Emerging roles of brain metabolism in cognitive impairment and neuropsychiatric disorders

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ABSTRACT

Here we discuss the role of diverse environmental manipulations affecting cognition with special regard to psychiatric conditions. We present evidence supporting a direct causal correlation between the valence of the environmental stimulation and some psychopathological traits and how the environment influences brain structure and function with special regard to oxidative stress and mitochondrial activity. Increasing experimental evidence supports a role for mitochondrial dysfunctions in neuropsychiatric disorders. Brain mitochondria are considered crucial mediators of allostasis, that is the capability to adapt to stress via a complex interaction between the autonomic, metabolic, and immune systems to maintain cellular homeostasis. In this process, mitochondria act as highly dynamic integrators by sensing and transducing stressors into adaptation mechanisms via metabolic stress mediators, such as glucocorticoids and catecholamines. Alterations in cellular homeostasis induced by chronic stress are thought to predispose to disease by triggering the so-called "mitochondrial allostatic load". This process is characterized by functional and structural changes of the mitochondria, ultimately leading to oxidative stress, inflammation, mitochondrial DNA damage and apoptosis. In this review we discuss the role of diverse environmental manipulations to affect cognition with special regard to psychiatric conditions. How the environment influences brain structure and function, and the interactions between rearing conditions, oxidative stress and mitochondrial activity are fundamental questions that are still poorly understood. As will be discussed, increasing experimental evidence supports a role for mitochondrial dysfunctions in neuropsychiatric disorders. Brain mitochondria are considered crucial mediators of allostasis, that is the capability to adapt to stress via a complex interaction between the autonomic, metabolic, and immune systems to maintain cellular homeostasis. In this process, mitochondria act as highly dynamic integrators by sensing and transducing stressors into adaptation mechanisms via metabolic stress mediators, such as glucocorticoids and catecholamines. Alterations in cellular homeostasis induced by chronic stress are thought to predispose to disease by triggering the so-called "mitochondrial allostatic load". This process is characterized by functional and structural changes of the mitochondria, ultimately leading to oxidative stress, inflammation, mitochondrial DNA damage and apoptosis. The brain requires considerable mitochondrial reserve not only to sustain basal neuronal needs but also to provide increasing energy demands during stress. Consistently with these high energetic requirements, it is reasonable to hypothesise that the brain is particularly vulnerable to mitochondrial defects. Thus, even subtle metabolic alterations might have a substantial impact on cognitive functions. Over the last decade, several experimental evidence supported the hypothesis that a suboptimal mitochondrial function, which could be of genetic origin or acquired following adverse life events, is a key vulnerability factor for stress-related psychopathologies. Chronic psychological stress is a major promoter of anxiety as well as of oxidative damage, as shown in several studies. Recent evidence from mouse models harbouring mutations in mitochondrial genes demonstrated the role of mitochondria in modulating the response to acute psychological stress. However, it has yet to be determined whether mitochondrial dysfunctions are the cause or the consequence of anxiety. In this review, we discuss how adverse psychosocial environments can impact mitochondrial bioenergetics at the molecular level and we gather evidence from several studies linking energy metabolism and stress resilience/vulnerability. Moreover, we review recent findings supporting that metabolic dysfunction can underlie deficits in complex social behaviours. As will be discussed, aberrations in mitochondrial functionality have been found in the nucleus

accumbens of highly anxious mice and mediate low social competitiveness. In addition, alterations in sociability can be reversed by enhancing mitochondrial functions. Recent evidence also demonstrated that a specific mutation in mitochondrial DNA, previously linked to autism spectrum disorder, produces autistic endophenotypes in mice by altering respiration chain and reactive oxygen species (ROS) production. Finally, we discuss a "Negative Enrichment" model that can explain some of the psychopathological conditions relevant to humans. Evidence of a direct causal correlation of valence of environmental stimulation and psychopathological traits will be presented, and possible molecular mechanisms that focus on oxidative stress. Collectively, the findings described here have been achieved with a wide set of behavioural and cognitive tasks with translational validity. Thus, they will be useful for future work aimed to elucidate the fine metabolic alterations in psychopathologies and devise novel approaches targeting mitochondria to alleviate these conditions.

