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Review

Fatty acids and their therapeutic potential in neurological disorders

Enie Lei [a], Kristina Vacy [a], Wah Chin Boon [a, b, *]

[a] The Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville, Victoria 3052, Australia
[b] Dept of Anatomy and Developmental Biology, Monash University, Clayton, Victoria 3800, Australia

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ABSTRACT

There is little doubt that we are what we eat. Fatty acid supplementation and diets rich in fatty acids are being promoted as ways to a healthier brain.

Short chain fatty acids are a product of intestinal microbiota metabolism of dietary fibre; and their derivatives are used as an anti-convulstant. They demonstrated therapeutic potential in neurodegenerative conditions as HDAC inhibitors; and while the mechanism is not well understood, have been shown to lower amyloid β in Alzheimer's Disease in preclinical studies. Medium chain fatty acids consumed as a mixture in dietary oils can induce ketogenesis without the need for a ketogentic diet. Hence, this has the potential to provide an alternative energy source to prevent neuronal cell death due to lack of glucose. Long chain fatty acids are commonly found in the diet as omega fatty acids. They act as an anti-oxidant protecting neuronal cell membranes from oxidative damage and as an anti-inflammatory mediator in the brain.

We review which agents, from each fatty acid class, have the most therapeutic potential for neurological disorders (primarily Alzheimer's disease, Parkinson's disease, Autism Spectrum Disorder as well as possible applications to traumatic brain injury), by discussing what is known about their biological mechanisms from preclinical studies.

Contents

1. Introduction

The average western diet is characterised by refined carbohydrates and fatty meats, with a reduction of whole grains and dietary fibre. It is strongly associated with obesity and a number of related

* Corresponding author. Steroid Neurobiology Laboratory, The Florey Institute of Neuroscience and Mental Health, University of Melbourne, Parkville Victoria 3052, Australia
E-mail address: wah.chin.boon@florey.edu.au (W.C. Boon).

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Table 1
A summary of the therapeutic potentials, mechanisms and possible drawbacks of the 3 classes of fatty acids.

Fatty acid	Possible mechanism	Therapeutic potential	Possible drawbacks
Short chain fatty acids (SCFA)	• Histone Deacetylase inhibitor (Licciardi et al., 2011) • Anti-oxidant (Valvassori et al., 2015)	• Down- regulate production of disease associated molecules e.g. amyloid β in Alzheimer's (St Laurent et al., 2013; Ferrante et al., 2003; Monti et al., 2010) • Up-regulate neurogenesis (Dehghan et al., 2015)	• Associated with Autism Spectrum Disorder and foetal abnormalities during pregnancy (Frye et al., 2015; Macfabe, 2013; Rosenfeld, 2015; Codagnone et al., 2015; Kang, 2015)
Medium chain fatty acids (MCFA)	• Induce ketogenesis (Newman and Verdin, 2014) • Anti-oxidant or sources also contain anti-oxidants (Kamisah et al., 2015; Yeap et al., 2015)	• Prevent neuronal death from lack of glucose uptake (Newman and Verdin, 2014; Winkler et al., 2015; Ding et al., 2013)	• May increase insulin resistance (Marcal et al., 2013)
Long chain fatty acids (LCFA)	• Anti-oxidant • Anti-inflammatory mediator (Hosono et al., 2015)	• Mitigate ischaemic damage (Belayev et al., 2009; Hong et al., 2015) • Aid cognition and memory (Yurko-Mauro et al., 2015; Kelly et al., 2011)	• Products from anti-oxidant mechanism are toxic (Maruyama et al., 2014) • Omega-6 inhibits neurite growth (Novak et al., 2008)

conditions, including neurodegeneration (Grotto and Zied, 2010). Thus, dietary modifications and supplementation may have neuroprotective and therapeutic effects.

It has long been shown that fatty acids in diet affect the fatty acid composition of the brain (Horwitt et al., 1959). In the last couple of decades, it has been proposed that the consumption of fatty acids are beneficial to the brain in many respects; from neural development (Farquharson et al., 1992) and neuroprotection (Packer et al., 1997) to being potential treatments to a multitude of neurological disorders (Horrocks and Farooqui, 2004).

This review will focus on three main groups of fatty acids: Short Chain Fatty Acids (SCFA), Medium Chain Fatty Acids (MCFA) and Long Chain Fatty Acids (LCFA). Each group has different functions and effects on the body and brain, often conferring some degree of neuroprotection through a variety of mechanisms, allowing them to be potential treatments to a wide range disorders from Alzheimer's disease (AD) and Parkinson's disease (PD) to traumatic brain injury. Here, we review the current uses of fatty acids and their potential as therapeutic agents (Table 1), focusing on *in vitro* and preclinical studies, on what is known about the mechanisms of how each fatty acid acts, and how they may either reduce the risk for or alleviate symptoms associated with neurological conditions.

1.1. Nomenclature of Fatty Acids (FA)

Fatty acids are carboxylic acid with a long hydrocarbon chain. They can be referred to by their trival/common names or IUPAC names. Under the IUPAC nomenclature, the carboxyl carbon is referred to as C-1. Alternatively, the carbon positions can be referred as α, β, γ, δ, ε, etc from C-1 and the carbon farthest from carboxyl carbon is referred to as ω (omega). Fatty acids can be classified according to the length of the hydrocarbon chain: short-, medium-, long- and very long-chain. They can also be classified according to the presence of C—C double bond: saturated FA have no C—C double bonds; unsaturated FA have at least one C—C double bond; monounsaturated FA have only one C—C double bond; polyunsaturated FA has more than one C—C double bond. Positions of double bonds are indicated by Δ^n whereby n indicates the lower numbered carbon of each C—C double bond pair. The double bond can exist as trans or cis, with the latter producing a kink in the hydrocarbon chain. For example, the long chain polyunsaturated Linoleic acid has a chemical structure $CH_3(CH_2)_4CH{=}CHCH_2CH{=}CH(CH_2)_7COOH$, is cis,cis-$\Delta^9$,$\Delta^{12}$-Octadecadienoic acid under the IUPAC nomenclature system. Alternatively, the C—C double bond position can be counted from the omega (ω-; i.e. the last carbon) position. Hence, Linoleic acid is an omega-6 fatty acid. Refer to Table 2 for the list of FA we will discuss in this review.

