Review

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Molecular effects of dietary fatty acids on brain insulin action and mitochondrial function

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Abstract: The prevalence of obesity and its co-morbidities such as insulin resistance and type 2 diabetes are tightly linked to increased ingestion of palatable fat enriched food. Thus, it seems intuitive that the brain senses elevated amounts of fatty acids (FAs) and affects adaptive metabolic response, which is connected to mitochondrial function and insulin signaling. This review will address the effect of dietary FAs on brain insulin and mitochondrial function with a special emphasis on the impact of different FAs on brain function and metabolism.

Keywords: brain; fatty acids; insulin signaling; ketone bodies; mitochondrial function; neuronal health.

Introduction: brain insulin signaling and mitochondrial function regulate metabolism

The brain receives peripheral signals of metabolic stimuli, processes this information and executes respective actions to properly orchestrate metabolism and behavior. This complex and energy-consuming process depends on the crosstalk of hormone signaling cascades in multiple organs with the brain. Glycolysis and subsequent

oxidative phosphorylation within mitochondria produce the required energy for the brain to integrate all information, whereas serum insulin levels among other hormones reflect the metabolic state of the body, which is sensed by the brain. Insulin signaling in the brain, more specifically in the hypothalamus, regulates food intake and energy expenditure. In addition, insulin action in the brain controls food reward circuitry and cognitive function (Kleinridders et al., 2014; Heni et al., 2015). This regulation depends on proper mitochondrial function as altered mitochondrial dynamics, excessive reactive oxygen species or increased mitochondrial uncoupling in, e.g. insulin sensitive, anorexigenic proopiomelanocortin (POMC) and orexigenic agouti-related protein (Agrp) neurons affects food intake and weight gain (Nasrallah and Horvath, 2014). Thus, metabolic control can only be maintained with proper neuronal action which requires a high amount of energy (Shetty et al., 2012). To facilitate the high energy demand of the brain, mitochondria mainly metabolize the end product of glycolysis – pyruvate – to generate ATP and moreover provide the ion homeostasis for a functional neuronal response. Although the brain is able to metabolize fatty acids (FAs) for energy production, it is well established that FAs are predominantly used by neurons to synthesize membrane components (Panov et al., 2014). Mitochondrial dysfunction can deteriorate ion homeostasis and lead to increased reactive oxygen species (ROS) production which causes insulin resistance. The increased amount of mitochondria-derived ROS can also be induced by excessive intake of saturated fatty acids (SFAs) like palmitic acid (PA) in high fat diet (HFD)-induced obesity, which *per se* induces hypothalamic insulin resistance and results in deregulated food intake (Nakamura et al., 2009; Posey et al., 2009; Kleinridders et al., 2013). Consequently, mice with a brain-specific insulin receptor knockout (NIRKO) are obese. Interestingly, this is associated with oxidative stress, mitochondrial dysfunction as well as an altered response to hypoglycemia (Bruning et al., 2000; Kleinridders et al., 2015; Magnan et al., 2015). In line, type 2 diabetic (T2D) mice and patients exhibit hypothalamic insulin resistance and increased ROS production and

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mitochondrial dysfunction. As disruption of mitochondrial function in the hypothalamus is sufficient to induce insulin resistance, it reveals the importance of insulin signaling and mitochondria to properly control neuronal metabolism (Kleinridders et al., 2013).

The nutritional status of the body is, on the one hand, sensed and mirrored by the β -cells of the pancreas and, on the other hand, reflected by the amount of fat in the body resulting in the release of their respective hormones insulin and leptin to regulate food intake. The brain also senses the nutritional status via insulin-sensitive glucose-sensing neurons within the hypothalamus to control food intake, metabolism and weight (Schwartz and Porte Jr, 2005; Diggs-Andrews et al., 2010). The accumulation of FAs or lipids can also serve as a signal to communicate the limitation of nutrients entering the circulation (Cermenati et al., 2015). Thus, the brain is also able to sense alterations in lipid levels and adapt the metabolism, respectively (Rasmussen et al., 2012). This process is called lipid sensing and is further discussed in the following paragraph. Overall, data is emerging that FAs can enter the brain, impact mitochondrial function, insulin action and whole-body physiology.

