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ORIGINAL ARTICLE

Mitochondria and the Brain: Bioenergetics and Beyond

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Abstract

The view of mitochondria acting solely as a powerhouse of the cell is no longer accurate. Besides cell bioenergetics, primary targets of mitochondrial studies include their interplay with essential processes within the cell, including redox and calcium homeostasis, and apoptosis. Recent studies evidence the dynamic behavior of mitochondria, continuously moving, fusing, and dividing, and the interaction of these events with cellular degeneration and plasticity in neural cells. Our review summarizes novel data and technologies that are developed and applied to the identification and clarification of the mitochondrial role in neural plasticity using both cultured cells and in vivo approaches. The complete understanding and modulation of such mechanisms may represent a novel and promising therapeutic approach for treatment of diseases affecting central and peripheral nervous system.

Keywords Mitochondria · Neurogenesis · MRS · Brain metabolism

Introduction: Mitochondria Overview

Mitochondria are key organelles for cell bioenergetics. In the 1960s, Mitchell (1966) proposed the chemiosmotic hypothesis, a landmark in the field of mitochondrial bioenergetics. According to this theory, reduced equivalents are oxidized by respiratory chain complexes during oxidation of nutritional fuels, hence pumping protons out to the mitochondrial intermembrane space. The process leads to differences of charges and pH across inner mitochondrial membrane (mitochondrial membrane potential, $\Delta\Psi m$). The energy conserved on this electrochemical gradient is used for ATP synthesis by F_OF_1-ATPase through the proton motive force (Mitchell 1966; Tedeschi 1980). CNS has a very demanding energy request, especially to coordinate neurotransmission (Hyder et al. 2006). Mitochondrial oxidative phosphorylation accounts for the vast majority of ATP generation in the CNS (Hyder et al. 2013).

Mitochondrial membrane potential fluctuates depending on mitochondrial mass, stimulus, or cell type (Tedeschi 1980; Nicholls and Ward 2000; Nicholls 2004; Aryaman et al. 2017; Zorova et al. 2017). A low mitochondrial membrane potential is associated with limited ATP and superoxide production, and signals mitochondria for elimination by mitophagy (Geisler et al. 2010; Sun et al. 2019). Conversely, even a subtle increase on mitochondrial membrane potential boosts ATP synthesis and superoxide production (Klingenberg 1980; Korshunov et al. 1997; Lambert and Brand 2004; Twig et al. 2008; Chinopoulos et al. 2009; Kawamata et al. 2010). Dyshomeostasis of mitochondrial membrane potential (either low or persistently high) is a signal of dysfunctional mitochondria and can trigger cell death, representing an important tool for mitochondrial quality control (Gergely et al. 2002; Nicholls 2004; Twig et al. 2008; Iannetti et al. 2015; Zorova et al. 2017).

Cations such as iron and calcium are taken up by mitochondria (Rottenberg and Scarpa 1974; Zorova et al. 2017), while

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molecules bearing negative charges, such as ATP, tend to be exported to the cytosol (Klingenberg 1980). Calcium plays several roles in cell. Intramitochondrial calcium is crucial not only for intracellular calcium buffering but also for metabolic regulation. Calcium activates important enzymes involved in intermediary metabolism, including pyruvate dehydrogenase, isocitrate dehydrogenase, and α-ketoglutarate dehydrogenase (Denton 2009; Griffiths and Rutter 2009). Therefore, low intramitochondrial calcium levels impair oxidative phosphorylation and signals autophagy; intracellular calcium accumulation induces necrosis and apoptosis processes (Rizzuto et al. 2012; Orrenius et al. 2015).

Mitochondria may also dictate cell fate by participating in processes of regulated cell death. Regulated cell death is engaged in organismal homeostasis in both physiological (by eliminating damaged and/or potentially dangerous cells and in synaptic plasticity process) and pathological scenarios, such as in neurodegenerative diseases (Li et al. 2010; Fuchs and Steller 2011; Galluzzi et al. 2016a, 2016b; Nagata and Tanaka 2017).

Besides the well-known participation of increased mitochondrial reactive oxygen species (ROS) and bioenergetics failure in cell demise (Simon et al. 2000; Niquet et al. 2006; Franklin 2011), mitochondria can directly participate in cell death processes, including apoptosis and necroptosis (Thornton and Hagberg 2015). Intrinsic apoptosis is the mitochondria-centered cell death mediated by B cell lymphoma 2 (Bcl-2) protein and the caspase pathway (Danial and Korsmeyer 2004; Galluzzi et al. 2012). Caspase cascade is activated following mitochondrial outer membrane permeabilization or the opening of the mitochondrial permeability transition pore, and consequent cytochrome c release from mitochondria (Bernardi et al. 2006; Thornton and Hagberg 2015). Caspase activation following disturbed mitochondrial permeability may also occur in necrosis (Niquet et al. 2006).

A myriad of mechanisms associating mitochondrial dysfunction to the pathophysiology of several neurodegenerative diseases, including Alzheimer's and Parkinson's diseases, have been described (DuBoff et al. 2012; Iijima-Ando et al. 2012; Zhang et al. 2012; Bros et al. 2014; Cardoso et al. 2017; Martinez et al. 2017; Patergnani et al. 2017). In the following section, we will summarize known mechanisms driving mitochondrial dynamics, as well as their possible participation in pathological processes.

When Mitochondrial Plasticity Meets Neuronal Plasticity

Mitochondrial Dynamics: Fusion and Fission

Mitochondria show various morphologies, as indicated by their name, coined by Benda (1898). They can appear as filaments ("mitos" in Greek) or granules ("chondros" in Greek), depending on the conditions and cell type. Mitochondrial morphology is controlled by dynamic events of fission and fusion of the organelle that were first described in 1914 by Lewis and Lewis. When fusion prevails over fission, mitochondria appear as an interconnected network of filaments, whereas they turn into isolated particles when fission prevails.

The molecular mechanisms of so-called mitochondrial dynamics were unraveled with the help of genetic screens and studies performed in yeast (Bleazard et al. 1999; Sesaki and Jensen 1999). This process, together with the major proteins involved, was then shown to be evolutionarily conserved (for a review see Bertholet et al. 2016). The GTPase DRP1 is recruited to the mitochondrial outer membrane (OM), due to the coordinated actions of mitochondrial adaptors, actin polymerization, and endoplasmic reticulum (ER) contacts, and constricts the membranes into spirals, inducing the scission of mitochondria upon GTP hydrolysis (for a review, see Richter et al. 2015). Moreover, a recent publication shows that Dynamin 2 works in concert with DRP1 to orchestrate sequential constriction events (Lee et al. 2016). Mitochondrial fusion requires the coordinated action of three GTPases: mitofusins 1 and 2 (MFN1 and 2) and OPA1. Mitofusins are integral OM proteins. Their dimerization leads to membrane tethering and their GTPase activity contributes to membrane fusion (for a review, see Schrepfer and Scorrano 2016). Two recent papers have provided further details on the mechanisms of OM fusion. The first shows that mitofusins can adopt conformations, directed by intramolecular interaction, that either constrain or are permissive for fusion (Franco et al. 2016). The second shows that cycles of GTP hydrolysis first induce the progressive formation of tethering and ring docking structures and then trigger local OM fusion at the periphery of the contact region (Brandt et al. 2016). Inner membrane (IM) fusion requires OPA1 and involves a different mechanism than that of OM fusion, as the presence of the GTPase is only required on one of the two mitochondria destined to fuse (Song et al. 2009). Recent work shows that OPA1 and cardiolipin cooperate in heterotypic mitochondrial IM fusion (Ban et al. 2017).