1. Introduction

The regulation of energy metabolism represents a major challenge for the nervous system. It is estimated that the energetic needs of the adult human brain account for approximately 20 % of the body's oxygen consumption, although the brain represents just 2 % of total body's weight (Raichle and Gusnard, 2002), while the metabolic cost in the developing brain is even higher (Kuzawa et al., 2014) (Steiner, 2019). This is mainly due to the complexity of neuronal morphology and the highly energetic processes required to sustain and regulate neuronal transmission and synaptic plasticity. Stress and higher cognitive functions underlying complex behaviours further increase cerebral energy demands in terms of glucose oxidation and oxygen consumption (Bryan, 1990). Overall, the energetic cost of brain activities must be efficiently covered by mitochondrial respiration. Thus, it is not surprising that even small alterations in metabolic processes may severely affect neural functions, thereby increasing vulnerability for brain disorders (Pei and Wallace, 2018).

Cellular energy metabolism is regulated mainly by mitochondria which are the cells' powerhouse for producing ATP but also acknowledged as key regulators of a variety of processes, including reactive oxygen species (ROS) production, calcium buffering, apoptosis, lipid biogenesis and hormones biosynthesis (Spinelli and Haigis, 2018).

Over the last decade, emerging studies have highlighted a bidirectional interplay between mitochondria bioenergetics and psychosocial stress. However, it remains elusive whether mitochondrial dysfunctions are cause or consequence of psychopathology. In this review, we examine the role of mitochondria in regulating neuronal energy metabolism and allostasis. We also discuss recent advances linking energy metabolism and brain disorders, with a special emphasis on stress-related psychopathologies and social behaviours. Finally, we present a "Negative enrichment model", that could explain specific neuropathological traits relevant for humans (Shaw et al., 2020).

2. Mitochondrial functions in energy metabolism and allostasis

Mitochondria are cellular organelles evolved from a bacterial progenitor via symbiosis within a eukaryotic cell. They are the only organelles present in all eukaryotes possessing their own genome, the mitochondrial DNA (mtDNA), with 37 genes (in humans and mice) encoding for proteins of the electron transport chain and ATP synthase, as well as ribosomal and transfer RNAs for the mitochondrial translation machinery. In the mitochondria, nutrients are oxidized to produce energy in the form of ATP. Pyruvate, the product of glycolysis, and fatty acids are metabolized into acetyl-coenzyme A which enters the Krebs cycle leading to the production of the reducing equivalents NADH and $FADH_2$. These coenzymes carry electrons into the electron transport chain located in the inner mitochondrial membrane ultimately leading to the production of ATP by oxidative phosphorylation. This mechanism is also closely related to the release of ROS that, when produced at high levels and exceeding the antioxidant capacity, can lead to oxidative stress, inducing DNA damage, oxidative modifications and eventually cell death (Spinelli and Haigis, 2018).

Despite being mainly considered as "cellular power plants",

mitochondria can also coordinate a plethora of processes, including biosynthesis of macromolecules (Spinelli and Haigis, 2018), as well as calcium homeostasis (Giorgi et al., 2018).

Importantly, mitochondria are crucial mediators of "allostasis", which refers to the active process of physiological adaptation to stress via a complex interplay between stress mediators and the autonomic, metabolic, and immune systems (McEwen, 1998). In response to stressors, mitochondria bidirectionally communicate with stress mediators, thereby inducing protective biological responses of adaptation that are sustained for a limited time window during stress challenge and then turned off. The most known stress mediators, glucocorticoids (i.e. cortisol in humans and corticosterone in rodents) and catecholamines (i. e. epinephrine and norepinephrine), can in turn regulate the production of pro- and anti-inflammatory cytokines. In addition, the parasympathetic and sympathetic nervous system oppose each other and finely tune this allostasis network (McEwen, 2006). Mitochondrial fission/fusion dynamics are also critical to stress response and constantly shaped during the lifetime of a cell. Moreover, either the quality or the number of mitochondria must be strongly monitored to avoid the accumulation of dysfunctional organelles that can be detrimental for cellular physiology. Thus, damaged or unwanted mitochondria constantly undergo "mitophagy", a lysosomal-dependent degradation process (Youle and van der Bliek, 2012). Upon environmental challenges, mitochondrial metabolic intermediates and ROS can also influence gene expression by activating specific signalling pathways (i.e. mTORC1, AMPK) that in turn regulate downstream molecules and transcription factors to enable cellular adaptation (Shaughnessy et al., 2014). In addition, mitochondrial substrates derived from the Krebs cycle or other metabolic pathways within the mitochondria are required as substrates or cofactors for epigenetic modifications, thus mediating gene expression. For instance, citrate is exported from the mitochondria to the cytoplasm and transformed into Acetyl-CoA, a substrate of histone acetylation (Wellen et al., 2009). In addition, histone demethylation requires a-ketoglutarate, a metabolic intermediate of the Krebs cycle (Klose and Zhang, 2007).