Fatty acid uptake and sensing in the brain regulates food intake and behavior

Lipid sensing in the brain, including the hypothalamus, regulates glucose homeostasis, insulin secretion and food intake. An important question arises with this: How do FAs enter the brain? In healthy subjects, the blood-brain barrier (BBB) restricts the passage of hydrophilic molecules into the brain but allows for the passage of small polar and hydrophobic molecules. There are so far three main mechanisms which facilitate FA entry into the brain: a reversible flip-flop mechanism to cross the plasma membrane into brain cells, simple diffusion through the extracellular space bound or unbound to fatty acid-binding protein (FABP) and specific transporters like fatty acid translocase CD36 and fatty acid transporter (FATP) (Hamilton and Brunaldi, 2007) (Figure 1). Interestingly, during development the expression levels of the different FATPs in the BBB are changed. The expression of FATP1, FATP4 and CD36 increase during the development and decrease during aging in microvessels potentially

Figure 1: Uptake of dietary FAs into the brain through the BBB.

(Top) Dietary FAs can enter the brain through 1a) specific transporters like FA translocase CD36 and FATPs. 1b) Some FAs are bound by different FABPs or cross the BBB by 2) diffusion or 3) a reversible flip-flop mechanism. (Bottom) Cytosolic transport of long-chain FA transport into mitochondria via CPT-1 is required for mitochondrial β -oxidation of FAs. The β -oxidation generate acetyl-CoA, which enters the TCA cycle and the products are used in the ETC. These processes are influencing the insulin signaling pathway and which, in turn, promotes mitochondrial metabolism. ATP, Adenosintriphosphat; CPT-1, carnitine palmitoyltransferase 1; ETC, electron transport chain; FABP, fatty acids-binding protein; FATP, fatty acid transporter; TCA, tricarboxylic acid.

explaining the reduction of neuroprotective FAs, like omega-3 FAs, in the aged brain (Pelerin et al., 2014; Denis et al., 2015).

FAs can be categorized depending on their chain length. Short-chain fatty acids (SCFAs) are characterized as FAs with less than six carbon atoms, while medium-chain fatty acids (MCFAs) have a chain length up to 12 carbon atoms. Long-chain fatty acids (LCFAs) exhibit an aliphatic tail of 13–21 carbons and very long-chain fatty acids (VLCFAs) have an aliphatic tail of 22 or more carbon atoms. They can be further classified as SFAs when containing no double-bonds, mono- when containing one or PUFAs when containing several. Depending on their properties FAs exert different effects on brain insulin signaling and mitochondrial function. To induce intracellular signals determining the response to food intake, dietary FAs can enter the cells via CD36 and be metabolized causing intracellular effects but also can be recognized by G-protein-coupled receptors 40 and 120 (GPR40/GPR120) depending on their chain-length with varying affinity (Sundaresan and Abumrad, 2015; Miyamoto et al., 2016).

Circulating FAs like oleic acid (OA), butyric acid, myristic acid, PA, lignoceric acid, linoleic acid or the omega-3 FA docosahexaenoic acid (DHA) enter the brain through specific transporters such as CD36 and FATP (also known as SLC27) (Mitchell et al., 2011). While SCFAs can be also transported via monocarboxylate transporters (MCTs), CD36 plays a major role in LCFA transport across the BBB and FATPs are important for LCFA and VLCFA transport (Gupta et al., 2006; Mitchell et al., 2011). Thus, the dietary DHA uptake into the brain is mediated by FATP1 and FATP4 (Pan et al., 2018), while an inhibition of FATP and CD36 in the endothelial cells of the BBB decreases OA transport through the BBB (Mitchell et al., 2009). Once in the cell, FAs can be activated by acyl-CoA synthetases forming FA-CoA in the cytosol. The accumulation of cytosolic LCFA-CoAs activates protein kinase C (PKC) and alters the activation of K_{ATP} -channels in neurons and subsequently neuronal transmission (Yue and Lam, 2012). In addition, cytosolic LCFA-CoAs are transported into the mitochondria for β -oxidation via carnitine palmitoyltransferase 1 (CPT-1). CPT-1 mediates long-chain acyl-CoAs transport into mitochondria for β -oxidation for fuel production showing the importance of lipid flux in the central nervous system (CNS). Demonstrating the importance of functional FA metabolism in the brain, knockout (KO) of brain-specific *Cpt1c* in mice causes reduced food intake and body weight while paradoxically increasing the susceptibility to HFD-induced obesity (Wolfgang et al., 2006). Similarly, inhibition of

CPT1A activity normalizes hypothalamic levels of LCFA-CoA and inhibits food intake. Moreover, it is sufficient to normalize lipid sensing in the brain after short-term over-feeding in rats (Pocai et al., 2006). The intermediate in FA biosynthetic pathway malonyl-CoA can inhibit CPT-1 and alters food intake (Gao et al., 2013). Inhibition of the fatty acid synthase (FAS) in the brain increases hypothalamic malonyl-CoA levels and reduces food intake (Gao et al., 2013). Consequently, reduced malonyl-CoA and LCFA-CoA levels due to hypothalamic overexpression of malonyl-CoA decarboxylase leads to increased food intake and impaired liver glucose homeostasis (He et al., 2006). Thus, it seems that hypothalamic lipid sensing and FA uptake is required for the maintenance of glucose homeostasis.