2. Short Chain Fatty Acids (SCFA)

Ranging from 2 to 5 carbon atom chains, unlike other types of fatty acids, SCFA (also known as Volatile Fatty Acids) naturally occur as products of fibre metabolism in the gut by the gastrointestinal microbiome. The source of dietary SCFA is fermentation of non-digestible carbohydrates (e.g dietary fibre) by the gut microbiota (Lunn and Buttriss, 2007), which results in the production of mainly acetic acid, propionic acid, and butyric acid (Fig. 1), with the amount of each depending on the microbiome (composition of bacterial species in the gut). In turn, the SCFA metabolites can alter the microbiome (Licciardi et al., 2010; Schwiertz et al., 2010; Topping and Clifton, 2001; Wisker et al., 1988). The concentrations of plasma SCFA in the morning were positively correlated with the contents of indigestible carbohydrates included in the evening test meals (Nilsson et al., 2010).

SCFA such as butyrate was found to be a competitive inhibitor of Histone Deacetylase (Sekhavat et al., 2007), which indicates that it associates with the substrate-binding site; and since have been shown to have epigenetic effects as a Histone Deacetylase inhibitor (HDACi) (Licciardi et al., 2011).

As HDACi, SCFA act upon Histone Deacetylase (HDAC) which in turn modifies the histone complex which eukaryotic DNA is wrapped around when it is not required for replication or transcription. Histones are protein complexes that when acetylated allow compact storage of DNA within the nucleus. As the name suggests, HDAC deacetylates these histone complexes allowing the wound DNA to be released for replication or transcription. By contrast, HDACi inhibit the action of HDAC, thus preventing the unwinding and the transcription of the gene. SCFA is thought to act as a HDACi by interacting with the active site of HDAC, in particular the Zn^{2+} cation, and are most efficient at inhibiting class 1 and 2 HDAC enzymes (Grayson et al., 2010; Lu et al., 2004). However, when compared to other HDACi, SCFA are weak HDACi due to their inability to access the Zn^{2+} cations, as they are required at higher concentrations of millimolar range instead of nanomolar range to elicit the same effects as other HDACi (Lu et al., 2004).

Given that SCFA act as HDACi and are products of the gut microbiome, there is considerable growing interest in dietary HDACi in promoting bowel health (reviewed by Berni Canani et al., 2012) and lowering insulin resistance. It has been reported that the SCFA propionate acts on human colonic cells to release Peptide YY and Glucagon-like peptide-1 to regulate appetite (Chambers et al., 2015). Also, three percent of acetate, the most common SCFA produced by the gut microbiome, crosses the blood brain barrier (BBB) in mice to regulate appetite (Frost et al., 2014). Interestingly, it has been proposed that through regulating gut metabolism, SCFA produced from a high fibre diet have the potential to lower the risk of