However, the same adaptation mechanisms that are protective upon acute stress can cause pathological changes when overused and imbalanced, thus triggering cardiovascular and metabolic dysregulations as well as alterations in neuronal networks. Such detrimental effects of chronic exposure to environmental challenges are collectively referred to as "allostatic overload", a concept proposed by Stellar and McEwen back in 1993 (McEwen and Stellar, 1993). Specifically, at the mitochondria level, multiple and chronic stressors can provoke the so called "mitochondrial allostatic overload" (MAL). This process includes dysfunctions in mitochondrial fission/fusion dynamics, decrease in ATP synthesis, excessive ROS production, mtDNA mutations as well as abnormalities in glucose and lipids metabolism that collectively increase disease risk (Picard et al., 2017).

3. Mitochondria in neuronal functions

In the brain, a key mitochondrial function is to provide energy to essential neuronal functions by producing ATP via oxidative phosphorylation of nutrients. Based on early evidence, glycolysis was

thought to occur in astrocytes to produce lactate, subsequently shuttled to neurons and converted into pyruvate to generate ATP in neuronal mitochondria (Pellerin and Magistretti, 1994). However, more recent evidence seems to support the idea that nerve terminals can also metabolize glucose (Diaz-Garcia et al., 2017). Part of the energy generated by neuronal mitochondria is used for housekeeping functions, such as cytoskeletal dynamic and synthesis of macromolecules, although the most energetically demanding processes occur at the synapses, for the maintenance of membrane resting potential, for firing action potentials and especially for sustaining synaptic transmission, synaptic plasticity and for regulating the release and uptake of neurotransmitters (Harris et al., 2012). In neurons, mitochondria are actively transported along axons and dendrites and recruited to metabolically active regions, such as the pre-synaptic terminals. In this highly dynamic process, mitochondria constantly undergo fusion and/or fission in response to synaptic changes (Mattson et al., 2008).

Apart from ATP production, mitochondria also regulate thermogenesis by converting the metabolic substrates into heat. This process is achieved via proton leak from the inner mitochondrial membrane and is required for the maintenance of body temperature, the regulation of carbon flux and nutrient response as well as the prevention of oxidative damage (Bertholet and Kirichok, 2022).

Mitochondria are also crucially involved in the homeostasis of calcium, a second messenger crucial for neurotransmission and synaptic plasticity. In pathophysiological situations of high energy demands, characterized by low levels of ATP and high concentrations of cytosolic calcium, calcium is driven into the mitochondrial matrix, resulting in an upregulation of the Krebs' cycle and ATP synthase leading to ATP production. This process provides the energy required to extrude the excess of intracellular calcium via the Na^{2+}/Ca^{2+} exchanger and the mitochondrial permeability transition pore (Gleichmann and Mattson, 2011). At the pre-synaptic sites, mitochondria can also modulate the release of neurotransmitters by either persistently sequestering cytosolic calcium or releasing calcium from the mitochondrial matrix (Jonas, 2014).

During the electron-transfer process, mitochondria generate superoxide (O_2^-), the precursor of other ROS. Mitochondrial manganese superoxide converts O_2^- into O_2 and H_2O_2, which is turned into hydroxyl radicals (OH^-) or into water. On the other hand, mitochondria also produce several antioxidants, such as coenzyme Q10, creatine, nicotinamide, and glutathione, to counteract the negative effects of free radicals on macromolecules and DNA (Mattson et al., 2008). ROS imbalances can promote apoptosis via Bcl-2 proteins in pathological conditions when the levels of ROS exceed the antioxidant capacity. However, in physiological conditions ROS are crucial regulators of synaptic activity by promoting selective synapse loss and have been shown to be involved in learning and memory (Jonas, 2014; Massaad and Klann, 2011; Mattson and Goodman, 1995; Mattson and Liu, 2002).