Mitochondrial dynamics is modulated by a variety of signals and stimuli, including bioenergetics, cell cycle transitions, and cell differentiation (Benard et al. 2006; Hyde et al. 2010; Sauvanet et al. 2010; Chan 2012; Liesa and Shirihai 2013; Mitra 2013; Hoppins 2014; Labbe et al. 2014; Zorzano et al. 2015). This may involve post-translational modifications of the main actors of fission and fusion (for a review, see Bertholet et al. 2016; Flippo and Strack 2017). The mitochondrial recruitment, activity, and stability of DRP1 are indeed regulated by phosphorylation, ubiquitination, sumoylation, S-nitrosylation, and O-GlcNacylation, as well as by interaction with phosphatidic

acid (Adachi et al. 2016). Mitofusins are ubiquitinated and phosphorylated and interact with members of the Bcl2 family. The functions of OPA1 are tightly controlled by proteolytic cleavage, but ubiquitination, O-GlcNacylation, and acetylation have also been reported.

The main role of fusion is to protect mitochondria. Fusion enables functional complementation between mitochondria through exchange of their components (Legros et al. 2002; Legros et al. 2004; Wilkens et al. 2013). Furthermore, cells are protected in response to various stresses by mitochondrial "hyperfusion," which stimulates ATP synthesis and spares mitochondria from degradation by autophagy and cells from death (Tondera et al. 2009; Gomes et al. 2011; Rambold et al. 2011). The loss of mitofusins not only induces mitochondrial fragmentation, but provokes defects in mtDNA maintenance, oxidative phosphorylation, and the redox state (Chen et al. 2003; Chen et al. 2005; Amati-Bonneau et al. 2008; Hudson et al. 2008; Chen et al. 2010; Elachouri et al. 2011; Millet et al. 2016). In addition, MFN2 is involved in the homeostasis of key metabolites, such as Co-enzyme Q, glucose, and Ca^{2+} (the latter through interaction with the ER), and mitochondrial transport, as well as insulin signaling, cell proliferation, and differentiation (for a review, see Bertholet et al. 2016; Schrepfer and Scorrano 2016). OPA1 also has anti-apoptotic (sequestration of cytochrome c into the cristae) and metabolic (modulation of local substrate concentrations) functions, which both depend on its cristae shaping activity and appear to be independent of its fusogenic activity (Cipolat et al. 2004; Frezza et al. 2006; Olichon et al. 2007; Yamaguchi et al. 2008).

Mitochondrial fission is essential for mtDNA nucleoid structure and distribution (Parone et al. 2008; Ban-Ishihara et al. 2013; Murley et al. 2013; Ishihara et al. 2015). Fission also enables the generation of small mitochondria which, when damaged, can be selectively engulfed by autophagosomes to be eliminated by mitophagy (Twig et al. 2008). The loss of DRP1 not only induces an increase in the length and connectivity of the mitochondriome but lowers oxidative phosphorylation and impairs cell proliferation and differentiation (Otsuga et al. 1998; Smirnova et al. 2001; Benard et al. 2007; Parone et al. 2008).

Recent findings show that mitochondrial dynamics plays a major role in the switch between pluripotent and differentiated states according to its impact on respiratory energy metabolism, nutrient utilization, cell cycle, and proliferation (for a review, see Arrázola et al. 2018). Mitochondrial dynamics also affect apoptotic OM permeabilization by mechanisms that are not fully understood (for a review, see Martinou and Youle 2011).

Finally, ablation or mutation of the genes encoding central factors of mitochondrial dynamics is lethal at mid-gestation, as expected from their physiological importance (Chen et al. 2003; Alavi et al. 2007; Davies et al. 2007; Ishihara et al. 2009; Wakabayashi et al. 2009).

Mitochondrial Fission/Fusion Dynamics in Neurons

Mitochondria undoubtedly play an important role in neuron plasticity and functioning, as they are the main energy providers and play a major role in Ca^{2+} homeostasis (for a review, see Mattson et al. 2008). Mitochondrial dynamics not only modulates the morphology and principal functions of the organelle, but regulates their transport, which is critical in neurons (Barnhart 2016). It is thus not surprising that inactivation of this process is associated with severe diseases, notably neurodegenerations. Mutations in genes encoding MFN2 and OPA1 are responsible for Charcot-Marie-Tooth (CMT) disease and dominant optic atrophy (DOA), respectively (Delettre et al. 2000; Zuchner et al. 2004). Mutations in GADP1 and SLC2A46, two mitochondrial proteins with pro-fission activity, are also linked to CMT disease (Baxter et al. 2002; Abrams et al. 2015). Furthermore, very rare de novo mutations of DRP1 lead to severely impaired development of the nervous system (Waterham et al. 2007; Fahrner et al. 2016; Sheffer et al. 2016) and its was recently shown that some mutations of DRP1 induce isolated DOA (Gerber et al. 2017). In addition, defects in mitochondrial dynamics are also associated with Alzheimer's, Parkinson's, and Huntington's diseases (Gao et al. 2017).

Data concerning the neurological defects associated with impaired mitochondrial dynamics have been accumulating for a long time, but the role of this process in various physiological contexts in neurons is only beginning to be established. Mitochondrial remodeling is observed in vivo during developmental and adult neurogenesis (Choi et al. 2013; Steib et al. 2014; Mils et al. 2015) and accompanies neuritogenesis and synaptogenesis in primary cultured neurons and neuroblasts (Bertholet et al. 2013; Li et al. 2004; Chang and Reynolds 2006; Bertholet et al. 2013). Moreover, numerous studies, which will be presented below, show that impairment of mitochondrial dynamics affects neuronal development, differentiation, and maturation, both in vivo and in vitro.

Neural cell-specific $DRP1^{-/-}$ mice display a smaller forebrain, with evidence of apoptosis (Ishihara et al. 2009), and a smaller cerebellum, with decreased proliferation (Wakabayashi et al. 2009). Post-natal DRP1 depletion in forebrain neurons leads to hippocampal atrophy, as well as deficits in learning and memory (Oettinghaus et al. 2015; Shields et al. 2015). Consistent with these results, DRP1 overexpression enhances in vivo neuronal maturation of adult-born hippocampal neurons known to improve adult hippocampal neurogenesis and memory (Steib et al. 2014). Drosophila mutants carrying mutations in DRP1 show defects in mobilization of the synaptic vesicle reserve pool and a failure to

maintain normal neurotransmission during intense stimulation at the neuromuscular junction (Verstreken et al. 2005).

In vitro, knock-down (KD) of DRP1, or inhibition of its catalytic activity, reduces neuronal differentiation of embryonic stem cells (ESC) (Wang et al. 2014), as well as adult neural stem cells (NCS), which also show impaired migration (Kim et al. 2015). This is associated, in the latter case, with altered mitochondrial distribution and activity. In primary hippocampal or forebrain cultured neurons, KD or knockout (KO) of DRP1, as well as overexpression of a dominant negative mutant of DRP1, are associated with decreased neurite numbers, synaptic marker levels, dendritic spine density, synaptic vesicle cycling, and synaptic transmission (Li et al. 2004b; Ishihara et al. 2009; Wang et al. 2009; Oettinghaus et al. 2015; Shields et al. 2015).