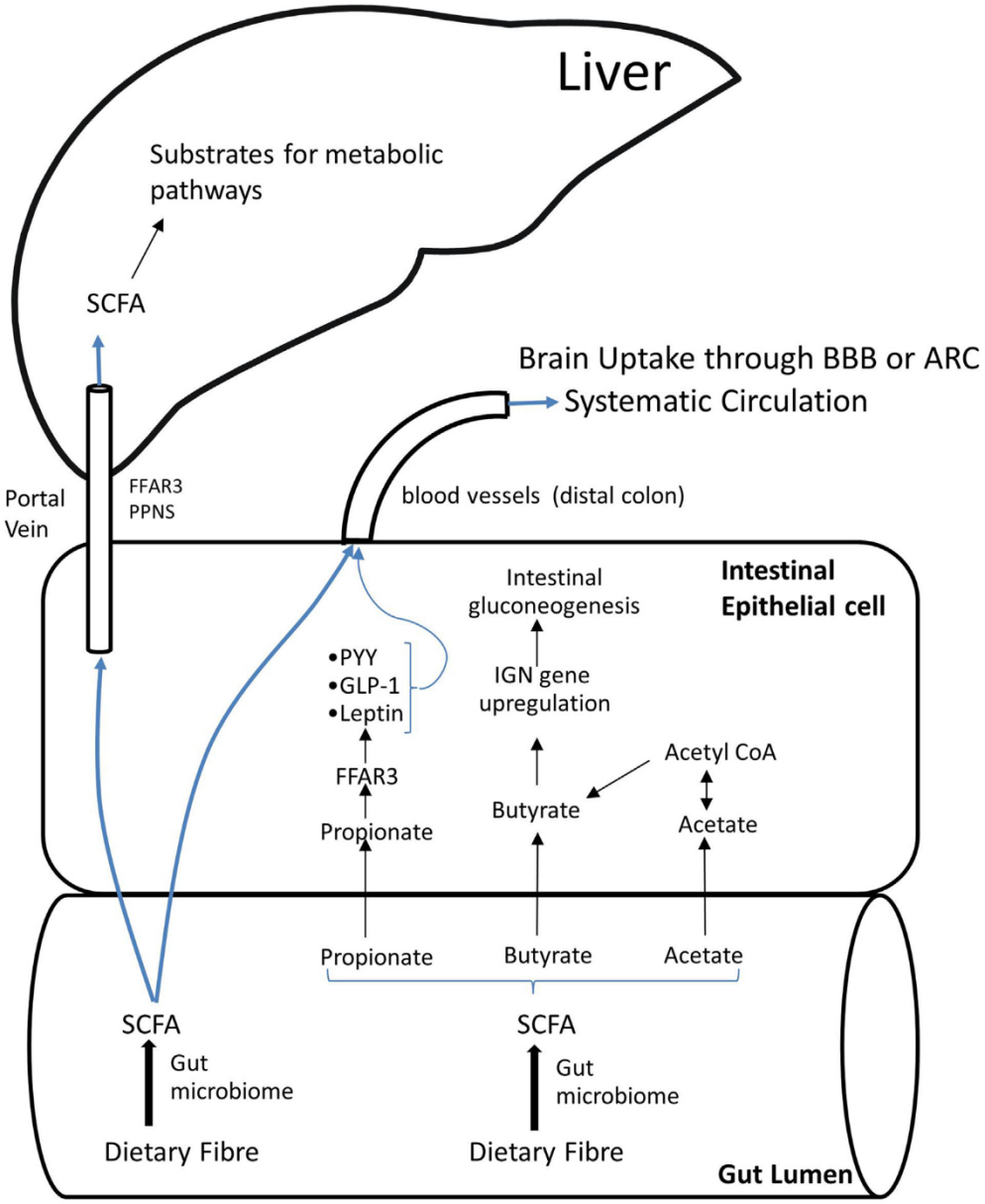

Fig. 1. Proposed metabolism, uptake and regulation of dietary SCFA. Butyrate and propionate regulate intestinal gluconeogenesis through complementary mechanisms, either by direct use as a substrate or through free fatty acid receptor (FFAR) 3 signalling at the periportal nervous system (PPNS) (De Vadder et al., 2014; Donohoe et al., 2011), which in term is thought to affect the energy homeostasis of the organism. Propionate preferentially activates FFA3 on colonic cells to release the hormones GLP-1 and PYY, which in turn, act on the brain(De Vadder et al., 2014), namely the hypothalamus. Acetate can enter the brain through the systemic circulation. The majority of butyrate is metabolised in the colon (directly involved in intestinal gluconeogenesis by entering the TCA cycle), but all three SCFA enters the liver through the portal vein. Hepatocytes oxidise butyrate, but acetate and propionate may be used as substrates for various metabolic pathways, depending on species and energy status (reviewed by Reilly and Rombeau, 1993). Finally, leftover SCFA may enter systemic circulation, where it may act on free fatty acid receptors expressed in peripheral tissues.

AD due to insulin resistance (Funato et al., 2011).

The interplay between dietary fibre intake, the gut microbiome and neuroprotective effects is a recent avenue of inquiry (reviewed by Bourassa et al., 2016). Further research is required to determine the effects of each SCFA produced by the microbiome, what circulating levels are required and what types of foods may be consumed to get those levels without any adverse effects. In addition, derivatives of these SCFA may be taken to confer neuroprotection.

SCFA such as Sodium Butyrate and Valproic Acid have been synthesised to be used as drugs to treat epilepsy, and more recently have been considered in the treatment of various neurodegenerative diseases such as AD, Huntington's Disease and PD (Hahnen et al., 2008; Xu et al., 2011).

2.1. Butyric acid

Besides being present in the colon as a product of anaerobic fermentation by gastrointestional bacteria, butyric acid or its triglyceride are also found in milk, especially goat, sheep and buffalo milk, butter, parmesan cheese. Sodium butyrate (SB) is the sodium salt of butyric acid that has been shown to be anti-inflammatory in microglial cells, hippocamal slices *in vitro* (Huuskonen et al., 2004), and therefore may be beneficial for neuropathological conditions where inflammation is present (Huuskonen et al., 2004). In support of this observation, a single intracerebroventricular injection of SB prevented aversive memory impairment induced by sepsis in male rats (as a consequence of cecal ligation and perforation), with a

Table 2
A summary of the IUPAC name, chemical structure, carbon chain length and class of common fatty acids

Common Name	IUPAC name	Chemical structure	Class types	Number of carbons
Formic acid	Methanoic acid	HCOOH	SCFA	1
Acetic acid	Ethanoic acid	CH_3COOH	SCFA	2
Propionic acid	Propanoic acid	CH_3CH_2COOH	SCFA saturated	3
Butyric acid	Butanoic acid	$CH_3(CH_2)_2COOH$	SCFA saturated	4
Valeric acid	Pentanoic acid	$CH_3(CH_2)_3COOH$	SCFA saturated	5
Valproic acid	2-propylpentanoic acid	$(CH_3CH_2CH_2)_2CHCOOH$	SCFA saturated	Two chains of 3 carbons, total 8
Caprylic acid	Octanoic acid	$CH_3(CH_2)_6COOH$	MCFA saturated	8
Lauric acid	Dodecanoic acid	$CH_3(CH_2)_{10}COOH$	MCFA saturated	12
Linoleic acid	*cis*,*cis*-Δ^9,Δ^{12} Octadecadienoic acid	$CH_3(CH_2)_4\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}(CH_2)_7COOH$	LCFA Polyunsaturated ω-6 FA	18
Eicosopentaenoic acid	*cis*,*cis*,*cis*,*cis*,*cis*-Δ^5,Δ^8,Δ^{11},Δ^{14},Δ^{17} icosapentaenoic acid	$CH_3CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}(CH_2)_3COOH$	LCFA Polyunsaturated ω-3 FA	20
Docosahexaenoic acid	*cis*,*cis*,*cis*,*cis*,*cis*,*cis*-Δ^4,Δ^7,Δ^{10},Δ^{13},Δ^{16},Δ^{19}- -hexaenoic acid	$CH_3CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}CH_2\mathbf{CH{=}CH}(CH_2)_2COOH$	LCFA Polyunsaturated ω-3 FA	22

concomitant inhibition of the HDAC activity in prefrontal cortex and hippocampus (Steckert et al., 2015).