As already mentioned, intracellular FAs can be metabolized by mitochondrial β -oxidation but also used for the formation of ketone bodies (KB) (Auestad et al., 1991). This process is found in astrocytes and can replace glucose as the major energy supply for the brain under conditions like fasting (Guzmán and Blásquez, 2001). Especially during neonatal development, the KB 3-hydroxybutyrate and acetoacetate are precursors for the synthesis of amino acids and lipids (Morris, 2005). However, neurons, microglia and oligodendrocytes do not use FAs as a direct, main energy supply, but they are able to use KB derived from astrocytes and hepatocytes in the liver, which are the major distributors of KB for the brain (Guzmán and Blásquez, 2001). That only astrocytes are able to oxidize FAs is controversially discussed, as some studies show that neurons are capable of β -oxidation and also microglia express LCFA-CoA ligase to potentially use FAs as an energy supply (Takahashi et al., 2014; Zhang et al., 2014) (own observation).

Family members of GPR can be activated by FAs in the brain (Sundaresan and Abumrad, 2015; Miyamoto et al., 2016). SCFAs are mainly recognized by GPR41 and GPR43 while omega-3, omega-6 PUFAs and LCFAs like OA are mainly recognized by GPR40 and GPR120 (Talukdar et al., 2011; Dragano et al., 2017). It has been shown that the administration of a GPR120 agonist in mice acutely reduces food intake and chronically improves anxiety-like behavior (Auguste et al., 2016). Activation of GPR40, also called free FA receptor 1, improves cognitive function in an Alzheimer's disease (AD) mouse model by increasing neurotrophic factors and increases neurogenesis in hippocampal neurons (Khan et al., 2016). Interestingly, these behavioral effects are also modulated by insulin signaling and mitochondrial function (Kleinridders et al., 2014; Hollis et al., 2015; Kleinridders et al., 2015).

Altered fatty acid uptake in the brain

Research has focused on brain lipid sensing and understanding the effects of different FAs on brain function. Yet, the complex uptake of dietary FAs into the brain has not been intensively investigated. Animals fed a HFD exhibit increased levels of SFAs in the brain which are enriched in the diet, suggesting that increased fat consumption increases dietary fat uptake into the brain (Rodríguez-Navas et al., 2016). Indeed, uptake of PA, which represents the second most abundant FA in the cerebrospinal fluid (CSF) of obese patients, is increased in brains of these patients (Karmi et al., 2010; Jumpertz et al., 2012). Increased PA levels in the brain can disrupt brain nutrient sensing, as it specifically decreases lipid uptake into astrocytes and induces hypothalamic insulin resistance and weight gain (Posey et al., 2009; Gao et al., 2017). Reduced astrocytic lipid uptake triggered by lipoprotein lipase deficiency is also responsible for hypothalamic insulin resistance and increased ceramide content (Gao et al., 2017). Furthermore, arachidic acid and PA can activate toll-like receptor 4 (TLR4) signaling, induce hypothalamic inflammation and insulin resistance (Kleinridders et al., 2009; Milanski et al., 2009). Adding to this, overload of FAs increases hypothalamic ceramide synthesis which in turn can disrupt the endocrine signaling of insulin and leptin. With that, dysfunction of lipid sensing might be contributing to the development of obesity and type 2 diabetes (Morgan et al., 2004; Magnan et al., 2015; Gao et al., 2017).

Not only the consumed amount of FAs but also the quality of dietary fat may influence FA transport into the brain. Thus, uptake of PA is lower in tallow diets compared to corn oil diets, although tallow diets are enriched in SFAs (Wang et al., 1994). Additionally, studies feeding male C57BL/6 mice an SFA-enriched diet for 6 months revealed not only clear differences in lipid classes in plasma compared to chow diet-fed mice, but also significant differences in several lipid species in the brain (Giles et al., 2016). Studies conducted to investigate sex-specific dimorphism in FA composition of the brain after feeding chow or HFD revealed that males exhibit increased levels of SFAs in the brain compared to females. At the same time, omega-6 FAs were reduced after 16 weeks of feeding a HFD compared to females. In contrast to these results, plasma concentrations of FAs were not changed between the sexes suggesting a sex-specific difference in processing or uptake of FAs from the plasma into the brain (Morselli et al., 2016; Rodríguez-Navas et al., 2016). A different uptake and metabolism of FAs into the brain in females