The impact of DRP1 on neuronal plasticity correlates with changes in mitochondrial morphology in cerebellar Purkinje cells and forebrain hippocampal neurons, but not granule neurons (Ishihara et al. 2009; Wakabayashi et al. 2009; Kageyama et al. 2012; Oettinghaus et al. 2015; Shields et al. 2015). Low mitochondrial number in neurites (Berthet et al. 2014; Oettinghaus et al. 2015) and energetic failure (Shields et al. 2015), associated with DRP1 inactivation, may also be involved in hippocampal neuron alterations. The effect of DRP1 on neuronal maturation is regulated by PKA and Cdk5-mediated phosphorylation in primary hippocampal and cultured cortical neurons (Dickey and Strack 2011; Cho et al. 2014). Furthermore, the association of DRP1 with Bcl-XL in mitochondria from cultured hippocampal neurons stimulates its GTPase activity (Li et al. 2008). Surprisingly, DRP1/Bcl-XL complexes are also recruited to synaptic vesicle membranes, where they may enhance the rate of synaptic vesicle uptake to ensure maximal synaptic activity (Li et al. 2013). It was recently shown that the DRP1 receptor MFF regulates presynaptic release and axonal branching by acting on mitochondrial size and therefore on mitochondrial Ca^{2+} uptake during neurotransmission (Lewis Jr et al. 2018).

Mitochondrial fusion also affects neuronal plasticity. In primary cultured cortical neurons, downregulation of OPA1 leads to mitochondrial fragmentation, alteration of the distribution of the organelles, decreased respiration, and an imbalance of the redox state (Bertholet et al. 2013; Millet et al. 2016), disrupting dendritogenesis and synaptogenesis (Bertholet et al. 2013). Similar synaptic and dendritic defects were shown in vivo in retinal ganglion cells from a DOA mouse model (Williams et al. 2010; Williams et al. 2012), suggesting that impairment of neuronal plasticity could be involved in DOA pathogenesis.

Conditional brain-specific MFN2 ablation in mice leads to degeneration of the cerebellum, shown by reduced dendritic arborization, decreased spine number, and axonal morphological defects of Purkinje cell, together with alterations of mitochondrial oxidative phosphorylation, morphology, and distribution (Chen et al. 2007). $MFN2^{-/-}$ dopaminergic neurons also show alterations of mitochondrial morphology, mass, function, and transport, associated first with the loss of dopaminergic terminals in the striatum and then cell bodies in the substantia nigra (Lee et al. 2012; Pham et al. 2012). KD of MFN2 in human-induced pluripotent stem cells (hiPSC), which alters mitochondrial morphology, mobility and functions, impairs their differentiation into cortical neurons (Fang et al. 2016). Decreased dendritic length, synapse number, and synaptic transmission have been observed, whereas overexpression of MFN2 had the opposite effects (Fang et al. 2016).

Moreover, recent work indicates that acute loss of function of MFN2 or OPA1 impairs NSC self-renewal and increases neural commitment in developing cortex, without impairing mitochondrial energetics (Khacho et al. 2016). Mitochondrial dynamics coordinate self-renewal versus differentiation through NRF2/ROS-mediated retrograde signaling, involving activation versus inhibition of the Notch pathway, respectively (Khacho et al. 2016). MFN2 inactivation also affects adult NCS fate by reducing the number of uncommitted cells and neuroblasts in the hippocampal dentate gyrus (Khacho et al. 2016).

Overall, these data clearly demonstrate the implication of mitochondrial dynamics in neurogenesis from neuronal fate to neuronal maturation and functioning, according to its involvement in neurodegeneration. The underlying molecular mechanisms are yet to be unraveled. Besides the regulation of metabolism by mitochondrial dynamics that is clearly an active participant, the influence of mitochondrial dynamics on nuclear programs is a new and exciting avenue. The manipulation of mitochondrial dynamics may be a novel therapeutic approach to improve mitochondrial and neuronal function and prevent neurodegeneration.

Mitochondrial Metabolism Probed In Vivo

Brain Energy Metabolism

The brain depends on exceptionally high metabolic activity supported by continuous supply of oxygen and glucose from the blood circulating in the capillary bed (Siesjö 1978). Although the brain oxidizes multiple carbon sources, glucose is the primary fuel in the adult brain, which constitutes only about 2% of the total body weight but takes up to 20% of the body's glucose disposal at rest (e.g., Rolfe and Brown 1997). Glucose metabolism in the brain occurs mainly through the mitochondrial tricarboxylic acid (TCA) cycle, providing the means to generate large amounts of adenosine triphosphate (ATP). In the cytosol, glycolysis splits glucose into two pyruvate molecules that, in turn, are metabolized with oxygen in the TCA cycle coupled to oxidative phosphorylation, leading to the formation of CO_2 and water, and production of ATP.

Regulation of brain metabolism is highly compartmentalized between neurons and astrocytes, the most abundant type of glia (e.g., Lanz et al. 2013; Bonvento et al. 2017; Sonnay et al. 2017). Neurons are characterized by high rates of oxidative metabolism, whereas astrocytes are generally considered glycolytic cells. In the 1990s, Pellerin and Magistretti (1994) proposed that glutamate released by neurons into synapses is taken by astrocytes, stimulating glycolysis and the production of lactate, which in turn can be released and further oxidized in neurons. Furthermore, pioneering ^{13}C MRS experiments in vivo in the rodent brain under a variety of anesthesia depths suggested that the rate of the glutamate-glutamine cycle between neurons and astrocytes is coupled to the rate of glucose oxidative metabolism (Sibson et al. 1998). This cycle is not stoichiometric since it interacts with different metabolic pathways (McKenna, 2007). Although an important fraction of brain's energy expenditure is attributed to fueling neuronal activity, the contribution of glial cells for the global energy budget cannot be neglected. Indeed, there is evidence from experiments in the rodent brain in vivo suggesting that stimulation of brain activity leads to increments in the TCA cycle rate within both neurons and astrocytes (Sonnay et al. 2016). More recently, a tight coupling between glutamatergic neurotransmission and the rates of oxidative metabolism in neurons and in astrocytes was reported in the visual cortex of the tree shrew (Sonnay et al. 2018). In addition to oxidizing glucose, astrocytes have been proposed to oxidize the glutamate (released by neurons into the synapse) though the TCA cycle (Sonnewald 2014). The energy generated by oxidative metabolism of both glucose and glutamate, as well as other substrates, in astrocytes is crucial for fueling their active participation in K^+ uptake, in the regulation of blood volume and flow, as well as of neurotransmission, synchronization and plasticity (reviewed in Sonnay et al. 2017). The relative contribution of metabolic pathways in major cellular compartments, that is neurons and astrocytes, to the whole energy budget is still matter of debate (Pellerin and Magistretti 2012; Dienel and McKenna 2014; Dienel 2017; Sonnay et al. 2017). Notwithstanding this controversy, the role of metabolism regulation in the energy deficiency of brain disorders is of crucial importance to understand their pathophysiological mechanisms (Bonvento et al. 2017).

MRS to Study Brain Metabolism

A number of methodological approaches exist to manipulate and study mitochondrial function both in vitro and in the brain in vivo, including oxygen consumption and ATP production, membrane potential, calcium handling, and events associated with biogenesis, trafficking, fusion, and fission (Oliveira 2011). However, investigation of brain metabolism must be performed non-invasively with preserved cellular interactions. Although positron emission tomography (PET) with the tracer [^{18}F]2-fluoro-2-deoxy-D-glucose (FDG) is well established for measurements of the cerebral metabolic rate of glucose (CMR_{glc}), magnetic resonance spectroscopy (MRS) has been a tool of election for the study of mitochondrial metabolism in the brain in a non-invasive manner, particularly when coupled with infusion of ^{13}C-labeled substrates (Lanz et al. 2013). As indicated below, MRS has also been importantly used for measuring tissue's energy status (^{31}P) and for neurochemical profiling (^{1}H) (Duarte et al. 2012). Altogether, these MRS tools provide a wealth of information on brain metabolism that otherwise would have to be collected with more invasive techniques. However, one should keep in mind that MRS deals with poor sensitivity, and thus poor spatial resolution, and is rarely employed for mapping metabolism throughout the brain. For metabolic mapping, positron emission tomography with radiotracers or invasive imaging techniques have been preferred (Bonvento et al. 2017).