The role of SB as an HDACi is being exploited as a treatment for neurodegenerative diseases such as PD or AD as aberrant histone acetylation have been implicated in both (Harrison and Dexter, 2013; Stilling and Fischer, 2011). In particular, it has been shown to improve rotenone-induced models of PD by preventing the death of dopaminergic neurons, a primary cause of disease although the exact mechanism has yet to be found (St Laurent et al., 2013). Furthermore, 6-week treatment with SB (1.2 g/kg body weight, via intraperitoneal injection) improved associative memory in double transgenic AD mouse model (APPPS1-21), even when administered at a very advanced stage of pathology, i.e. 15 months of age (Govindarajan et al., 2011). Smilarly, SB treatment significantly delayed the neuropathological phenotype in the R6/2 transgenic mouse model of Hungtington's disease, extended its survival in a dose-dependent manner, improved body weight and motor performance (Ferrante et al., 2003). This is not unexpected because mutant huntingtin can bind to histone acetyltransferase domains and reduce its activity, resulting in a reduction in histone acetylation and hence repressed gene transcription.

Recently, the anti-oxidative effects of SB (ip, 500 mg/kg, twice a day) was attributed to reversing the manic-like behaviour in sheep model of mania, as induced by icv injection of ouabain (Valvassori et al., 2015). In summary, *in vitro* and *in vivo* studies have demonstrated that SB has therapeutic potential in several neurological disorders.

2.2. Valproic acid

Another commonly used SCFA for treatment of neurological disorders is Valproic acid (VPA), a structurally similar compound to propionic acid but with an additional propyl branch. It was originally discovered as an analogue of valeric acid found naturally in a herb valerian root, a dietary supplement which may have sedative and anxiolytic effects (Burton, 1882).

Since the discovery of the anti-convulsant properties of VPA in France in 1962, it is primarily used as an anti-epileptic drug from 1967 (Perucca, 2002). The mechanism of action has yet to be fully elucidated but was initially found to be primarily related to neurotransmission (Perucca, 2002). Recent research showed that VPA could be a possible therapeutic for AD and PD, once again through its HDACi activity by reducing production of the amyloid-β protein (Qing et al., 2008) and α-synuclein aggregates (Monti et al., 2010) as well as providing neuroprotection against ischaemic insults (Suda et al., 2013, 2015). This mechanism is suggested to be through up-regulation of platelets from acute doses (Dekker et al., 2014; Jin et al., 2012; Schnuriger et al., 2010) whereas chronic VPA usage is associated with lowered platelet count in humans. (Gidal et al., 1994; Koenig et al., 2008). In mice, VPA also encourages neurogenesis through epigenetic up-regulation of neural progenitors when co-administered with transcription factor Oct4 (Dehghan et al., 2015), which opens up questions about co-administration of SCFA with transcription factors to reprogram adult neural stem cells to aid in neuro-regeneration.

2.3. Potential toxicity and adverse effects of SCFA

Despite the potential benefits of SCFA as a therapeutic treatment, it has been found that SCFA, in particular propionic acid and to a lesser degree butyric acid, are implicated in non-genetically related Autism Spectrum Disorder (ASD), a condition with multiple aetiologies, in children, through the elevated levels of these SCFA produced by gut microbiome or from food as propionic acid is a popular food preservative (Frye et al., 2015; Macfabe, 2013; Rosenfeld, 2015). The underlying mechanism has yet to be elucidated. Epidemiological investigations in children exposed to VPA treatment *in utero* have reported a significant risk associated with ASD and other neurodevelopmental disorders (reviewed by Chomiak et al., 2013); and indeed VPA could induce ASD-like behaviour in rodents when exposed *in utero* (Codagnone et al., 2015; Kang and Kim, 2015). Thus, careful consideration must be taken to decide whether or not SCFA would be suitable as therapeutics, especially in pregnant women or women who are planning to conceive.

3. Medium Chain Fatty Acids (MCFA)

MCFA have carbon chains of 6–12 carbons and differ to SCFA as they must be ingested rather than produced by gastrointestinal microbes. Coconut oil is one of the most common source of MCFA. Unlike most other oils, coconut oil contains predominantly saturated chains of MCFA, the most common being Lauric Acid. In addition to being easily available and cheap, coconut oil is becoming more and more popular as a potential treatment for neurological disorders such as AD, epilepsy and other disorders where neurons appear to have an insufficient access to glucose or the need for a ketogenic diet.