might be caused by an estrogen-receptor-mediated mechanism. Indeed, 40 years ago, it was already shown that estrogen increases FA utilization in peripheral tissues, suggesting that this might also happen in the brain (Ockner et al., 1979). Interestingly, estrogens are able to stimulate mitochondrial biogenesis, regulate mitochondrial gene expression and dynamics as well as maintaining calcium homeostasis and with that influence mitochondrial function, morphology – and ultimately – insulin sensitivity and glucose metabolism (Klinge, 2017; Allard et al., 2018; Min et al., 2018). Clearly more research is needed to decipher the precise effect of estrogens on mitochondrial function and FA utilization in the brain.

Saturated fatty acids and high fat diet

The fat fractions of a HFD used in research can vary and account for 20–60% of energy content of the diet, but most of them are hypercaloric in comparison to rodent normal chow diets. The basic fat component of the diets varies between animal-derived fats or plant oils. Feeding rodents a HFD enriched in SFAs can induce body weight gain, glucose intolerance, central and peripheral insulin as well as leptin resistance and mitochondrial dysfunction (Table 1). These characteristics of diet-induced obesity and metabolic disorders in rodents are comparable to the human metabolic syndrome, establishing HFD-induced obesity in rodents as an accepted model for the in-depth research of these metabolic diseases.

PA, the most abundant SFA in the brain, can be provided by the diet or synthesized endogenously from other FAs. It is categorized as a LCFA and is highly abundant in HFDs. Studies have shown that about 50% of radiolabeled PA is oxidized in the brain rapidly after administration. Hence, plasma-derived PA may enter to an equal extent into both the oxidative pathway used for energy supply and the synthetic pathway by being incorporated into phospholipids of the plasma membrane (Gnaedinger et al., 1988). It is well known that the administration of PA is able to induce insulin resistance in the brain as well as in other peripheral tissues like the liver (Benoit et al., 2009; Kleinridders et al., 2009; Milanski et al., 2009; Posey et al., 2009). Along with it, PA increases oxidative stress, neuroinflammation and is able to contribute to the onset of neuronal apoptosis, especially in the hypothalamus (Zhang et al., 2005; Moraes et al., 2009). The mechanism of how PA induces neuroinflammation might be multifactorial. A recent study in hypothalamic N42 cells revealed that the induction of proinflammatory interleukin 6 (IL-6) and tumor necrosis factor α (TNF α)

Table 1: FAs affect mitochondrial function and insulin sensitivity.

Fatty acid	<i>In vivo</i>	<i>In vitro</i>	Effect on mitochondria	Effect on insulin signaling
HFD	Body weight gain, glucose intolerance (Freeman et al., 2014)	–	Mitochondrial dysfunction (Schneeberger et al., 2013; Freeman et al., 2014), altered mitochondrial dynamics (Schneeberger et al., 2013)	Insulin resistance (Freeman et al., 2014)
PA	Neuroinflammation, oxidative stress, apoptosis (Zhang et al., 2005; Moraes et al., 2009) attenuates insulin-induced brain activity (Neschen et al., 2018)	Neuroinflammation, oxidative stress, apoptosis (Zhang et al., 2005; Moraes et al., 2009)	Disrupts mitochondrial dynamics (Diaz et al., 2015; Jiang et al., 2018)	Insulin resistance (Benoit et al., 2009)
OA (MUFA)	Reduces food intake, decreases ROS (Schwinkendorf et al., 2011)	Decreases ROS (Schwinkendorf et al., 2011)	Increases mitochondrial uncoupling (Davis et al., 2008)	Prevents PA-induced insulin resistance (Kwon et al., 2014)
PA	Decreases ROS (Schwinkendorf et al., 2011)	Decreases ROS (Schwinkendorf et al., 2011)	Increases mitochondrial uncoupling (Davis et al., 2008)	–
ALA	Neuroprotective effect, decreases ROS, decreases TNF α expression (Maczurek et al., 2008; Han et al., 2012)	Decreases ROS (Maczurek et al., 2008; Han et al., 2012)	–	Activation of insulin signaling, improves insulin sensitivity (Maczurek et al., 2008; Han et al., 2012; Wang et al., 2018)
Omega-6 PUFA (e.g. AA)	–	Decreases ROS, increases SOD activity, neuroprotective effect (Wang et al., 2006)	Induces mitochondrial swelling (Hillered and Chan, 1989)	–
Omega-3 PUFA (e.g. DHA)	Neuroprotective function (Afshordel et al., 2015; Zarate et al., 2017)	Neuroprotective function (Afshordel et al., 2015; Zarate et al., 2017)	Improves mitochondrial function (Mayurasakorn et al., 2016)	Increases AKT activation (Akbar et al., 2005)
KB	Improves cognitive function in neurodegeneration (Fuehrlein et al., 2004), reduces ROS (Sullivan et al., 2004)	–	Upregulates mitochondrial biogenesis, respiration and uncoupling (Sullivan et al., 2004; Bough et al., 2006; Ahola-Erkila et al., 2010)	Induces systemic insulin resistance in healthy subjects (Kinzig et al., 2010; Ellenbroek et al., 2014), but increases cerebral insulin sensitivity in neurodegeneration