Neuroenergetics by Heteronuclear MRS

Carbon 13 (^{13}C) is the sole isotope of carbon possessing a nuclear magnetic moment. Its low natural abundance of about 1.1% is advantageous for ^{13}C MRS experiments because it renders brain metabolites nearly invisible in vivo (most carbon is ^{12}C), and allows tracing ^{13}C incorporation into brain metabolites when ^{13}C-enriched substrates are administered. [1-^{13}C]- and [1,6-^{13}C]glucose are widely used tracers to probe mitochondrial metabolism in the brain, although other ^{13}C-labeled tracers are available and have been employed (Gruetter et al. 2001; Duarte et al. 2011; Tiret et al. 2015; Dehghani et al. 2016; Jeffrey et al. 2013; Duarte and Gruetter 2013). Given the appetence of the brain for metabolizing glucose, labeled glucose molecules rapidly cross the blood-brain-barrier (BBB) and are phosphorylated by hexokinase (discussed in Duarte and Gruetter 2012). At the end of the glycolytic pathway, pyruvate molecules will then appear labeled in the position C3. Labeled pyruvate enters the TCA cycle mostly through pyruvate dehydrogenase. ^{13}C will be incorporated into the position C4 of 2-oxoglutarate in the first turn of the TCA cycle, and in the positions C3 and C2 in the second turn. Since 2-oxoglutarate readily exchanges with cytosolic glutamate, this amino acid will also be labeled in positions C4, C3, and C2 (see Duarte et al. 2011 for details on ^{13}C labelling). Given the large concentration of glutamate, the brain's primary excitatory neurotransmitter, these are the first carbon resonances detected in ^{13}C spectra (Fig. 1). The label is then exchanged between glutamate and glutamine through the glutamate-glutamine cycle that links energy metabolism in neurons and astrocytes (McKenna and Ferreira 2016). Aspartate is produced from the TCA cycle intermediate oxaloacetate and carries its labelling pattern, and therefore can also provide information on the rate of

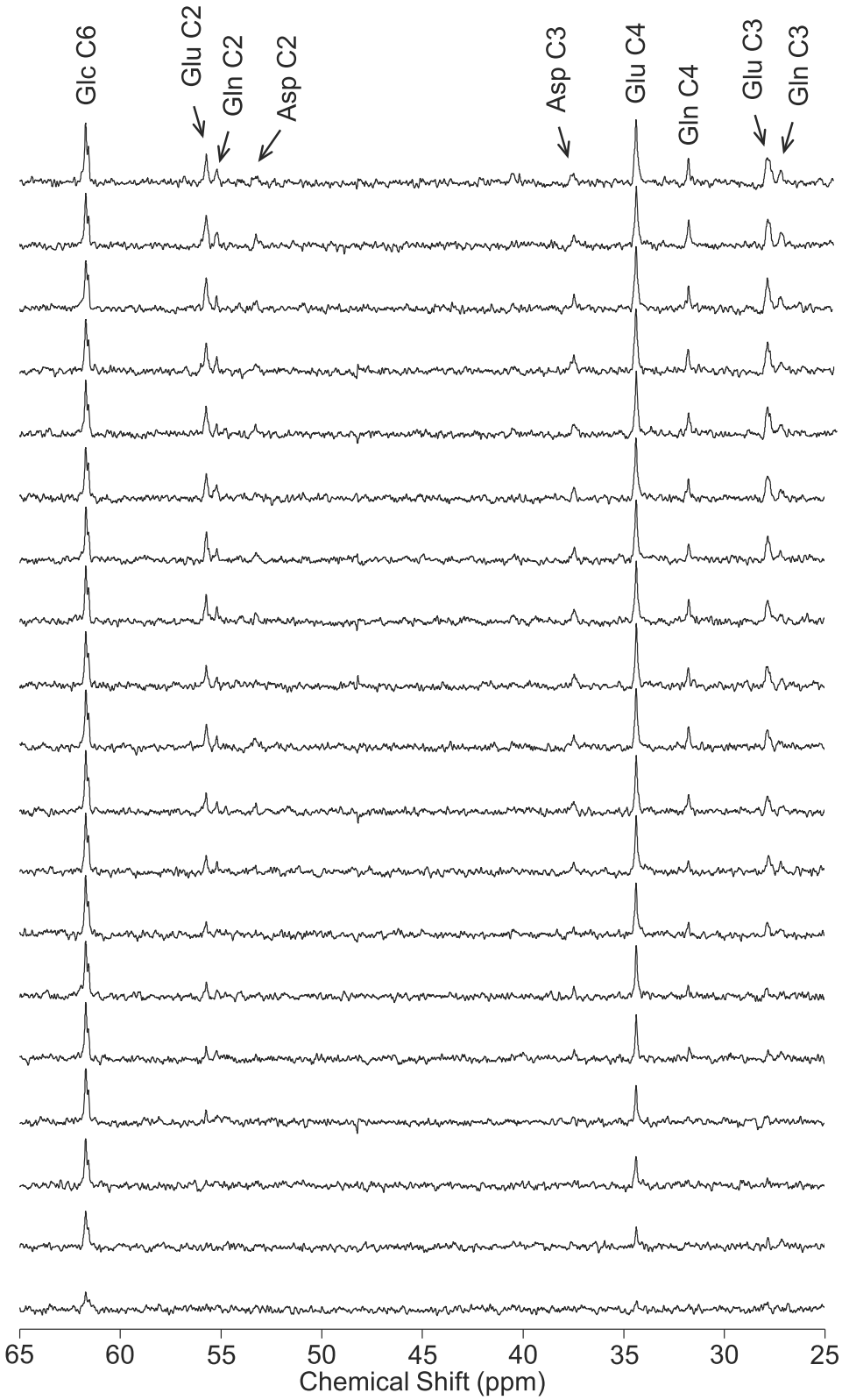

Fig. 1 Typical ^{13}C MRS in the rat brain upon infusion of [1,6-^{13}C]glucose. Spectra were sequentially acquired with a temporal resolution of about 5 min (see Duarte et al. 2011 for details). Abbreviations: Asp, aspartate; Gln, glutamine; Glu, glutamate; Glc, glucose

oxidative metabolism in mitochondria (Duarte et al. 2011; Duarte and Gruetter 2013).

Cerebral compartmentation of energy metabolism is observable in ^{13}C MRS only because the activity of pyruvate carboxylase is practically specific to astrocytes (Sonnay et al. 2017), and it transfers ^{13}C labelling from pyruvate C3 into oxaloacetate C3 but not C2 (see Duarte et al. 2011 for details on ^{13}C labelling). Localization of glutamine synthetase

is specific to astrocytes (Sonnay et al. 2017). Because glutamine is synthetized and mostly located in astrocytes, while glutamate is mainly within neurons, the rate of labelling appearance in glutamine C2 is faster than C3, and such difference reflects the rate of astrocytic pyruvate carboxylation (Lanz et al. 2013). Importantly, this prior knowledge on the metabolic compartmentation of pyruvate carboxylase, glutamine synthetase, and distribution of glutamate and glutamine allows using ^{13}C MRS data to distinguish the rates of mitochondrial metabolism in neurons and astrocytes.

While qualitative assessments of labelling patterns in specific carbon positions within different brain metabolites can provide insight into relative flux rates, the employment of advanced mathematical modeling of ^{13}C MRS data allows estimating rates of isotopic incorporation and serve to estimate fluxes through important metabolic pathways (Lanz et al. 2013). Namely studies with two-compartment models of brain energy metabolism are routinely used to estimate rates of the neuronal and astrocytic TCA cycles, glutamate-glutamine cycle and glutamine synthesis, pyruvate carboxylation, among others (Gruetter et al. 2001; Duarte et al. 2011; Tiret et al. 2015; Dehghani et al. 2016). Measurement of carbon resonances from GABA can further allow distinguishing metabolic rates in mitochondria from glutamatergic and GABAergic compartments in the living brain (Duarte and Gruetter 2013).