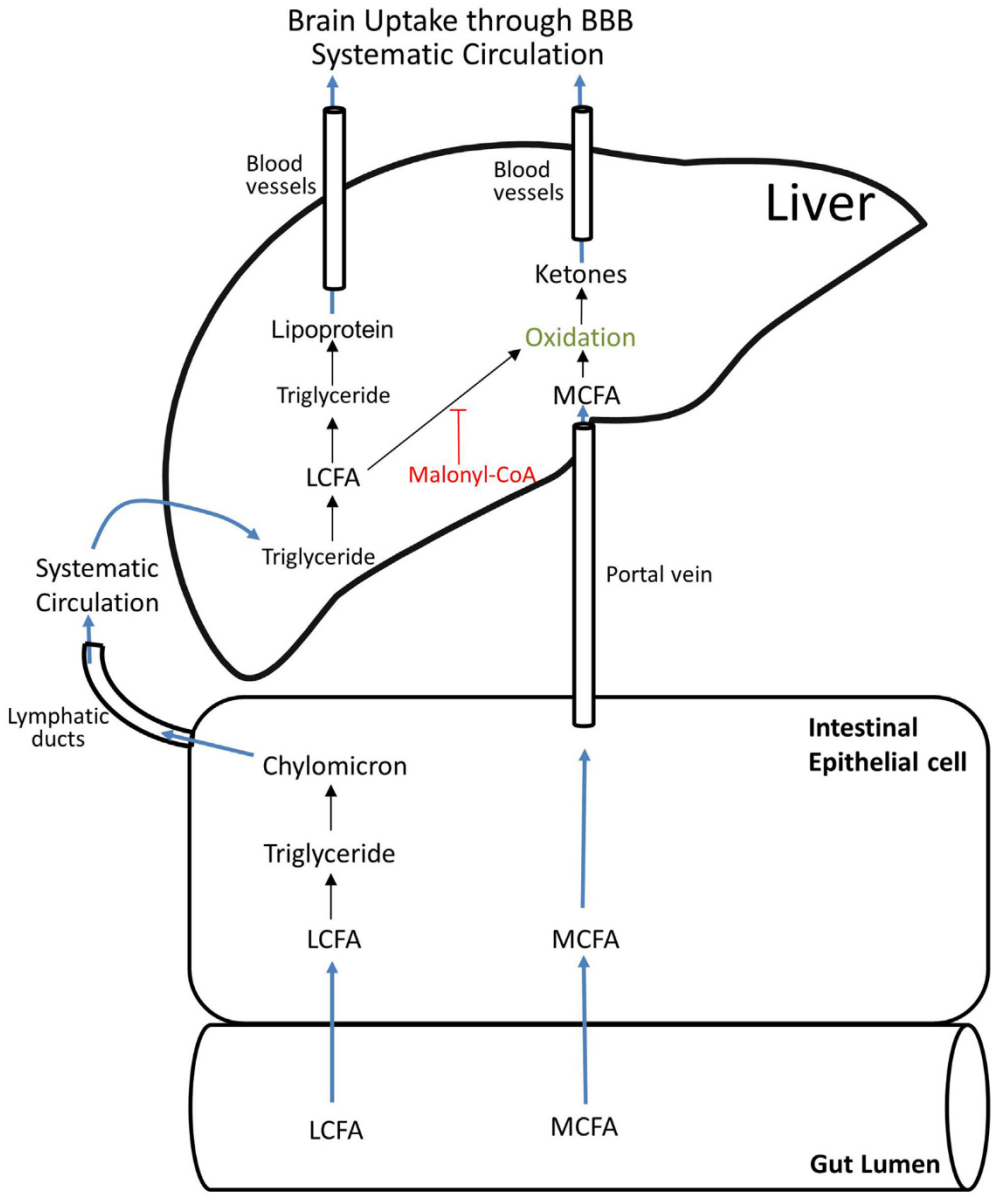

Fig. 2. Proposed Metabolism of MCFA versus LCFA. MCFA are absorbed directly into the portal vein whereas LCFA are packaged into Chylomicron and absorbed into lymphatic system. In the liver, MCFA are quickly oxidised into ketone bodies, whereas the fate of LCFA is dependent on the metabolic state of the organism. LCFA are transported to the mitochondria for oxidation using CPT1 if energy is required. When conditions favour fat storage, malonyl-CoA is produced as an intermediate in lipogenesis. As a consequence, the oxidation of LCFA in the mitochondria is prevented as malonyl-CoA inhibits CPT1. MCFA are not subject to the regulations that control the oxidation of LCFA because they can enter the mitochondria without the use of CPT1. In summary, MCFA enter the liver rapidly and are quickly oxidised to produce ketone bodies which will be available to the brain through crossing the blood brain barrier (BBB). CoA, coenzyme A; CPT1, carnitine palmitoyltransferase I; LCFA, long-chain fatty acid.

The MCFA have been proposed to be a good alternative energy source through ketogenesis (Kesl et al., 2016). Once the MCFA entered the blood stream, they are metabolised into ketone bodies (Acetate, Acetoacetate, and D-β-hydroxybutyrate) in the liver (Fig. 2), which are capable of being converted to acetyl-CoA, a key substrate in the citric acid cycle to provide ATP (Newman and Verdin, 2014). There are evidences in AD that neurons have limited access to glucose (reviewed by Chen and Zhong, 2013), most likely from the disintegration of the blood rain barrier (BBB) integrity and function, for example the dysfunction of BBB glucose transporter 1 (GLUT1) as seen in AD (Winkler et al., 2015). If the BBB is compromised and thus limiting neuronal access to glucose, ketones have been shown to be an excellent alternative energy source especially in early disease (Ding et al., 2013); ketone levels are usually monitored through the presence and uptake of the major ketones β-hydroxybutyrate (Hasselbalch et al., 1995) in the serum. Additionally, the fact that MCFA are saturated means they do not require other reactions to break a double bond within the carbon chain, and as they are relatively small molecules, they do not require the aid of a transport protein – ATP dependent or otherwise – to transport them across the cell membrane, thus increasing the gained energy to expended energy ratio (Fernando et al., 2015). In addition, ketones from ketogenic diets with high fat and low carbohydrate intake were shown to reduce amyloid β production and deposition in the brain (Van der Auwera et al., 2005), potentially through the rescue of astroglial cells (Hertz et al., 2015). Besides being an important alternative energy source, β-hydroxybutyrate was demonstrated to act as a weak HDACi (Shimazu et al., 2013) to

confer protection against paraquat-induced oxidative stress in mouse kidney; and therefore ketones may protect the aging brain against oxidative stress. This makes MCFA a highly attractive avenue of AD treatment.