Dietary FAs and their studied effects *in vivo* as well as *in vitro* experiments are displayed. Their main effects in central insulin signaling and mitochondrial function are shown. AA, Arachidonic acid; AKT, protein kinase B; ALA, α -lipoic acid; DHA, docosahexaenoic acid; FA, fatty acid; HFD, high fat diet; KB, ketone bodies; MUFA, monounsaturated fatty acids; OA, oleic acid; PA, palmitic acid; PUFA, polyunsaturated fatty acid; ROS, reactive oxygen species; TNF α , tumor necrosis factor α .

can be independent of TLR4, but rather – at least partially – through the accumulation of ceramides. Interestingly, this PA-induced accumulation of ceramides in neurons could be decreased by simultaneous treatment with OA and eicosapentaenoic acid (EPA) (Sergi et al., 2018). Other studies have shown that PA activates TLR4 signaling, though PA seems not to directly bind to the receptor (Milanski et al., 2009; Lancaster et al., 2018). In adipocytes, however, it was shown that PA deriving from a HFD can bind fetuin-A, the major carrier protein of FAs in the circulation, which then binds to TLR4, unveiling a mechanism of PA-induced TLR4 activation (Pal et al., 2012). Furthermore, PA can decrease mitofusion 2 (Mfn2) protein levels in the arcuate nucleus of the hypothalamus, a crucial player of mitochondrial

dynamics. It has been shown that disrupted dynamics due to neuron-specific KO of Mfn2 deteriorate mitochondrial function, cause increased oxidative stress and insulin resistance (Diaz et al., 2015; Jiang et al., 2018). Additionally, β -oxidation of PA almost exclusively takes place in the mitochondria, which can increase oxidative stress and lead to mitochondrial abnormalities such as membrane rupture and swelling caused by ‘overheating’ of the mitochondria in diet-induced obesity as shown in enterocytes (Sun et al., 2018). Along with these metabolic dysfunctions, PA administration can induce anxiety-like behavior, a phenotype also present in brain-insulin receptor deficient mice (Moon et al., 2014; Kleinridders et al., 2015; Cai et al., 2018). Interestingly, studies showed that acute PA application in the brain

attenuates insulin-induced brain activity but is able to amplify insulin action in the periphery, while chronic PA infusion into the brain causes insulin resistance (Kleinridders et al., 2009; Neschen et al., 2018). These data demonstrate differences between acute and chronic effects of FAs in the brain as well as differential effects of PA administration in the brain compared to peripheral tissues. Overall, PA negatively impacts brain function and along with it, whole body metabolism by inducing neuroinflammation, oxidative stress, mitochondrial dysfunction and insulin resistance. As it is the most abundant FA in HFDs and enriched in the brains of obese people, this diet can lead to the discussed effects and cause obesity as well as metabolic disorders.

In contrast to PA, SCFAs can be beneficial for metabolic health. For example, butyric acid is mainly known for its health promoting effects in colon cells (Wong et al., 2006). It is recognized by GPR41/43 and can also cross the BBB, like other SCFAs, through MCTs (Tsuji, 2005; Talukdar et al., 2011). Its structural relation to KB suggests a microbiota-gut-brain axis where butyrate is utilized by mitochondria and may be used for treating neurological disorders (Stilling et al., 2016). Another SCFA – acetic acid – enters the brain, is metabolized by mitochondria and causes a reduction in food intake via a central homeostatic mechanism (Frost et al., 2014). Studies with the MCFA α -lipoic acid (ALA), recognized by GPR120, show that ALA in the brain exerts neuroprotective effects mediated by the activation of proteins (extracellular signal-regulated kinase and phosphatidylinositol 3-kinase) implicated in the insulin signaling pathway (Talukdar et al., 2011; Wang et al., 2018). Furthermore, in diabetic neuropathy and AD patients, the application of ALA improves insulin sensitivity, decreases oxidative stress, down-regulates the expression of TNF α and improves brain function (Maczurek et al., 2008; Han et al., 2012). MCFAs like lauric acid, caprylic acid and octanoic acid are discussed as being beneficial in neurodegenerative diseases like amyotrophic lateral sclerosis, reduces epileptic episodes and have been shown to promote insulin signaling (Zhao et al., 2012; Thevenet et al., 2016; Rial et al., 2018). VLCFAs can enter the cell and are first metabolized in peroxisomes before being completely metabolized in mitochondria. They can accumulate in the brain as well in the plasma and are linked to severe neurological disorders like adrenoleukodystrophy characterized by lipotoxic neuroinflammation and demyelination (Khan et al., 2010). Overall, compared to LCFAs, there is a lack of data about the impact of SCFAs and VLCFAs on brain function and further research is needed to address this important aspect.