Collectively, this evidence suggests that mitochondria sustain energy homeostasis in neurons but also shape synaptic structure and plasticity that mediate higher cognitive functions. Therefore, mitochondrial deficits might promote neuropathology by disrupting synaptic plasticity and cellular resilience to environmental stressors. Hence, it is also logic to assume that more demanding cognitive task are the most affected by mitochondrial dysfunction and bioenergetic imbalance similarly to what has been previously reported for genetic defects affecting glutamatergic synapses (More et al., 2017).

4. Mitochondrial dysfunctions contribute to stress and anxiety disorders

Chronic stress has been considered as a key factor for the development and progression of many neuropsychiatric conditions, including anxiety and mood disorders, currently affecting millions of individuals worldwide. These mental disorders represent a major personal, societal, and economic burden due to their chronic nature, the associated cognitive and functional impairments, and the limited efficacy of the available treatments. Hence, there is an urgent need to understand the biological mechanisms underlying these conditions and find novel therapeutic strategies.

An early line of evidence supporting the role of mitochondria in neuropsychiatric conditions comes from the observation of patients with mitochondrial disorders who often presented psychiatric symptoms. A study showed that 70% of patients diagnosed with mitochondrial disorders met diagnostic criteria for mental disorders (Fattal et al., 2007).

Further lines of evidence rely on the fact that mitochondria are involved in the synthesis of glucocorticoids. These stress hormones regulate processes aimed at increasing systemic glucose and lipids to fuel energy to multiple tissues, such as the brain and the heart, under stressful conditions (Bose et al., 2002). As suggested by Munck and Naray-Fejes-Toth in 1992, glucocorticoids-mediated effects follow a biphasic, inverted U-shape (Munck and Naray-Fejes-Toth, 1992). At the brain level, mild-to-moderate stress has a protective effect by promoting mitochondrial adaptation and mobilization of energy stores to enhance neural plasticity. Conversely, increased release of glucocorticoids suppresses synaptic function and promotes brain aging via accumulation of free radicals and extra-synaptic glutamate (Du et al., 2009). In addition, chronic exposure to glucocorticoids can negatively impact mitochondrial dynamics, trafficking and mitophagy with a detrimental effect on neuron survival (Du et al., 2009; Hunter et al., 2016). In this regard, hyperactivity of hypothalamic pituitary adrenal (HPA) axis resulting in increased cortisol levels and mitochondrial dysfunctions have been reported in Alzheimer's disease (Choi et al., 2017; Green et al., 2006), Parkinson's disease (Smith et al., 2002) and Huntington's disease (Aziz et al., 2009; Chen et al., 2020). Furthermore, sleep disorders, which are becoming progressively prevalent in our modern society and are often present in comorbidity with neuropsychiatric conditions, hyperactivate the HPA axis resulting in cortisol secretion (Meerlo et al., 2008). Several studies on both sleep-deprived humans and animals reported dysregulation in mitochondrial functions and oxidative phosphorylation activity leading to oxidative damage (Andreazza et al., 2010a; Gulec et al., 2012; Rodrigues et al., 2018) as well as global changes in mitochondrial proteins (Ren et al., 2016).

Another element connecting mitochondria and stress is the presence of monoamine oxidases MAO-A and MAO-B in the outer mitochondrial membrane. These enzymes mediates the catabolism of catecholamines, released in response to certain stressors (Binda et al., 2011).

Further to this, downregulation of type 2 metabotropic glutamate receptors (mGluR2), which is related with L-acetylcarnitine (LAC) deficiency, has been shown to promote loss of synaptic spines and dendritic shrinkage. This dysfunction in glutamatergic transmission is believed to be one of the key features of stress-related disorders, including major depression. LAC can epigenetically regulate mGluR2 gene expression by acetylation and its supplementation has been shown to provide antidepressant effects in both chronically stressed mice and genetically vulnerable Flinders Sensitive rats (Nasca et al., 2013).