MCFA are a better source of ketone bodies than LCFA (Fig. 2). Firstly unlike LCFA, uptake from the gut delivers MCFA directly to the liver through the portal vein where they are oxidised (Marten et al., 2006). Secondly, due to the shorter chain length, MCFA do not require a transport protein to be taken up into mitochondria where they are oxidised, giving rise to high levels of fatty acetyl Co-A which in turn induce high levels of ketones. Furthermore, the metabolism of MCFA results in reduced uptake and metabolism of LCFA into mitochondria due to synthesis of Malonyl Co-A, in response to high ketone levels, which inhibits the LCFA transport protein.

Coconut oil, a rich source of MCFA, has also been shown to have an anti-oxidant and anti-inflammatory mechanism (Kamisah et al., 2015; Yeap et al., 2015), thus is capable of mitigating damage from reactive oxygen species during inflammation which often accompany neurodegeneration. However, it is possible another class of compounds – polyphenolics – within virgin coconut oil used in the studies, and not the MCFA present that confers these beneficial effects (Vysakh et al., 2014). Coconut oil was demonstrated to reduce the toxic effect of amyloid β in rat cortical neuronal cultures (Nafar and Mearow, 2014) when it had been emulsified into the culture media with final concentrations of 0.1%, 0.01%, and 0.001% (v/v) via sonication.

Incidentally, medium chain triglyceride (MCT, Caprylic Triglyceride) derived from fractionated coconut oil (Axona®) has been approved by FDA in 2009 as a prescription medical food for the clinical dietary management of the hypometabolic processes associated with mild to moderate AD. The approval was based on two clinical trials. The first trial was a randomized, placebo-controlled, crossover-design study on 20 subjects between the ages of 55–85 years old and diagnosed with probable AD or mild cognitive impairment. A single dose of MCT (40 g) led to elevated D-β-hydroxybutyrate serum levels (to ~0.5 mM at 90 min after administration) that were positively correlated with improvement in paragraph recall ($P = 0.02$; Costantini et al., 2008). The second trial (ClinicalTrials.gov Identifier: NCT00142805) was a small randomized, double-blind 90-day clinical trial (152 subjects with mild to moderate AD). As seen in the previous trial, serum ketone body D-β-hydroxybutyrate levels were significantly elevated 2 h after MCT administration when compared to placebo. MCT administered AD patients, not carrying the APOE4 allele, showed improved scoring on AD Assessment Scale-Cognitive subscale (ADAS-Cog) from baseline whereas the placebo group continued to decline in scoring at days 45 and 90 (Henderson et al., 2009). It was proposed that MCT was processed by enzyme in the gut into MCFA which was further processed by the liver into ketones. Indeed, medium chain triglyceride (MCT) caprylidene was one of the first nutraceuticals approved by FDA.

Clinical trials and experiments seeking to induce ketosis in subjects to observe its effect on AD and its symptoms utilising MCT have shown positive results in minor to moderate cognitive impaired patients (Henderson et al., 2009; Rebello et al., 2015). This indicates MCFA alone – as they are the hydrolysed product of synthesised MCT – do have a beneficial effect in AD (Reger et al., 2004). Granted, there are other compounds in the coconut oil that could possibly contribute to the beneficial effects it has on AD, such as polyphenols that are often found in plant derived foods (Pasinetti, 2012; Smid et al., 2012).

Another feature of AD is insulin resistance (De Felice et al., 2014), which has been shown to reduce hippocampal plasticity thus affecting learning and cognition (Petrov et al., 2015; Stranahan et al., 2008). Insulin resistance affects the uptake of glucose in the brain, further accelerating neuronal loss from the inability to uptake sufficient amounts of glucose. While the exact mechanism is unknown, it has been shown that MCFA improve insulin resistance (Sun et al., 2013), but there is conflicting evidence that suggests MCFA increases insulin resistance (Marcal et al., 2013) thus, further investigation of MCFA and its effect on insulin resistance is warranted.

4. Long Chain Fatty Acids (LCFA)

Like MCFA, LCFA (13–22 carbons) must be ingested, most commonly in the forms of polyunsaturated omega-3 or omega-6 fatty acids. There is a focus on LCFA with numerous claims on health benefits ranging from cardiovascular disease (Nestel et al., 2015), chronic inflammation (Yates et al., 2014), and cancer to various neurological disorders, not restricting to traumatic brain injury and ischaemic insults (Lin et al., 2015). These fatty acids comprise between 15% and 30% of the dry weight of neural tissues (Yetimler et al., 2012). The mechanism of fatty acids crossing the blood brain barrier is still relatively unknown. It has been proposed that SCFA and MCFA can cross the lipid bilayers by passive diffusion due to their lipophilic properties (Kamp et al., 2003). LCFA (>12 carbons) are less soluble, thus are more challenging to be transported across the cell membrane than shorter fatty acids (Hamilton, 1999). Recent studies have indicated that the passage of fatty acids into the cell is aided by the presence of fatty acid transport proteins within the cell membrane (Mitchell et al., 2011; Pan et al., 2015).