Monounsaturated fatty acids (MUFAs)

OA is the highest abundant MUFA in the CSF in healthy and obese patients (Illingworth and Glover, 1971; Jumpertz et al., 2012). It passes the BBB via FATP1 and CD36 (Mitchell et al., 2009). Increased levels of OA in the CSF reduce food intake via melanocortin 4 receptor signaling in the hypothalamus and increases mitochondrial uncoupling (Schwinkendorf et al., 2011). Further administration of OA into the brain exhibits insulin-like effects via K_{ATP} -channels and suppression of glucose production (Obici et al., 2002). The shorter MUFA palmitoleic acid (16:1n7) also impacts mitochondrial function. It increases mitochondrial uncoupling via increased activation of uncoupling protein (UCP)-mediated respiration and decreases ROS in the mitochondria, thereby exerting neuroprotective effects after neurological insult (Davis et al., 2008). Interestingly, OA preconditioning can prevent palmitate-induced insulin resistance as well as mitochondrial dysfunction in primary rat cortical neurons highlighting the beneficial effect of OA on neuronal insulin action (Kwon et al., 2014). Yet, intracerebroventricular application of OA in combination with a short-term HFD feeding impairs the hypothalamic nutrient sensing by deteriorating the anorectic effect of OA contributing to the induction of hepatic insulin resistance as well as rapid weight gain (Morgan et al., 2004). These data demonstrate the importance and complexity of the interaction of different FAs for neuronal health as well as regulation of food intake.

Preventive administration of MUFAs before the lipotoxic insult of SFAs in the brain can rescue its deteriorating effects on energy homeostasis. It has been shown that supplementation of OA in combination with PA alters the metabolic fate of PA by not increasing diacylglycerol levels which can activate PKC and further insulin resistance but rather being incorporated into triglycerides and increasing the expression of genes involved in mitochondrial β -oxidation in the presence of OA (Coll et al., 2008). These data once again highlight that more research is needed to understand the complex interplay of FAs on insulin action.

Polyunsaturated fatty acids

PUFAs are part of all membranes in the body and make up the hydrophobic boundary between cell compartments. They have profound effects on brain health and function by mostly acting as neuroprotective compounds in the brain (Zarate et al., 2017). Because they cannot be synthesized *de novo*, they have to be taken up by the diet and are recognized in the brain by GPR40/120 (Benatti et al.,

2004; Oh et al., 2010; Dragano et al., 2017). A diet being in perfect balance has a ratio of omega-6 to omega-3 PUFAs of about 1:1, while Western diets, which are strongly associated with the establishment of insulin resistance, have an unbalance of this ratio with elevated omega-6 PUFAs levels compared to omega-3 PUFAs levels (10:1–20:1) (Simopoulos, 2011). As this unbalance of omega-6 PUFAs in common Western diets affects neuronal health (Haag, 2003), an enrichment of omega-3 PUFAs is discussed as a therapeutic approach for neurological diseases. A possible supplementation with fish or krill oil is discussed as a therapeutic approach due to high amounts of omega-3 PUFAs which can enter the brain and affect its function (Ahn et al., 2018). This approach has even been used in studies to treat bipolar episodes in patients with depression, because an increased omega-6 PUFAs uptake correlates with the severity of depression, a disease which is linked to brain insulin resistance (Lavori et al., 1993; Adams et al., 1996; Stoll et al., 1999; Kleinridders et al., 2015). However, the studies concerning these effects on depressive behavior are highly controversial. Krill oil contains elevated amounts of the long-chained omega-3 PUFAs EPA and DHA. DHA is an abundant, essential FA in brain phospholipids and must pass the BBB as the brain cannot synthesize DHA. This uptake is mediated via major facilitator superfamily domain containing 2A (MFSDA2A), a receptor highly enriched in brain microvessels (Nguyen et al., 2014). As an enrichment of omega-3 PUFAs in neuronal membranes increases its fluidity, it enables effective and fast neuronal transmission (Cunnane et al., 2009). DHA exerts neuroprotective functions via suppression of the nuclear factor-kappa B (NF κ B) or via conversion to neuroprotection D-1 which is anti-inflammatory and neuroprotective (Afshordel et al., 2015; Zarate et al., 2017). Along with it, DHA enhances the activation of insulin-responsive protein kinase B/AKT (Akbar et al., 2005) and protects the brain from hypoxic ischemia. Consequently, dietary restriction, which activates the expression of insulin receptor substrate-1 (IRS-1) and AKT, improves neuronal survival and reduces BBB damage after hypoxic ischemia (Tu et al., 2016). Thus, insulin signaling and DHA treatment seem to have a synergistic neuroprotective effect. A neuroprotective effect is also propagated by the improvement of mitochondrial function after DHA supplementation (Mayurasakorn et al., 2016). It has been observed, that especially omega-3 PUFAs concentration in the brain declines in neurodegenerative diseases like AD and Parkinson's disease (PD). In line with this, rodent models lacking these omega-3 PUFAs exhibit severe cognitive impairment, which is associated with decreased brain insulin action (Innis, 1991; Talbot et al., 2012).

