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Brain energy metabolism spurns fatty acids as fuel due to their inherent mitotoxicity and potential capacity to unleash neurodegeneration

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ABSTRACT

The brain uses long-chain fatty acids (LCFAs) to a negligible extent as fuel for the mitochondrial energy generation, in contrast to other tissues that also demand high energy. Besides this generally accepted view, some studies using cultured neural cells or whole brain indicate a moderately active mitochondrial β-oxidation. Here, we corroborate the conclusion that brain mitochondria are unable to oxidize fatty acids. In contrast, the combustion of liver-derived ketone bodies by neural cells is long-known. Furthermore, new insights indicate the use of odd-numbered medium-chain fatty acids as valuable source for maintaining the level of intermediates of the citric acid cycle in brain mitochondria. Non-esterified LCFAs or their activated forms exert a large variety of harmful side-effects on mitochondria, such as enhancing the mitochondrial ROS generation in distinct steps of the β-oxidation and therefore potentially increasing oxidative stress. Hence, the question arises: Why do in brain energy metabolism mitochondria selectively spurn LCFAs as energy source? The most likely answer are the relatively higher content of peroxidation-sensitive polyunsaturated fatty acids and the low antioxidative defense in brain tissue. There are two remarkable peroxisomal defects, one relating to α-oxidation of phytanic acid and the other to uptake of very long-chain fatty acids (VLCFAs) which lead to pathologically high tissue levels of such fatty acids. Both, the accumulation of phytanic acid and that of VLCFAs give an enlightening insight into harmful activities of fatty acids on neural cells, which possibly explain why evolution has prevented brain mitochondria from the equipment with significant β-oxidation enzymatic capacity.

Contents

Abbreviations: AcAc, acetoacetate; BBB, blood-brain barrier; CRC, Ca^{2+} retention capacity; ETF, electron transfer flavoprotein; IMM, inner mitochondrial membrane; LCFAs, long-chain fatty acids; LCHAD, long-chain 3-hydroxyacyl-CoA dehydrogenase; MCFAs, medium-chain fatty acids; $\Delta\psi_m$, mitochondrial membrane potential; MTP, mitochondrial trifunctional protein; PUFAs, polyunsaturated fatty acids; PPAR, peroxisome proliterator activator receptor; RBM, rat brain mitochondria; RLM, rat liver mitochondria; ROS, reactive oxygen species; βOHB, ß-hydroxybutyrate; VLCFAs, very long-chain fatty acids; X-ALD, X-linked adrenoleukodystrophy.

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1. Introduction: brain lipids and cerebral energy metabolism at a glance

Brain consists mostly of fat. Therefore, already Stone Age people used animal brains for tanning of hides. Brain fat contains a high variety of complex lipids, which are characterized by a unique composition of polyunsaturated fatty acids (PUFAs), dominated by arachidonic and docosahexaenoic acid (Brenna and Diau, 2007; Brenna and Carlson, 2014; Chen and Bazinet, 2015). Docosahexaenoic acid plays a particular role within the brain, mostly due to its involvement in the neuron-to-neuron communication (Cunnane and Crawford, 2014). It is also crucial that the abundance of cerebral fatty acids is modulated by the diet (Horwitt et al., 1959; Brenna and Carlson, 2014). Moreover, the content of major lipids, such as phosphatidylcholine and sphingomyelin, alters in an age-dependent manner (Dawson, 2015). Some lipids operate at low quantities in signaling pathways.

From the bioenergetic point of view it is important to emphasize that brain is a high oxygen consumer, accounting in the newborn human brain for up to 74% and in the adult brain to about 20–23% of the body's daily energy intake (Cunnane and Crawford, 2014). Several features, such as high oxygen consumption, a large content of peroxidation-sensitive PUFAs and a strong dependency on the supply of glucose are features that make the brain vulnerable to even small metabolic changes. In this review, we discuss the contribution of the β-oxidation of medium- and long-chain fatty acids to the cerebral energy metabolism. Moreover, toxic activities of fatty acids are considered in this context. We take Refsum disease and X-linked adrenoleukodystrophy (X-ALD) to illustrate the pathobiochemical consequences of accumulation of specific fatty acids in the neural tissue.

In the mammalian brain, energy is used mostly for neurotransmission plus maintenance of excitability, intracellular signaling, axonal or dendritic transport, synthesis of neurotransmitters, and to a lower extent protein synthesis (see for review (Ames, 2000) and citations therein). More than 90% of the ATP is generated in mitochondria using oxidative phosphorylation. The largest portion of the ATP turnover occurs in the grey matter, probably during presynaptic and postsynaptic signaling (Clarke and Sokoloff, 1994; Attwell and Laughlin, 2001). Consequently, neurons demand for most of the energy, whereas the energy consumption of astrocytes amounts to only about 5–15% of the total energy requirement of the brain (Clarke and Sokoloff, 1994). The energy metabolism of neurons is mainly aerobic respiration and that of astrocytes mainly anaerobic glycolysis.

