P.; Hahn, A.; Flöel, A. Impact of omega-3 fatty acid supplementation on memory functions in healthy older adults. *J. Alzheimers Dis.,* **2016**, *51*(3), 713-725. [http://dx.doi.org/10.3233/JAD-150886] [PMID: 26890759]

[290] Jackson, P.A.; Forster, J.S.; Bell, J.G.; Dick, J.R.; Younger, I.; Kennedy, D.O. DHA supplementation alone or in combination with other nutrients does not modulate cerebral hemodynamics or cognitive function in healthy older adults. *Nutrients,* **2016**, *8*(2), 86. [http://dx.doi.org/10.3390/nu8020086] [PMID: 26867200]

[291] Nilsson, A.; Radeborg, K.; Salo, I.; Björck, I. Effects of supplementation with n-3 polyunsaturated fatty acids on cognitive performance and cardiometabolic risk markers in healthy 51 to 72 years old subjects: a randomized controlled cross-over study. *Nutr. J.,* **2012**, *11*, 99. [http://dx.doi.org/10.1186/1475-2891-11-99] [PMID: 23173831]

[292] Yurko-Mauro, K.; McCarthy, D.; Rom, D.; Nelson, E.B.; Ryan, A.S.; Blackwell, A.; Salem, N., Jr; Stedman, M. Beneficial effects of docosahexaenoic acid on cognition in age-related cognitive decline. *Alzheimers Dement.,* **2010**, *6*(6), 456-464. [http://dx.doi.org/10.1016/j.jalz.2010.01.013] [PMID: 20434961]

[293] Andrieu, S.; Guyonnet, S.; Coley, N.; Cantet, C.; Bonnefoy, M.; Bordes, S.; Bories, L.; Cufi, M.N.; Dantoine, T.; Dartigues, J.F.; Desclaux, F.; Gabelle, A.; Gasnier, Y.; Pesce, A.; Sudres, K.; Touchon, J.; Robert, P.; Rouaud, O.; Legrand, P.; Payoux, P.; Caubere, J.P.; Weiner, M.; Carrié, I.; Ousset, P.J.; Vellas, B. Effect of long-term omega 3 polyunsaturated fatty acid supplementation with or without multidomain intervention on cognitive function in elderly adults with memory complaints (MAPT): a randomised, placebo-controlled trial. *Lancet Neurol.,* **2017**, *16*(5), 377-389. [http://dx.doi.org/10.1016/S1474-4422(17)30040-6] [PMID: 28359749]

[294] Terano, T.; Fujishiro, S.; Ban, T.; Yamamoto, K.; Tanaka, T.; Noguchi, Y.; Tamura, Y.; Yazawa, K.; Hirayama, T. Docosahexaenoic acid supplementation improves the moderately severe dementia from thrombotic cerebrovascular diseases. *Lipids,* **1999**, *34*(Suppl.), S345-S346. [http://dx.doi.org/10.1007/BF02562338] [PMID: 10419198]

[295] Mazereeuw, G.; Herrmann, N.; Oh, P.I.; Ma, D.W.; Wang, C.T.; Kiss, A.; Lanctôt, K.L. Omega-3 fatty acids, depressive symptoms, and cognitive performance in patients with coronary artery disease: Analyses from a randomized, double-blind, placebo-controlled trial. *J. Clin. Psychopharmacol.,* **2016**, *36*(5), 436-444. [http://dx.doi.org/10.1097/JCP.0000000000000565] [PMID: 27529771]

[296] Phillips, M.A.; Childs, C.E.; Calder, P.C.; Rogers, P.J. No effect of omega-3 fatty acid supplementation on cognition and mood in individuals with cognitive impairment and probable alzheimer's disease: A randomised controlled trial. *Int. J. Mol. Sci.,* **2015**, *16*(10), 24600-24613. [http://dx.doi.org/10.3390/ijms161024600] [PMID: 26501267]

[297] Shinto, L.; Quinn, J.; Montine, T.; Dodge, H.H.; Woodward, W.; Baldauf-Wagner, S.; Waichunas, D.; Bumgarner, L.; Bourdette, D.; Silbert, L.; Kaye, J. A randomized placebo-controlled pilot trial of omega-3 fatty acids and alpha lipoic acid in Alzheimer's disease. *J. Alzheimers Dis.,* **2014**, *38*(1), 111-120. [PMID: 24077434]