Furthermore, it has been shown that omega-3 PUFAs like DHA also promote the clearing of amyloid- β from the brain through the glymphatic system pointing again to the protective effects of omega-3 PUFAs against neurodegenerative diseases like AD (Ren et al., 2017). In the aged brain, DHA is significantly reduced with a decreased mitochondrial function and insulin receptor expression (Zhao et al., 2004; Afshordel et al., 2015). Oral supplementation of DHA in aged mice not only improves brain mitochondrial function (Afshordel et al., 2015), but also inhibits ROS production in neurons and prevents oxidative stress-induced apoptosis. It further ameliorates mitochondrial dysfunction by improving mitochondrial dynamics in early brain injury (Zhang et al., 2018). Additional studies using the omega-6 PUFA arachidonic acid (AA) on rat hippocampal slices after hypoxic brain injury have revealed that AA increases the antioxidant capacity demonstrating potential neuroprotective effects of also omega-6 PUFAs (Wang et al., 2006). Concluding, these data show the importance of balanced PUFA-enriched diets for a functional and healthy brain, with positive effects of DHA on central insulin sensitivity and mitochondrial function. Due to its complex interaction, more research is needed to fully elucidate the precise interaction and impact of omega-3 and -6 PUFAs on brain insulin action.

Ketone bodies

In the event of a lack of glucose such as prolonged fasting or by feeding a high fat/low carbohydrate diet, KB are an important energy source for the brain, which can be also generated by FAs as stated earlier (Morris, 2005). A low carbohydrate/HFD – known and further referred to as a ketogenic diet (KD) – is composed of high fat (80–90%), low carbohydrate, and low protein. A KD induces fasting-like effects by increasing the production of KB (f.e. acetoacetate, β -hydroxybutyrate and acetone) and increases hepatic FA oxidation. KD is a nutritional approach where liver mitochondria oxidize free FAs to acetoacetate and β -hydroxybutyrate (Morris, 2005; Cahill, 2006). A KD contains high amounts of SFAs and PUFAs and increases plasma circulating free FAs and cerebral KB levels. Studies conducted to treat seizures with a KD, enriched in medium chain triglycerides, show an increase of plasma decanoic acid concentration, which is able to cross the BBB (Rogawski, 2016). It has been shown that an elevated availability of circulating free FAs like DHA and EPA increases the FA levels in the brain which may affect brain function (Spector, 2001). Yet, the uptake of dietary FAs from a KD into

the brain has not been well investigated. Importantly, the ratio of SFAs and PUFAs in a KD influences glucose and insulin sensitivity. Healthy patients treated with a KD containing high levels of PUFAs exhibited reduced blood glucose levels and increased insulin sensitivity compared to patients treated with a KD containing high levels of SFAs (Fuehrlein et al., 2004). Whether this also affects brain insulin sensitivity has not yet been elucidated. But it has been shown that a KD can cause an upregulation of transcripts for energy metabolism, oxidative phosphorylation, mitochondrial biogenesis and other mitochondrial proteins in the brain as well as being described in neuronal cell cultures (Bough et al., 2006; Ahola-Erkila et al., 2010). Furthermore, KD increases maximal mitochondrial respiration, enhances mitochondrial uncoupling proteins and reduces ROS in the brain showing its beneficial effect on brain mitochondrial function (Sullivan et al., 2004). Furthermore, the medium-chain FA octanoic acid, which has been shown

to promote insulin action, serves also as a substrate for β -oxidation in astrocytes and stimulates ketogenesis by formation of acetyl-CoA, a process known to be neuroprotective (Thevenet et al., 2016).