Unlike MCFA, LCFA are not directly taken up to the liver through the portal vein. Instead, LCFA are taken up and modified into chylomicrons – a type of micelle – within the gut epithelium for transport through the lymphatic duct, then enter the body through systematic circulation. When there is a need for oxidation of LCFA, they are taken up by hepatocytes and into their mitochondria through carnitine palmitoyl transferase 1 (CPT1), however there is a preferential uptake of MCFA for oxidation as they do not require a transport protein. When there is no need for LCFA oxidation to provide ketones for energy, LCFA are taken up to be deposited in adipose tissue instead (Marten et al., 2006; Costantini et al., 2008). The systematic circulation of LCFA also allows for the brain to take up essential LCFA such as DHA and EPA from the blood. There are currently two suggested mechanisms for this: the first is simple passive diffusion across the cell membrane of the BBB (Pélerin et al., 2014) and the second is a protein mediated transport across the BBB (Mitchell et al., 2011).

4.1. Omega-3 fatty acids

Omega-3 fatty acids are considered as essential fatty acids, meaning that human cells cannot synthesize these acids *de novo* and have to be derived from diet. Oral supplement of these fatty acids do result in changes in omega-3 profiles in the cerebrospinal fluid (Guest et al., 2013; Freund Levi et al., 2014).

Of the omega-3 fatty acids, possibly the most well researched is decosahexaenoic acid (DHA), a LCFA derived from cold water marine oils. With a 22 carbon chain and 6 double bonds, it is the longest of the omega-3 fatty acids and the least saturated by ratio. Unlike shorter LCFA such as eicosapentaenoic acid (EPA) which were oxidised once they entered the brain from the plasma, unesterified DHA is largely (>80%) and selectively delivered *via* an acyl-CoA synthetase and acyltransferase to the *sn*-2 position of membrane phospholipids, particularly ethanolamine glycerophospholipid and phosphatidylcholine (Rapoport, 2013). As a constituent of cellular membranes, DHA contributes to membrane fluidity and is normally found in cells of the brain and retina.

A recent dose-response meta-analysis (Wu et al., 2015) reported that an increment of 100 g per week of fish intake was associated with an 11% lower risk of AD (RR = 0.89, 95% CI 0.79–0.99). However, there was no statistical evidence for similar inverse association between omega-3 fatty acids intake and risk of dementia or AD, nor between fish intake and risk of dementia.

Nonetheless, using amyloid-beta (Aβ) (1–40)-infused AD-model rats, Hashimoto et al. demonstrated that dietary administration of DHA reduced the amyloid burden from Aβ-infused brains, protected against and ameliorated the Aβ-induced learning impairment, with concurrent increases in DHA levels and decreases in the levels of lipid peroxide and reactive oxygen species in the cortico-hippocampal tissues (reviewed by Hashimoto and Hossain, 2011). Conversely, omega-3 LCFA deficiency in AD transgenic mice Tg2576 resulted in a decrease in N-methyl-D-aspartate (NMDA) receptor subunits, NR2A and NR2B, in the hippocampus and the cortex with a concomitant increase in apoptosis (Calon et al., 2005) Hence, highlighting the therapeutic potential of DHA.

Previous studies have shown that this LCFA is an important beneficial contributor to blood flow, brain structure and function (Haast and Kiliaan, 2015). Due to this, it is thought DHA levels have some relevance to the progression of neurodegenerative diseases such as AD. To support this, it has been observed post-mortem that DHA levels are reduced in brains of AD patients (Grimm et al., 2013), but whether this is directly linked to reduced blood flow, brain structure and function from DHA depletion has yet to be shown.

Alternatively, it has been reported that DHA supplementation does improve episodic memory, as well as semantic and working memory to a lesser degree, in normal adults (18 years and above) with no identifiable memory issues to minor memory issues to some degree (Yurko-Mauro et al., 2015), suggesting that DHA levels may be linked to cognitive function. Indeed, omega-3 deficient diet has been correlated with cognition decline in rats (Agrawal and Gomez-Pinilla, 2012). However, unlike the MCFA which was successful in clinical trial as a treatment for dementia, a recent randomised controlled trial of omega-3 fatty acid on cognitive impairment (600 mg EPA and 625 mg DHA per day, for 4 months; 75 participants) did not detect significant benefit on mood nor cognition (Phillips et al., 2015).

During injury caused by focal cerebral ischemia, it has been reported that DHA intravenous injection 3 h after assault improves motor and memory function compared to vehicle treated rats or mice (Belayev et al., 2009; Hong et al., 2015). In so far, there is no report of placebo-controlled trials in the treatment of TBI, although case studies of using high-dose omega-3 fatty acid concentrates – a mixture DHA and EPA, (1:2 ratio; 200–400 mg/kg) with (Sears et al., 2013) or without polyphenols (Lewis et al., 2013) – in the treatment of brain injury in comatose patients showed positive outcomes.

It is possible that the oxidation of DHA protects the neurons from oxidative stress. Indeed, DHA is under two clinical trials as a treatment for sport-related concussions (ClinicalTrials.gov Identifier: NCT01903525, NCT01814527). However, the resulting products from lipid oxidation are toxic to cells as they become lipid peroxides, further causing oxidative damage (Maruyama et al., 2014), so DHA as a safe treatment for ischemic assaults would need to be further investigated.

Deficiency of LCFA has been associated with attention deficit hyperactivity disorder. (reviewed by Janssen and Kiliaan, 2014). A small open-label pilot study of 6 boys and 3 girls diagnosed with ADHD (aged 8–16) reported significant improvements in behaviour after 8 weeks of daily EPA/DHA (16.2 g) treatment (Sorgi et al., 2007).