Tracers with other nuclei have been employed to measure metabolic pathways in the brain. For example, the rates of the glutamate-glutamine cycle and the glutamine synthetase activity have been estimated by using ^{15}N MRS in the rat brain in vivo during infusion of [^{15}N]NH_3 (Kanamori and Ross 1993; Cudalbu et al. 2012). However, such studies are challenging because NH_3 is toxic, and increased brain NH_3 induces continuous glutamine accumulation. Since metabolic steady state is not achieved in such experiments, mathematical modeling for metabolic flux analysis is not straight forward (see Cudalbu et al. 2012). Oxygen 17 (^{17}O) has also been used to determine mitochondria-driven bioenergetics by MRS (Zhu et al. 2009), namely the cerebral metabolic rate of oxygen (CMR_{O2}). In general, the rate of incorporation of ^{17}O into brain water during inhalation of $^{17}O_2$ gas is measurable by MRS and can be used to calculate CMR_{O2}.

MRS of ^{31}P provides a way of detecting non-invasively the phosphorus-containing metabolites in the brain, including the high-energy phosphate compounds, ATP and phosphocreatine, and P_i, which can be used to estimate the tissue's energy status. Additional information can be obtained from the ^{31}P spectrum, namely the intracellular pH and the concentration of free Mg^{2+} (Zhu et al. 2009). Moreover, the employment of magnetization transfer techniques in ^{31}P MRS can be used to determine rates of creatine kinase and ATP_{ase} in vivo (see methodological details in Zhu et al. 2009).

Despite the enormous amount of parameters on energy metabolism that can be quantified by heteronuclear MRS, ^{1}H remains the most widely employed nuclei for the investigation of brain metabolism in vivo due to its higher sensitivity and simpler hardware and technical requirements (Duarte et al. 2012).

Metabolic Profiling by ^{1}H MRS

Energy metabolism defects are often reflected on the concentrations of abundant metabolites, which are detectable through metabolic profiling. Neurochemical profiling is the simultaneous quantification of several low molecular weight metabolites in a given brain area. MRS detection of ^{1}H nuclei is widely employed for non-invasive neurochemical profiling because this is the most sensitive nucleus in nuclear magnetic resonance (NMR). ^{1}H MRS allows detecting a neurochemical profile that can capture pathophysiological processes (Duarte et al. 2012), can be employed for non-invasive assessment of disease development and outcome of therapeutic interventions (Duarte et al. 2014b), and might even find suitability in epidemiological studies (McKay and Tkáč 2016). The number of quantifiable metabolites depends on factors in the MRS acquisition process such as the pulse sequence parameters, and the spectral signal-to-noise ratio and spectral resolution (discussed in Duarte et al. 2012; McKay and Tkáč 2016). At high magnetic fields, metabolic profiling by state-of-the-art ^{1}H MRS allows to quantify the concentration of about 20 compounds in the living brain (Fig. 2). In contrast, experiments at low magnetic fields (e.g., 1.5 T) are often performed with long echo times, in order to simplify the spectral analysis. This approach allows detecting *N*-acetylaspartate (NAA), glutamate plus glutamine (often called "Glx"), total creatine (creatine plus phosphocreatine), choline-containing compounds, and *myo*-inositol. The relevance of MRS-detectable metabolites for brain function was discussed elsewhere (Duarte et al. 2012). Most importantly, NAA is a marker for neuronal integrity since it is present in neurons but not in glial cells, elevated *myo*-inositol has been generally considered to represent astrogliosis, and choline has been referred as a marker for membrane turnover, cellular proliferation, or neuroinflammation. Since glutamate is mostly present in neurons and glutamine is synthetized in astrocytes (Sonnay et al. 2017), "Glx" variations are of difficult interpretation. Total creatine is generally assumed to be uniformly distributed across brain cells, thus reflecting cell density.

Rather than single-voxel MRS, more advanced MRS methods are available to map the neurochemical profile throughout the brain with relatively good spatial resolution. Spectroscopic imaging, also called chemical shift imaging, has been employed to map the concentration of metabolites (Ding and Lanfermann 2015), even in the small mouse brain (e.g., Alf et al. 2014). Notably, spectroscopic imaging was also employed to map glucose transport-to-consumption ratio in the brain by collecting images of the neurochemical profile

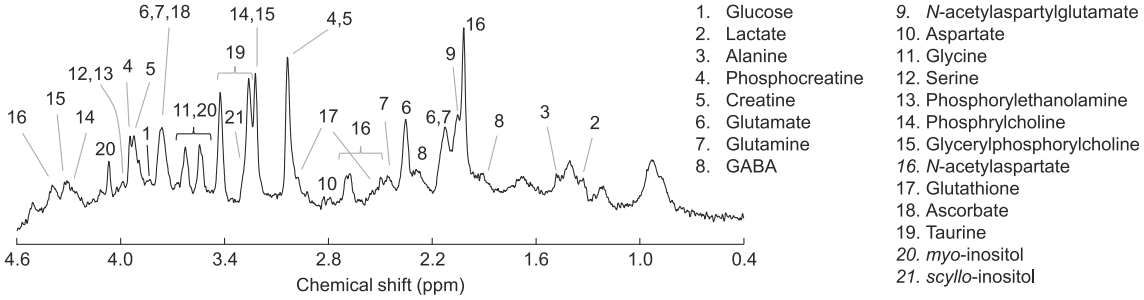

Fig. 2 Neurochemical profile detected by ^{1}H MRS in vivo. Spectrum was acquired in the mouse cortex at 14.1 T using SPECIAL with TE = 2.8 ms and TR = 4 s (for details see Gapp et al. 2017), and processed with a shifted Gaussian function (gf = 0.12, gfs = 0.02) prior to Fourier transformation

at different concentrations of plasma glucose (e.g., Alf et al. 2014). However, such methods require long acquisition protocols, particularly if one is interested in metabolites that occur in the brain parenchyma at low concentration. Alternatively, one can also map a single metabolite throughout the brain with high sensitivity and/or spatial resolution by using chemical exchange saturation transfer (CEST) MRI, a technique that was employed for detection of glutamate (Davis et al. 2015), glucose (Xu et al. 2015), and lactate (DeBrosse et al. 2016).

Dynamic acquisitions of ^{1}H MRS data have also been employed to determine rates of metabolic processes in the brain. Of particular interest is the measurement of brain (by MRS) and plasma (from blood samples) glucose during glucose infusion to simultaneously determine kinetic parameters for glucose transport across the blood-brain-barrier and for glucose utilization (Shestov et al. 2011; Duarte and Gruetter 2012).

Metabolism in Aging and Neurodegenerative Diseases Studied by MRS

Age-related neurodegeneration is attributed to oxidation of cellular components by free radicals, catalyzed by oxidative enzymes and traces of metal ions. In this realm, mitochondria have a pivotal role, and energetic dysfunction caused by mitochondria-related alterations (not exclusively due to oxidative stress) are an important drive for aging. Moreover, mitochondrial dysfunction, oxidative stress, and abatement in energy production have all been implicated in the etiology of neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease (PD), and Huntington's disease (HD) (Barnham et al. 2004; Lin and Beal 2006).