Though a KD improves cognitive and motor function in neurodegenerative disease patients (Stafstrom and Rho, 2012), it has been shown that a long-term KD results in systemic glucose intolerance, insulin resistance and dyslipidemia (all features that are also associated with metabolic syndrome) in healthy subjects (Kinzig et al., 2010; Ellenbroek et al., 2014). Studies with obese mice maintained on a KD demonstrated variable results regarding weight loss (Kennedy et al., 2007; Badman et al., 2009; Paoli, 2014). Despite this variance, it has been shown that a KD improves energy and glucose metabolism, insulin sensitivity and circulating lipid profile in obese and T2D mice and in humans (Kennedy et al., 2007; Badman et al., 2009; Mobbs et al., 2013; Paoli, 2014). Its precise effect on brain insulin action warrants further research.

Figure 2: Dietary FAs and their effect on insulin sensitivity and mitochondrial function in healthy and HFD-induced states.

In healthy conditions (left side), FAs like OA and DHA can enter the brain cell (through CD36 and FATPs, respectively). OA can induce the activation of UCP2 which leads to mitochondrial uncoupling and decreased ROS production. Functional mitochondria are implicated in increased insulin sensitivity in the brain. DHA can increase AKT-activation and with that increase insulin signaling in the cell. It is proposed that family members of GPR (GPR40/120) recognize both OA and DHA and increase insulin sensitivity. Under a HFD feeding (right side), the most abundant saturated FA PA can enter the cell through CD36 with not well-investigated intracellular effects on insulin signaling and mitochondrial function. It is known that a HFD induces mitochondrial dysfunction with increased ROS production and insulin resistance in the brain. Extracellular PA is proposed to be recognized by TLR4, downstream targeting MyD88 and the stress kinase IKK and in turn activating NF κ B-signaling inducing neuroinflammation and insulin resistance. AKT, protein kinase B; DHA, docosahexaenoic acid; GPR, G protein-coupled receptor; HFD, high fat diet; IKK, I κ B kinase; NF κ B, nuclear factor κ B; ROS, reactive oxygen species; TLR4, toll-like receptor 4; UCP2, uncoupling protein 2.

Conclusions

It is well known that the SFA PA enters the brain, is enriched in the CSF of patients with metabolic syndrome and causes insulin resistance and mitochondrial dysfunction in the brain, while MUFAs and omega-3 PUFAs seem to be beneficial for brain insulin action and mitochondrial function (Figure 2). Though research has focused on lipid sensing, the precise mechanisms for brain FA uptake need further research. Are there specific receptors and transporters in distinct brain regions for FAs of different chain length in healthy and metabolic diseased conditions? We have recently shown that glucose metabolism enzyme expression differs between brain regions and HFD can alter glucose transporter expression in the brain (Jais et al., 2016; Kleinridders et al., 2018). This observation seems also plausible for FA metabolism in various brain regions, as structures such as the corpus callosum are highly myelinated and contain elevated levels of lipids, whereas other brain regions enriched in astrocytes are more prone to use β -oxidation. Here research should focus on investigating regional differences in energy metabolism with an emphasis on FA utilization. Furthermore, it is important to keep in mind that during food intake, a mixture of FAs is ingested which will affect their metabolic fate. More studies concerning the quality of the FAs and their interaction with each other and their impact on brain insulin action as well as mitochondrial function are of crucial relevance. In recent studies, it has been shown that triglycerides are also able to cross the BBB, can induce leptin and insulin resistance, are associated with a decrease in cognition and satiety and can alter reward behavior (Cansell et al., 2014; Banks et al., 2018). Here, the impact of different FAs' composition in triglycerides will help to elucidate the complex effects of triglycerides on brain function and metabolism. Additionally, more studies regarding the direct or indirect effect of dietary FAs in the brain are necessary. For example, the precise molecular mechanism of several dietary FAs impacting mitochondrial function is rather unclear. The role of mitochondrial function in the regulation of energy homeostasis is linked to insulin action, as mitochondrial dysfunction can induce hypothalamic insulin resistance (Kleinridders et al., 2013). The role of FAs in regulating brain energy homeostasis is tightly connected to brain insulin action and mitochondrial function and with this essential for neuronal health. Overall dietary uptake of FAs in the brain affects brain function and metabolism and seems to be implicated in the development of metabolic syndrome as well as neurodegenerative diseases.

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