Plasma LCFA levels were significantly lowered in autistic children (Vancassel et al., 2001; Mostafa et al., 2015) and autistic adults (El-Ansary et al., 2011) in comparison with age-matched controls. Similarly, LCFA in red blood cells of autistic children were significantly lowered (Brigandi et al., 2015). A reduction in DHA in rodent brains have been correlated with changes in levels and signalling of neurotransmitters (reviewed by Müller et al., 2015). Thus, it is reasonable to test whether LCFA is a potential therapeutics for ASD. However, in so far, the reported trials were small. The first randomized, placebo-controlled pilot trial (Amminger et al., 2007) compared omega-3 fatty acids (6 weeks; 0.84 g/day EPA, 0.7 g/d DHA, n = 7) with placebo (n = 5) treatment in children with autism, and claimed 'an advantage of omega-3 fatty acids compared with placebo for hyperactivity and stereotypy, each with a large effect size' based on p = 0.098, repeated-measures analysis of variance. In contrast, the open label study of 6-week treatment of 0.93 g/day of EPA and DHA in 19 severe autistic adults did not report any improvement in behaviour (Politi et al., 2008). Another small double-blind, randomized, placebo-controlled trial (Yui et al., 2012), reported significant improvement in ABC social withdrawal scores and Social Responsiveness Scale communication subscale scores after 16-week of 240 mg/day ARA and DHA treatment (n = 7), as compared to placebo treated (olive oil, n = 6) autistic patients. More recently, a double-blind randomized trial of 48 children on a dietary DHA supplementation of 200 mg/day for 6 months reported no improvement in the core symptoms of autism (Voigt et al., 2014). Clinical trials of fatty acid as therapeutics for other neulogical disorder such as major depression and bipolar are similarly underpowered, i.e. very small sample sizes (Prior and Galduroz, 2012), and not reporting significant improvement.

Another well studied omega-3 LCFA is Docasopentaenoic Acid (DPA), a metabolite of the Eicosopentaenoic Acid (EPA) which is also found in cold water marine oils. Like DHA, it is an unsaturated LCFA and has been seen to attenuate spatial memory loss in older mice by protecting hippocampal cells (Kelly et al., 2011). It is thought to do so by reducing oxidative stress within the cells, similar to DHA.

4.2. Omega-6 fatty acids

A second group of LCFA is the omega-6 family. Similar to the omega-3 family, they differ by having a double bond at the ω-6 carbon, counting from the methyl end, instead of the ω-3 carbon. Like omega-3 LCFA, they are anti-inflammatory but are derived from plant sources instead of marine sources. The main types of omega-6 studied are linoleic acid due to the increase of its presence in the modern diet – particularly the North American diet (Blasbalg et al., 2011) – and arachidonic acid which is a product of metabolised linoleic acid (Sprecher, 2000). Arachidonic acid is necessary for the cell membrane integrity in the brain. There is a strong focus on arachidonic acid for its ability to down-regulate inflammation within the body – beneficial in diseases where there is inflammation of the brain. It has also recently been shown that an arachidonic acid diet can attenuate amyloid β deposition in Tg2576 mice by suppressing the proteolytic processing of the amyloid precursor protein (Hosono et al., 2015). This indicates that omega-6, in particular arachidonic acid may mitigate the progression of AD. This study however, has yet to be supported by other literature, so further investigation is warranted.

Notwithstanding the reported beneficial properties of these omega-6 LCFA, it has been reported that too much omega-6 during neural development of children negatively affects neurite growth, thus may contribute to poor neurodevelopment (Novak et al., 2008). There is a view that alteration of ratio of omega-6:omega-3 during early life may induce developmental changes in brain

connectivity, synaptogenesis, cognition and behaviour that are directly related to ASD (van Elst et al., 2014). This suggests that the use of omega-6 as a therapeutic agent may be inappropriate for young children or traumatic brain injury.

Despite the wealth of information on the action and potential uses of polyunsaturated LCFA, there is a very strong bias towards the study of DHA and other omega-3 fatty acids. Further investigation into the omega-6 fatty acids and other types of LCFA could potentially open other avenues of therapy for neurological disorders.

5. Conclusions

It can be seen that although preclinical studies demonstrated that fatty acids have a range of neuroprotective effects, potentially aiding prevention, recovery and slowing progression of neurological diseases in animal models. While the majority of research on fatty acids is conducted within relation to AD, much of what has been discovered can be transferred to other neurological disorders. The HDACi activity of SCFA can be utilized in PD, Huntington's disease, and even stroke (Hahnen et al., 2008), although careful consideration of its potential to cause ASD must be taken in account. However, in so far, there is a lack of report of clinical trials that support the application of fatty acids as a treatment for PD, Huntington's. In contrast, MCFA as a therapeutic is still a relatively new field of study, but it has shown significant potential for treating age-related neurological disorders; in particular providing an alternative energy source when glucose transports fails. In fact, the medium chain triglyceride – caprylidene has been approved by FDA as clinical dietary management of the metabolic processes associated with mild to moderate AD. On the other hand, LCFA, especially the marine oil derived DHA have been a subject of research for a long time. Preclinical studies have shown that DHA is essential to the normal functions of the brain and is protective against trauma or ischemic insults, all of which is highly relevant to understanding and treating any neurological disorder. However, clinical trials of omega-3 LCFA reported are not conclusive. Furthermore, there is a limited number of papers detailing the effects and the underlying mechanisms of SCFA and MCFA in the brain, nor is there much information on LCFA other than omega-3 LCFA, in particular DHA. As such, in the light of preclinical studies, the potential of using fatty acids in the treatment of neurological disorders is high, and should be further investigated, especially in terms of clinical trials with larger sample sizes.

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