[298] Lee, L.K.; Shahar, S.; Rajab, N.; Yusoff, N.A.; Jamal, R.A.; Then, S.M. The role of long chain omega-3 polyunsaturated fatty acids in reducing lipid peroxidation among elderly patients with mild cognitive impairment: a case-control study. *J. Nutr. Biochem.,* **2013**, *24*(5), 803-808. [http://dx.doi.org/10.1016/j.jnutbio.2012.04.014] [PMID: 22898566]

[299] Scheltens, P.; Twisk, J.W.; Blesa, R.; Scarpini, E.; von Arnim, C.A.; Bongers, A.; Harrison, J.; Swinkels, S.H.; Stam, C.J.; de Waal, H.; Wurtman, R.J.; Wieggers, R.L.; Vellas, B.; Kamphuis, P.J. Efficacy of Souvenaid in mild Alzheimer's disease: results from a randomized, controlled trial. *J. Alzheimers Dis.,* **2012**, *31*(1), 225-236. [PMID: 22766770]

[300] Eriksdotter, M.; Vedin, I.; Falahati, F.; Freund-Levi, Y.; Hjorth, E.; Faxen-Irving, G.; Wahlund, L.O.; Schultzberg, M.; Basun, H.; Cederholm, T.; Palmblad, J. Plasma fatty acid profiles in relation to cognition and gender in Alzheimer's Disease patients during oral omega-3 fatty acid supplementation: The OmegAD study. *J. Alzheimers Dis.,* **2015**, *48*(3), 805-812. [http://dx.doi.org/10.3233/JAD-150102] [PMID: 26402079]

[301] Burckhardt, M.; Herke, M.; Wustmann, T.; Watzke, S.; Langer, G.; Fink, A. Omega-3 fatty acids for the treatment of dementia. *Cochrane Database Syst. Rev.,* **2016**, *4*, CD009002. [PMID: 27063583]

[302] Freund-Levi, Y.; Eriksdotter-Jönhagen, M.; Cederholm, T.; Basun, H.; Faxén-Irving, G.; Garlind, A.; Vedin, I.; Vessby, B.; Wahlund, L.O.; Palmblad, J. Omega-3 fatty acid treatment in 174 patients with mild to moderate Alzheimer disease: OmegAD study: a randomized double-blind trial. *Arch. Neurol.,* **2006**, *63*(10), 1402-1408. [http://dx.doi.org/10.1001/archneur.63.10.1402] [PMID: 17030655]

[303] Masino, S.A.; Rho, J.M. Mechanisms of Ketogenic Diet Action.**2012**. [http://dx.doi.org/10.1093/med/9780199746545.003.0078]

[304] Coppola, G.; Veggiotti, P.; Cusmai, R.; Bertoli, S.; Cardinali, S.; Dionisi-Vici, C.; Elia, M.; Lispi, M.L.; Sarnelli, C.; Tagliabue, A.; Toraldo, C.; Pascotto, A. The ketogenic diet in children, adolescents and young adults with refractory epilepsy: an Italian multicentric experience. *Epilepsy Res.,* **2002**, *48*(3), 221-227. [http://dx.doi.org/10.1016/S0920-1211(01)00315-1] [PMID: 11904241]

[305] Coppola, G.; D'Aniello, A.; Messana, T.; Di Pasquale, F.; della Corte, R.; Pascotto, A.; Verrotti, A. Low glycemic index diet in children and young adults with refractory epilepsy: first Italian experience. *Seizure,* **2011**, *20*(7), 526-528. [http://dx.doi.org/10.1016/j.seizure.2011.03.008] [PMID: 21489826]

[306] Kverneland, M.; Selmer, K.K.; Nakken, K.O.; Iversen, P.O.; Taubøll, E. A prospective study of the modified Atkins diet for adults with idiopathic generalized epilepsy. *Epilepsy Behav.,* **2015**, *53*, 197-201. [http://dx.doi.org/10.1016/j.yebeh.2015.10.021] [PMID: 26588588]

[307] Cervenka, M.C.; Henry, B.J.; Felton, E.A.; Patton, K.; Kossoff, E.H. Establishing an adult epilepsy diet center: Experience, efficacy and challenges. *Epilepsy Behav.,* **2016**, *58*, 61-68. [http://dx.doi.org/10.1016/j.yebeh.2016.02.038] [PMID: 27060389]

[308] Wilder, R.M. The effect on ketonemia on the course of epilepsy. *Mayo Clin. Bull.,* **1921**, *2*, 307.