Aging

Mitochondria are major players on ATP generation, Ca^{2+} uptake and storage, production of ROS as well as their detoxification, and determination of cell survival or apoptosis. While these mitochondrial tasks depend on the good maintenance of the mitochondrial membrane potential ($\Delta\psi m$), release of cytochrome c from mitochondria into the cytoplasm is a primary trigger for apoptotic signals (Nicholls 2004). The mitochondrial theory of aging was developed with basis on the toxic ROS generation by this organelle, which cause mutations in the mitochondrial DNA (mtDNA) that in turn are a primary cause of age-related energy dysfunction. Complex I is primarily affected and becomes rate limiting for electron transfer (Feuers 1998; Lenaz et al. 2000), but aging is also associated with decreased activity of complexes III and IV (Feuers 1998), as well as impaired mitochondrial membrane potential, respiratory control ratio, and cellular O_2 uptake (Liu et al. 2002).

In a MRS study, elderly subjects displayed a reduction in glutamate and increase in *myo*-inositol concentrations in the brain, compared to young subjects (e.g., Boumezbeur et al. 2010). Similar observations were reported in rodents and may be associated to neurodegeneration and astrogliosis (Duarte et al. 2014a; Harris et al. 2014). Neurodegeneration results in reduced neurotransmission rates and thus imposes lower energy demand. In fact, aging is associated with reduced cerebral glucose utilization (e.g., Gage et al. 1984; Tack et al. 1989). A ^{13}C MRS study in the human brain found reduced neuronal and glial TCA cycle rates, reflecting impaired mitochondrial metabolism (Boumezbeur et al. 2010). A recent ^{31}P MRS study in the human brain found an important reduction in the ratio NAD^+/NADH with aging (Zhu et al. 2015), which is indicative of age-related redox changes caused by mitochondrial alterations that render the electron transport chain less efficient in oxidizing reducing equivalents for energy production. Altogether, these studies are indicative of reduced mitochondrial function, with impact on neuronal health. Neurochemical profiling studies in the rodent brain verified that aging induces general modifications of neurotransmission processes (reduced GABA and glutamate), primary energy metabolism (altered glucose, alanine, and lactate), and turnover of lipid membranes (modification of choline-containing compounds and phosphorylethanolamine) (Duarte et al. 2014a; Harris et al. 2014). The age-induced reduction of glutamate and GABA concentrations in the brains of aged mice compared to young adults may be associated with the loss of

synaptic efficiency, which can contribute to brain dysfunction and memory decline (e.g., Kennard and Woodruff-Pak 2011; Pistell et al. 2012). Accordingly, the density of pre- and post-synaptic proteins was found to decrease with aging in the rodent brain, including vesicular neurotransmitter transporters (e.g., Canas et al. 2009).

In contrast, the aging brain exhibits increases in glial activity which are likely accompanied by specific stimulation of mitochondrial metabolism in reactive astrocytes (Lynch et al. 2010). In line with some degree of astrogliosis, lower concentrations of neurotransmitters were accompanied by higher levels of *myo*-inositol in the aging rodent brain (Duarte et al. 2014a; Harris et al. 2014) and in elderly humans (e.g., Boumezbeur et al. 2010).

In the rodent brain, concentrations of phosphorylethanolamine and choline-containing phospholipid precursors (glycerylphosphorylcholine and phosphorylcholine) were found to be altered with age (Kulak et al. 2010; Duarte et al. 2014a; Harris et al. 2014; Cuellar-Baena et al. 2016), likely reflecting altered membrane lipid turnover (Duarte et al. 2012). In particular, choline-containing compounds are precursors of phosphatidylcholine and, in turn, of sphingomyelin, which is necessary for myelin production (Oshida et al. 2003). Sphingomyelin has also been implicated in immune responses and is important in neuroinflammation (Li et al. 2015). Altered choline concentration is also observed in the human brain during aging (reviewed in Duarte et al. 2012), and a ^{31}P MRS study found that the glycerylated forms of phospholipid precursors increase with age in the human brain, which may have implications for cell membrane fluidity (Blüml et al. 1999).

Brain taurine levels were found to be highest after birth and decay during early development until adulthood (Kulak et al. 2010), and small taurine decrements also occur with aging in the rodent brain (Duarte et al. 2014a; Harris et al. 2014; Cuellar-Baena et al. 2016). Modifications of taurine with age have not been reported in the human brain, likely due to its much lower concentration in humans than rats or mice. The main role of taurine is to act as an osmolyte, balancing modifications that occur in the concentrations of other major neurochemicals, although it also interacts with inhibitory $GABA_A$, $GABA_B$ or glycine receptors, thus being capable of modulating synaptic plasticity (Duarte et al. 2012).

Parkinson's Disease

Parkinson's disease (PD) is primarily associated with degeneration of dopaminergic neurons in the substantia nigra (Calne and Langston 1983). Among other features, it is characterized by severe mitochondrial dysfunction, namely a decrease in NADH dehydrogenase activity (respiratory chain complex I) in the substantia nigra (Schapira et al. 1990) as well as other brain regions (Parker Jr and Parks 2005; Parker Jr et al. 2008; Ravid and Ferrer 2012). Moreover, the administration of complex I inhibitors, such as rotenone and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), triggers neurological changes similar to PD in rodents, and genes associated with familial PD are involved in mitochondrial functioning (Annepu and Ravindranath 2000; Schapira 2008). PD has also been associated with other alterations of energy metabolism, namely at the level of glycolysis, oxidative decarboxylation of pyruvate and other components of oxidative phosphorylation system (reviewed in Duarte et al. 2014b).

In line with this marked neurodegeneration in PD, MRS studies have repeatedly found decreased NAA to creatine ratio across several brain areas of patients with PD (reviewed in Duarte et al. 2012), and some studies found that PD leads to a reduction of choline-containing compounds mainly in cortical areas (reviewed in Duarte et al. 2014b). These findings are consistent with neurodegeneration, and with impaired myelin deposition or inflammation (discussed above). Since mitochondrial dysfunction also contributes to neuronal degeneration in PD (Lin and Beal 2006), a reduction of high-energy phosphates and increased lactate concentration was observed in several brain areas of PD patients when compared to healthy subjects (Henchcliffe et al. 2008; Hattingen et al. 2009). At high magnetic field (7 T), GABA levels were found increased in the pons and putamen of early PD patients relative to healthy subjects, in the absence of other neurochemical modifications (Emir et al. 2012). This is an important observation, as the early detection of increased GABA levels in these areas may turn out a possible biomarker of PD, before irreversible neurodegeneration occurs. A recent study in two PD rat models also proposed decreased GABA in ^{1}H MRS as an early marker for nigrostriatal impairments prior marked neurodegeneration (Coune et al. 2013). In a recent MRS study at 9.4 T, GABA was also found reduced in the substantia nigra and striatum of marmosets intoxicated with MPTP (Heo et al. 2017).

MRS findings in neurotoxin-based models of PD that display synaptic degeneration and loss of nigrostriatal dopaminergic neurons generally include reduced NAA and increased lactate (Duarte et al. 2014b). However, despite useful to study the impairments in the dopamine system, they fail to fully reproduce the phenotype of patients with PD, including the accumulation of abnormal proteins. A recent ^{1}H MRS study at 9.4 T found decreased levels of lactate and increased levels of ascorbate in the frontal cortex of rats overexpressing α-synuclein, relative to controls (Cuellar-Baena et al. 2016). This animal model, however, does not reproduce the typical PD neurodegenerative process and, in this study, the known reduction in the neuronal marker NAA was not observed. Therefore, it is possible that a switch in energy metabolism occurs before typical PD markers are measurable.

Huntington's Disease

Huntington's disease (HD) is a neurodegenerative disease caused by modifications in the polyglutamine region of the huntingtin protein (Htt), leading to the accumulation of intracellular Htt aggregates, affecting especially GABAergic medium-sized spiny neurons, and leading to major cell loss in the striatum (Zheng and Diamond 2012). Mitochondrial dysfunction contributes to the pathogenesis of HD (Bossy-Wetzel et al. 2008; Oliveira 2010). Patients and animal models develop several mitochondrial defects, including altered calcium metabolism, impaired bioenergetics, increased oxidative stress, abnormal mitochondrial trafficking and mitochondrial dynamics, and enhanced apoptosis (Duarte et al. 2014b).