Moreover, chronic mild stress, an established paradigm of depression in rodents, reduces the activity of the mitochondrial respiratory chain complexes (Rezin et al., 2008) and induces alterations in mitochondrial ultrastructure (Gong et al., 2011). In a very recent paper, Weger and colleagues (Weger et al., 2020) carried out a bulk transcriptomic analysis on the prefrontal cortex (PFC) and nucleus accumbens (NAc) of mice following chronic restraint stress. The authors demonstrated a prominent upregulation of mtDNA genes encoding for the oxidative phosphorylation complexes I, III and IV in the PFC. Mitochondrial respiration capacity and glucose levels were also reduced in the PFC of mice following chronic stress.

Strong evidence has linked the role of mitochondria and oxidative stress to anxiety and depression (Filiou and Sandi, 2019; Picard et al., 2018; Picard and Sandi, 2021; Weger et al., 2020). Regarding generalized anxiety disorder, the role of mitochondria appears to be more complex. Different studies investigated the bioenergetic changes in

respiration capacity and oxidative phosphorylation leading to controversial results, depending on both the species/strain employed in the studies and the brain region analysed. For instance, cortical synaptosomes derived from a CD1 mouse model of high anxiety behaviour (HAB) displayed increase expression of oxidative phosphorylation complexes and low expression of glycolysis enzymes (Filiou et al., 2011). However, in other studies, high anxious Wistar rats showed lower levels of ATP and oxidative phosphorylation complexes in the Nucleus accumbens. (van der Kooij et al., 2018), as well as increased mitochondrial respiration in the prefrontal cortex (Hollis et al., 2018) and no change in the ventral tegmental area (van der Kooij et al., 2018).

Since alterations in mitochondrial functions may also cause an imbalance in ROS production and antioxidant capacity, the levels of oxidative damage markers have been also investigated. In this case, rodent anxiety models seem to consistently demonstrate an increase in oxidative stress. Behavioural assessment of six inbred mouse strains coupled with gene expression analysis across different brain areas identified 17 genes whose expression profiles correlated with anxiety phenotypes. Among these genes, glyoxalase 1 and glutathione reductase 1 seemed to be involved in the genesis of anxiety disorders since their lentiviral-mediated overexpression in mouse brains triggered anxiety behaviours. Conversely, RNA interference of glyoxalase 1 reduced anxiety (Hovatta et al., 2005). Glyoxalase 1, crucial mediator of cellular metabolism involved in the detoxification of the cytotoxic metabolite methylglyoxal, was significantly reduced in HAB mice, and thus is believed to be a potential biomarker of trait anxiety (Kromer et al., 2005). Other studies are in line with these observations, showing an increase in oxidative damage in several brain areas as well as in blood cells, although it is not clear whether the antioxidant capacity is also deregulated in these models (Rammal et al., 2008).

Collectively, these results indicate a complex relationship between mitochondrial activity and stress-related psychopathologies, although the causality of mitochondrial functions in the generation of these diseases still needs to be shown.

5. Emerging roles of mitochondria in mood disorders and schizophrenia

In addition to the above-mentioned role in stress and anxiety, mitochondrial dysfunctions may also contribute to the etiopathogenesis of other major metal conditions, such as mood disorders and schizophrenia, as indicated by studies both in humans and in animal models.

Neuroimaging studies evidenced a reduced energy metabolism in the prefrontal cortex, insula and basal ganglia in patients with major depression (Iosifescu et al., 2008; Moore et al., 1997; Volz et al., 1998). Proteomic analysis also revealed altered expression of proteins involved in pyruvate metabolism and tricarboxylic acid cycle (Scifo et al., 2018) as well as overexpression of cytochrome c, cytochrome c oxidase, subunits of the mitochondria electron transport chain complex I and ATP synthase (Beasley et al., 2006; Martins-de-Souza et al., 2012). An impaired oxidative phosphorylation was also found in patients with bipolar disorder (Stork and Renshaw, 2005).