[309] Wheless, J.W. History of the ketogenic diet. *Epilepsia,* **2008**, *49*(Suppl. 8), 3-5. [http://dx.doi.org/10.1111/j.1528-1167.2008.01821.x] [PMID: 19049574]

[310] Huttenlocher, P.R. Ketonemia and seizures: metabolic and anticonvulsant effects of two ketogenic diets in childhood epilepsy. *Pediatr. Res.,* **1976**, *10*(5), 536-540. [http://dx.doi.org/10.1203/00006450-197605000-00006] [PMID: 934725]

[311] Rho, J.M.; Anderson, G.D.; Donevan, S.D.; White, H.S. Acetoacetate, acetone, and dibenzylamine (a contaminant in l-(+)-beta-hydroxybutyrate) exhibit direct anticonvulsant actions *in vivo*. *Epi-*

lepsia, **2002**, *43*(4), 358-361. [http://dx.doi.org/10.1046/j.1528-1157.2002.47901.x] [PMID: 11952765]

[312] Likhodii, S.S.; Serbanescu, I.; Cortez, M.A.; Murphy, P.; Snead, O.C., III; Burnham, W.M. Anticonvulsant properties of acetone, a brain ketone elevated by the ketogenic diet. *Ann. Neurol.,* **2003**, *54*(2), 219-226. [http://dx.doi.org/10.1002/ana.10634] [PMID: 12891674]

[313] Viggiano, A.; Pilla, R.; Arnold, P.; Monda, M.; D'Agostino, D.; Coppola, G. Anticonvulsant properties of an oral ketone ester in a pentylenetetrazole-model of seizure. *Brain Res.,* **2015**, *1618*, 50-54. [http://dx.doi.org/10.1016/j.brainres.2015.05.023] [PMID: 26026798]

[314] Ma, W.; Berg, J.; Yellen, G. Ketogenic diet metabolites reduce firing in central neurons by opening K(ATP) channels. *J. Neurosci.,* **2007**, *27*(14), 3618-3625. [http://dx.doi.org/10.1523/JNEUROSCI.0132-07.2007] [PMID: 17409226]

[315] Juge, N.; Gray, J.A.; Omote, H.; Miyaji, T.; Inoue, T.; Hara, C.; Uneyama, H.; Edwards, R.H.; Nicoll, R.A.; Moriyama, Y. Metabolic control of vesicular glutamate transport and release. *Neuron,* **2010**, *68*(1), 99-112. [http://dx.doi.org/10.1016/j.neuron.2010.09.002] [PMID: 20920794]

[316] Bough, K.J.; Valiyil, R.; Han, F.T.; Eagles, D.A. Seizure resistance is dependent upon age and calorie restriction in rats fed a ketogenic diet. *Epilepsy Res.,* **1999**, *35*(1), 21-28. [http://dx.doi.org/10.1016/S0920-1211(98)00125-9] [PMID: 10232791]

[317] Viggiano, A.; Pilla, R.; Arnold, P.; Monda, M.; D'Agostino, D.; Zeppa, P.; Coppola, G. Different calorie restriction treatments have similar anti-seizure efficacy. *Seizure,* **2016**, *35*, 45-49. [http://dx.doi.org/10.1016/j.seizure.2016.01.003] [PMID: 26794009]

[318] Bough, K. Energy metabolism as part of the anticonvulsant mechanism of the ketogenic diet. *Epilepsia,* **2008**, *49*(Suppl. 8), 91-93. [http://dx.doi.org/10.1111/j.1528-1167.2008.01846.x] [PMID: 19049599]

[319] Rogawski, M.A.; Löscher, W.; Rho, J.M. Mechanisms of action of antiseizure drugs and the ketogenic diet. *Cold Spring Harb. Perspect. Med.,* **2016**, *6*(5), a022780. [http://dx.doi.org/10.1101/cshperspect.a022780] [PMID: 26801895]

[320] Rho, J.M. How does the ketogenic diet induce anti-seizure effects? *Neurosci. Lett.,* **2017**, *637*, 4-10. [http://dx.doi.org/10.1016/j.neulet.2015.07.034] [PMID: 26222258]

[321] Viggiano, A.; Stoddard, M.; Pisano, S.; Operto, F.F.; Iovane, V.; Monda, M.; Coppola, G. Ketogenic diet prevents neuronal firing increase within the substantia nigra during pentylenetetrazole-induced seizure in rats. *Brain Res. Bull.,* **2016**, *125*, 168-172. [http://dx.doi.org/10.1016/j.brainresbull.2016.07.001] [PMID: 27381979]