In addition, histochemical staining for lactate dehydrogenase and cytochrome *c* oxidase in regions of poor or rich capillary densities indicates that glycolytic and oxidative ATP generation in brain are frequently segregated anatomically (Ames, 2000). Furthermore, in active neural tissue the ATP production cannot rely on sufficient oxygen supply (Ames, 2000; Andres et al., 2008). The high energy required for brain tissue is supplied by multiple interactions between neurons, astrocytes and cerebral blood vessels which guarantees the supply with enough oxygen and oxidizable substrates (recent reviews (Bélanger et al., 2011; Shetty et al., 2012).

Glucose is the main energy substrate for neurons and glia cells (Hu and Wilson, 1997; Dienel, 2012). Generally, energy reserves are low in brain tissue (Ames, 2000) and are limited to a small amount of glycogen (about 3–12 μmol/g tissue), which is exclusively stored in astrocytes (Dienel, 2012; Pellerin and Magistretti, 2012). Glucose liberated from glycogen is degraded by the astrocytic glycolysis and the resulting lactate is supplied to neurons (Hu and Wilson, 1997; Dienel, 2012). This fact uncovers an intensive metabolic cooperation between astrocytes and neurons, and neuronal synaptic activity stimulates the glycolysis in astrocytes (Ames, 2000; Bélanger et al., 2011; Dienel, 2012).

Moreover, liver-derived ß-hydroxybutyrate (βOHB) and acetoacetate (AcAc) are used as fuel by neurons and glia cells extensively during suckling, maturation in young age and upon prolonged fasting (see for reviews (Veech, 2004; Morris, 2005; Cunnane and Crawford, 2014; Achanta and Rae, 2017) and references therein). The passage of βOHB across the blood-brain barrier (BBB) as well as its cellular uptake by neural cells is achieved by members of the monocarboxylate transporters (MCT1,2,4). It is of interest that the energy content of βOHB ($\Delta H^\circ = -243.6$ kcal/mol C_2 units) is higher than that of pyruvate (ΔH° = -185.7 kcal/mol C_2 units) (Veech, 2004), thus explaining that ketone bodies can mostly replace glucose as cerebral high energy fuel (up to 60%). During a long-lasting decline of blood glucose the ketone bodies function as security brain fuel (Cunnane and Crawford, 2014).

In contrast to other organs with high energy demand (heart, liver, kidney), the hydrogen-rich fatty acids are only poorly used in the brain for ATP generation [(Clarke and Sokoloff, 1994; Attwell and Laughlin, 2001; Speijer, 2011; Schönfeld and Reiser, 2013, 2017). Probable reasons for the low utilization of fatty acids as fuel in the brain are discussed in part 2.2 of this review.

2. Fatty acids in brain energy metabolism in health

2.1. Mitochondrial β-oxidation revisited

According to the commonly held view, mammalian brain does not substantially use long-chain fatty acids (LCFAs, C14:0 – C18:0) as fuel in the energy metabolism (for reviews see (Clarke and Sokoloff, 1994; Attwell and Laughlin, 2001; Speijer, 2011). The only exception known so far is that it has been claimed that cultured astrocytes from the developing rat brain (Edmond et al., 1987) and specialized mammalian hypothalamic neurons are able to oxidize fatty acids (McFadden et al., 2014; Byrne et al., 2015).

Nevertheless, several recent reports propose that to some degree mitochondrial β-oxidation takes place in brain tissue (Chen et al., 2014; Panov et al., 2014; Sayre et al., 2017). Firstly, the genetic knock-down of the carnitine palmitoyltransferase-2 in the fruit fly *Drosophila* results in a triglyceride accumulation in the adult brain, a process that is absent in wild-type fruit flies (Schulz et al., 2015). This finding has been taken as indication for the claim that the adult brain catabolizes LCFAs for energy production. Secondly, an active β-oxidation has been postulated from the effect of the carnitine palmitoyl transferase-1 inhibitor methyl palmoxirate on reactive oxygen species (ROS) generation in brain. Since the systemic application of palmoxirate to rats decreased the level of peroxidation products from PUFAs in brain tissue, it has been hypothesized that methyl palmoxirate-linked inhibition of fatty acid degradation prevents β-oxidation-associated ROS generation (Chen