^{1}H MRS of basal ganglia and cerebral cortex of patients with HD showed elevated lactate production, in line with the known defects in mitochondrial pyruvate utilization (Jenkins et al. 1993). Like in other neurodegenerative disorders, MRS studies showed reduced NAA and increased *myo*-inositol in the brain of patients with HD, relative to healthy subjects (Duarte et al. 2014b). Interestingly, levels of NAA and *myo*-inositol in the putamen were found to be correlated with measures of HD severity (Sturrock et al. 2010). Association was also found between cognitive dysfunction and both NAA and glutamate levels in the posterior cingulate (Unschuld et al. 2012). Recent longitudinal MRS studies in subjects with pre-manifest HD and early-stage HD (as well as healthy controls) over 2 years indicated metabolite changes in NAA and *myo*-inositol in the caudate nucleus and putamen as biomarkers of disease progression, and that NAA correlations with disease burden score suggest that this metabolite may be useful to monitor responses to therapy (van den Bogaard et al. 2014; Sturrock et al. 2015).

Different transgenic mouse models with mutated huntingtin have been generated to investigate HD mechanisms. In the R6/2 transgenic mouse model of HD, striatal concentrations of creatine, glycerophosphorylcholine, glutamine, and glutathione were found to be increased, whereas NAA levels decreased (Jenkins et al. 2000; Tkác et al. 2007). Further development of the disease leads to additional modifications, namely increased concentrations of phosphocreatine, taurine, ascorbate, glutamate, lactate, and *myo*-inositol and decreased phosphorylethanolamine (Tkác et al. 2007; Zacharoff et al. 2012). Reduced NAA concentration was particularly associated with neuron dysfunction, length of polyglutamine expansions, and progression of the pathological phenotype (Jenkins et al. 2005). Interestingly, these neurochemical modifications in the R6/2 mouse were found not only in the striatum but also in cortical areas, and preceded significant atrophy for the cortex and the striatum, as measured in vivo from MR images (Zacharoff et al. 2012).

Recently, Pépin et al. (2016) investigated the neurochemical profile in the striatum of 1-year-old knock-in mice expressing chimeric mouse/human exon 1 containing 140 CAG repeats inserted in the murine Htt gene. Compared to controls, this HD model (Ki140CAG) displayed reduced concentration of glutamate, NAA, taurine and choline, and higher content of glutamine. In addition to single-voxel MRS, the authors acquired brain maps of glutamate by CEST MRI. Pépin et al. (2016) found a reduction of glutamate signal in the striatum by 11–13%, piriform cortex by 11–14%, and corpus callosum by 28%, relative to wild-type mice. Interestingly, when compared to wild-type littermates, Ki140CAG heterozygous mice also had lowed glutamate signal in the corpus callosum (− 21%). Although CEST methods do not allow to determine absolute glutamate concentrations, its increased spatial resolution relative to single-voxel MRS allowed to detect HD-induced glutamate alterations in a thin brain structure, as the mouse corpus callosum (Pépin et al. 2016). In the zQ175 knock-in mouse, concentrations of the neurotransmitters glutamate and GABA were transiently reduced in the striatum between 4 and 8 months of age, but recover to control levels at 1 year of age (Heikkinen et al. 2012). At this age, glutamine, creatine, and taurine were also increased relative to wild-type mice. Levels of NAA in the striatum were always lower in zQ175 mice (Heikkinen et al. 2012). Such biphasic alterations suggest that neurochemical profiling by MRS is able to differentiate distinct HD stages. These findings were partially reproduced in a recent ^{1}H MRS study at 9.4 T (Peng et al. 2016). When animals were 1-year-old, Peng and co-authors (2016) found reduced total creatine, glutamate, NAA and increased glutamine, taurine, and *myo*-inositol in the striatum. However, Peng's study reports abnormal age-dependent alterations of neurochemicals in wild-type mice, when compared to previously published reports (Duarte et al. 2014a; Harris et al. 2014).

Inhibitors of the complex II of mitochondrial respiratory chain, namely 3-nitropropionic acid and malonate, effectively trigger behavioral changes and selective striatal lesions in animals that mimic HD symptoms. Rodents treated with 3-nitropropionic acid display reduced striatal NAA levels (reviewed in Lee and Chang 2004). Interestingly, 3-nitropropionic acid was shown to reduce NAA levels in the absence of neuronal loss, and NAA levels recover when toxin administration ceases (Dautry et al. 2000). This is explained by the fact that NAA is produced in neuronal mitochondria. Accordingly, mitochondrial dysfunction caused by chemical inhibition of the respiratory chain leads to increased lactate concentration (e.g., Jenkins et al. 1993, 1996; Tsai et al. 1997; Lee and Chang 2004). In line with the known deficits in mitochondrial bioenergetics, a recent ^{17}O MRS study at 16.4 T identified impaired CMR_{O2} in the brain of R6/2 mice upon administration of the mitochondrial uncoupler dinitrophenol, when compared to controls, while CMR_{O2} was similar in transgenic and wild-type mice at rest (Lou et al. 2016).

Alzheimer's Disease

Alzheimer's disease (AD) is a progressive age-associated neurodegenerative disease and the most common form of dementia, and is characterized by extracellular deposition of amyloid aggregates, accumulation of neurofibrillary tangles of hyperphosphorylated tau protein, loss of synapses, and neuronal death (Huang and Mucke 2012). Impaired brain glucose metabolism occurs in patients with mild cognitive impairment and AD and correlates with amyloid-β plaque deposition (reviewed and discussed in Duarte 2015). Moreover, mitochondrial dysfunction and oxidative stress, as well as bioenergetics deficits, are important components of this pathology (Lin and Beal 2006; Duarte et al. 2014b; Rosales-Corral et al. 2015).

Patients with AD display impaired cerebral energy metabolism (reviewed in Ferreira et al. 2010). Accordingly, in addition to confirming alterations in these neurochemical markers, Haley and colleagues measured brain glucose levels by MRS after glucose administration and found that there was more glucose in the brain of patients with AD than of healthy subjects (Haley et al. 2006). These increased brain glucose levels thus likely reflect reduced glucose metabolism, which could be linked to impaired insulin signaling (Duarte 2015). In a study that included both ^{1}H and ^{13}C MRS, Lin et al. (2003) administered [1-^{13}C]glucose to patients with AD and observed ^{13}C incorporation into major metabolites of the brain, namely glutamate and glutamine. Their study suggested that the brain of patients with AD displays reduced neuronal metabolism as well as reduced glutamate-glutamine cycle rate, compared to control subjects. Moreover, the authors reported that ^{13}C MRS measures of neuronal metabolism and the glutamate-glutamine cycle correlate with ^{1}H MRS measures of neuronal integrity, namely the metabolite ratios NAA/creatine and NAA/*myo*-inositol (Lin et al. 2003).

Reduced NAA and increased *myo*-inositol concentrations (depicting neurodegeneration and astrogliosis, respectively) have been consistently reported in the brains of patients with AD, compared to *cognitively healthy elderly individuals and, furthermore, these findings were often correlated with decline* in cognitive performance (Duarte et al. 2014a; Wang et al. 2015). The concentration of NAA in brain areas of patients with mild cognitive impairment has been found in-between that of patients with AD and of healthy subjects (e.g., Kantarci 2007; Jessen et al. 2009; Watanabe et al. 2010), corroborating the notion that NAA indicates progression of brain dysfunction. Indeed, NAA decrease has been associated to progression of cognitive decline from light dementia to AD (e.g., Chantal et al. 2002, 2004; Pilatus et al. 2009) and may help predicting the rate of future cognitive decline in AD (Kantarci 2007).