[322] Chwiej, J.; Skoczen, A.; Matusiak, K.; Janeczko, K.; Patulska, A.; Sandt, C.; Simon, R.; Ciarach, M.; Setkowicz, Z. The influence of the ketogenic diet on the elemental and biochemical compositions of the hippocampal formation. *Epilepsy Behav.,* **2015**, *49*, 40-46. [http://dx.doi.org/10.1016/j.yebeh.2015.04.042] [PMID: 25986320]

[323] Chwiej, J.; Skoczen, A.; Janeczko, K.; Kutorasinska, J.; Matusiak, K.; Figiel, H.; Dumas, P.; Sandt, C.; Setkowicz, Z. The biochemical changes in hippocampal formation occurring in normal and seizure experiencing rats as a result of a ketogenic diet. *Analyst (Lond.),* **2015**, *140*(7), 2190-2204. [http://dx.doi.org/10.1039/C4AN01857E] [PMID: 25705743]

[324] Paoli, A.; Rubini, A.; Volek, J.S.; Grimaldi, K.A. Beyond weight loss: a review of the therapeutic uses of very-low-carbohydrate (ketogenic) diets. *Eur. J. Clin. Nutr.,* **2013**, *67*(8), 789-796. [http://dx.doi.org/10.1038/ejcn.2013.116] [PMID: 23801097]

[325] Verrotti, A.; Iapadre, G.; Pisano, S.; Coppola, G. Ketogenic diet and childhood neurological disorders other than epilepsy: an overview. *Expert Rev. Neurother.,* **2016**, *21*, 1-13. [PMID: 27841033]

[326] Bozzetti, F.; Zupec-Kania, B. Toward a cancer-specific diet. *Clin. Nutr.,* **2016**, *35*(5), 1188-1195. [http://dx.doi.org/10.1016/j.clnu.2015.01.013] [PMID: 25707910]

[327] Branco, A.F.; Ferreira, A.; Simões, R.F.; Magalhães-Novais, S.; Zehowski, C.; Cope, E.; Silva, A.M.; Pereira, D.; Sardão, V.A.; Cunha-Oliveira, T. Ketogenic diets: from cancer to mitochondrial diseases and beyond. *Eur. J. Clin. Invest.,* **2016**, *46*(3), 285-298. [http://dx.doi.org/10.1111/eci.12591] [PMID: 26782788]

[328] Allen, B.G.; Bhatia, S.K.; Anderson, C.M.; Eichenberger-Gilmore, J.M.; Sibenaller, Z.A.; Mapuskar, K.A.; Schoenfeld, J.D.; Buatti, J.M.; Spitz, D.R.; Fath, M.A. Ketogenic diets as an adjuvant cancer therapy: History and potential mechanism. *Redox Biol.,* **2014**, *2*, 963-970. [http://dx.doi.org/10.1016/j.redox.2014.08.002] [PMID: 25460731]

[329] Lee, P.R.; Kossoff, E.H. Dietary treatments for epilepsy: management guidelines for the general practitioner. *Epilepsy Behav.,* **2011**, *21*(2), 115-121. [http://dx.doi.org/10.1016/j.yebeh.2011.03.008] [PMID: 21514240]

[330] Ułamek-Kozioł, M.; Pluta, R.; Bogucka-Kocka, A.; Czuczwar, S.J. To treat or not to treat drug-refractory epilepsy by the ketogenic diet? That is the question. *Ann. Agric. Environ. Med.,* **2016**, *23*(4), 533-536. [http://dx.doi.org/10.5604/12321966.1226841] [PMID: 28030918]

[331] Rho, J.M.; Sankar, R. The ketogenic diet in a pill: is this possible? *Epilepsia,* **2008**, *49*(Suppl. 8), 127-133. [http://dx.doi.org/10.1111/j.1528-1167.2008.01857.x] [PMID: 19049610]

[332] D'Agostino, D.P.; Pilla, R.; Held, H.E.; Landon, C.S.; Puchowicz, M.; Brunengraber, H.; Ari, C.; Arnold, P.; Dean, J.B. Therapeutic ketosis with ketone ester delays central nervous system oxygen toxicity seizures in rats. *Am. J. Physiol. Regul. Integr. Comp. Physiol.,* **2013**, *304*(10), R829-R836. [http://dx.doi.org/10.1152/ajpregu.00506.2012] [PMID: 23552496]