Mutations in genes associated with β-amyloid precursor protein (APP), presenillin 1 (PS1), and presenillin 2 (PS2) are involved in early-onset familial AD (Selkoe 1995). Researchers have generated mouse models of AD by inserting one or more of these human mutations into the mouse genome, and these models reveal β-amyloid deposition in the brain, the hallmark of AD. Double transgenic mice expressing human mutant APP and human mutated PS1 display decreased glutamate and NAA concentrations in the brain, particularly in the hippocampus, and such metabolic alterations were observed before the presence amyloid plaques (Marjanska et al. 2005; Oberg et al. 2008; Choi et al. 2010). Compared to wild-type mice, these transgenic mice also show increased brain *myo*-inositol to creatine ratio at later disease stages, when amyloid deposits are detectable (Jack Jr et al. 2007), along with astrogliosis (Chen et al. 2009). In addition to the hippocampus, also the mouse cortex shows AD-induced increases in levels of *myo*-inositol and glutamine, and decreased NAA and glutamate, and NAA levels were inversely associated with the area of cortex occupied by amyloid plaques (Choi et al. 2010). A study in the triple transgenic mouse at 7 T confirmed the reduction in NAA (as a ratio to creatine), which accompanied synaptic degeneration and mitochondrial damage (Chen et al. 2016). The authors further observed increase lactate levels by MRS, in line with mitochondrial deficits. Notably, Chen and colleagues were able to improve alterations in NAA and lactate levels, as well as synaptic damage and mitochondrial dysfunction by treatment with icariin, a compound previously shown to reduce amyloid-β deposition and abnormal tau hyperphosphorylation (Chen et al. 2016). A combination of ^{1}H and ^{31}P MRS at 14.1 T was used to investigate the 5xFAD transgenic mouse model of AD that over-expresses APP with three different familial mutations plus PS1 also with two mutations, resulting in robust β-amyloid deposition (Mlynárik et al. 2012). Compared to controls, 5xFAD mice showed increased *myo*-inositol and decreased NAA and GABA in the hippocampus. Furthermore, 5xFAD mice displayed lower brain glucose and higher lactate levels, in line with impaired energy metabolism (Mlynárik et al. 2012). However, this study failed to identify AD-associated bioenergetic alterations by ^{31}P MRS.

Diabetic Encephalopathy

Both type 1 (insulin-dependent) and type 2 (insulin-resistant) diabetes affect the brain. Diabetes is associated with chronic hyperglycemia, microvascular complications, insulin resistance, dyslipidemia, and hypertension, which are all important risk factors for cognitive dysfunction (Duarte 2015). In addition to direct glucose neurotoxicity, alterations of mitochondrial metabolism and signaling are present in the diabetic brain and constitute a mechanistic link between defective brain insulin signaling and AD-like cognitive impairment (Duarte 2015; Zilliox et al. 2016).

There is considerable heterogeneity in the reported MRS findings in the diabetic brain, which is mainly caused by the analysis of different brain areas in each independent study (brain anatomical structures have different functions and may be differently affected by diabetes), and likely caused by poor control over comorbidities of the recruited subjects that hampers the ability to detect small diabetes-induced changes in the concentration of neurochemicals (Duarte 2016). Nevertheless, there is a general trend for a reduction in the levels of the neuronal marker NAA, as well as an increase in *myo*-inositol content in diabetes patients (Duarte 2015, 2016), following the general pattern of neurodegenerative disorders. Interestingly, insulin sensitivity was suggested to correlate with cortical levels of these two metabolites (Karczewska-Kupczewska et al. 2013).

Rodents treated with streptozotocin to destroy pancreatic β cells and hamper insulin secretion are widely used to mimic type 1 diabetes with uncontrolled hyperglycemia. Streptozotocin-induced diabetic rats display a plethora of metabolic alterations in the hippocampus and cortex, relative to control rats (Duarte et al. 2009; Wang et al. 2012). Interestingly, these studies further demonstrate that most hyperglycemia-induced metabolic alterations are normalized with acute restoration of euglycaemia. Some of the metabolites more affected by hypoinsulinemia and hyperglycemia were the brain osmolytes *myo*-inositol, taurine, and creatine (Duarte et al. 2009; Wang et al. 2012). High *myo*-inositol levels were also reported in the hippocampus of Zucker diabetic fatty rats compared to controls (van der Graaf et al. 2004). A diabetes-induced increase in hippocampal taurine was also reported in other models of type 2 diabetes, namely insulin-resistant Goto-Kakizaki rats (Duarte et al. 2019) and diet-induced obese mice (Lizarbe et al. 2019). Altogether, MRS studies in these animal models indicate that diabetes-induced brain dysfunction involves an osmolarity shift, probably due to continuous exposure to high brain glucose levels. In addition, chronic hyperglycemia in streptozotocin-induced diabetic rats was reported to cause a reduction of NAA in the striatum and hippocampus but not in the cortex, when compared to controls (Zhang et al. 2015).

Rodents exposed to hyper-caloric diets have been used as models for diet-induced obesity and insulin resistance. Rats exposed to 1 week of high-fat and fructose diet displayed impaired hippocampal insulin signaling, and smaller hippocampal volume with synaptic degeneration, reduced neuronal processes, and astrogliosis (e.g., Calvo-Ochoa et al. 2014). Rats under a similar diet for 5 days displayed impaired performance in place but not object recognition tasks (Beilharz et al. 2014), which are dependent on the function of hippocampus and perirhinal cortex, respectively. Furthermore, synaptic deterioration and impaired learning and memory induced by high-fat and high-sucrose diet were found to be dependent on neurotrophic factors that modulate synaptic plasticity (Molteni et al. 2002). High-fat diet alone is also able to impair hippocampal-dependent spatial memory (McNay et al. 2010; Pistell et al. 2010; Lizarbe et al. 2019) and may potentiate the AD phenotype in AD animal models (Ettcheto et al. 2016). A recent MRS study found that mice exposed to high-fat diet for 6 months display lower phosphocreatine-to-creatine levels in the hippocampus, cortex and hypothalamus (Lizarbe et al. 2019), indicative of impaired mitochondrial metabolism and susceptibility for energy failure. Furthermore, this study shows that metabolic alterations in high-fat diet-exposed mice are accompanied by deterioration of excitatory and inhibitory synapses. In line with synaptic dysfunction in type 2 diabetes (Duarte et al. 2019; Lizarbe et al. 2019), a study in the present issue shows impaired neuronal oxidative metabolism and reduced glutamate-glutamine cycle rate in the brain of Goto-Kakizaki rats (Girault et al. 2019). Altogether, these findings suggest that deficient mitochondrial metabolism upon exposure to diets rich in fat and sugar leads to synaptic deficits, and likely results in memory impairments.

Conclusion

As summarized herein, fluctuations in mitochondrial metabolism and morphology are closely related to the functionality of mitochondria and ultimately of cells. Despite the widely known importance of mitochondria for cell bioenergetics and redox homeostasis, recent works yielded robust evidence of mitochondrial mechanisms directly contributing to a myriad of physiological and pathophysiological processes in brain cells, including neural plasticity and maturation, and neurodegeneration. Among the techniques available to investigate brain metabolism, MRS is particularly powerful because it allows the measurement of physiological parameters that are linked to brain metabolism and bioenergetics in a fully non-invasive manner. Such attribute facilitates the understanding of the etiology of neurodegenerative process and allows the monitoring of treatment efficacy. The precise underlying mechanisms of mitochondrial physiology are yet to be disentangled and the complete understanding and modulation of such mechanisms may represent a novel and promising therapeutic approach for diseases affecting central and peripheral nervous system.

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