In terms of oxidative stress, research has led to inconclusive results with few metanalysis reporting an increase in oxidative stress markers in major depression (Black et al., 2015; Liu et al., 2015) and other studies showing opposite results (as reviewed in (Rappeneau et al., 2020)). In bipolar patients, superoxide dismutase (SOD) activity appears to be increased during the manic and depressive episodes (Andreazza et al., 2007; Machado-Vieira et al., 2007), while another study reported a decreased SOD activity during the manic phase (Gergerlioglu et al., 2007). Research on glutathione peroxidase and catalase also produced contrasting results (Andreazza et al., 2007; de Souza et al., 2014; Kuloglu et al., 2002; Machado-Vieira et al., 2007).

At the genetic level, a downregulation of global mitochondrial genes was observed in patients with bipolar disorder (Iwamoto et al., 2005; Sun et al., 2006; Vawter et al., 2006) as well as oxidative damage due to

impaired mitochondrial electron transport chain complex I (Andreazza et al., 2010b).

The antioxidant enzymes superoxide dismutase 1, glutathione peroxidase 4 and glutathione S-transferase pi1 were decreased in patients with BD. The expression of complex I and IV genes NDUFS7 and COX6C was decreased in BD subjects and correlated with the pH of the tissue, that was significantly lower in BD patients (Sun et al., 2006). Another study (Vawter et al., 2006) previously showed that mitochondrial gene expression in post-mortem samples was sensitive to lower pH due to prolonged agonal states, caused by respiratory arrest or coma. Nevertheless, Sun et al. concluded that the lower pH in BD brains was due to the pathology itself due to mitochondrial dysfunction rather than agonal state as only 1 patients in the BD group died from respiratory failure (Sun et al., 2006).

Medications can also affect the expression of mitochondrial complex subunits. For instance, lithium treatment increased the expression of NDUFS7 while subjects treated with valproate and atypical antipsychotics showed decreased expression of NDUFS7, COX6C and complex V gene ATP5G3 (Sun et al., 2006).

A global down regulation of mitochondrial genes was found by Iwamoto et al. only in medicated BD patients, while non medicated subjects exhibited an up regulation of 27 mitochondrial related genes, including COX15, UQCRC2, ETFDH and NDUFS1 (Iwamoto et al., 2005).

Evidence for a possible implication of metabolic deficits in mood disorders also comes from preclinical models of depression and mania. For instance, chronically stressed rats and mice displayed a number of alterations, including reduced activity of the mitochondrial respiratory-chain complexes, increased SOD production and changes in mitochondrial membrane potential and ultrastructure (Lucca et al., 2009; Rezin et al., 2008). Treatment with amphetamine to induce mania in rats resulted in a reduction of creatine kinase activity and mitochondrial respiratory chain activity (Streck et al., 2008; Valvassori et al., 2010), and increased oxidative stress (Frey et al., 2006). Remarkably, the mood stabilizer valproate could effectively rescue the inhibition of the mitochondrial respiratory chain (Valvassori et al., 2010).

In support of a possible mitochondrial dysfunction hypothesis of bipolar disorder, Kasahara et al. observed altered day-night rhythms in a transgenic mouse line for a human mitochondrial disorder, called chronic progressive external ophthalmoplegia (Kasahara et al., 2006). This mouse line carried a neuron-specific accumulation of partially deleted mtDNA that caused a behavioural phenotype resembling bipolar disorder. Interestingly, these behavioural alterations could be improved by lithium.

Current evidence for specific mitochondrial dysfunctions correlated with schizophrenia appears to be more limited. In a mouse model of 22q11.2-deletion syndrome (DiGeorge Syndrome), mitochondrial electron transport chain genes were found to be upregulated (Jurata et al., 2006). An increased expression of protein subunits of complex I was also observed in rats with neonatal ventral hippocampal lesions, a neurodevelopmental model of schizophrenia (Ben-Shachar et al., 2009). In humans, alterations in mitochondrial structure have been observed in early studies on post-mortem brains (Kolomeets and Uranova, 1999; Kung and Roberts, 1999), although this effect could be due to the toxicity of antipsychotic medications on mitochondrial functions (Burkhardt et al., 1993). At the genetic level, evidence for a direct implication of mtDNA in the pathogenesis of schizophrenia is somewhat elusive (Bandelt et al., 2007; Fuke et al., 2008; Martorell et al., 2006). However, mutations in DISC1, a candidate gene for schizophrenia risk, have been linked to perturbations in mitochondrial dynamics in vitro (Norkett et al., 2016; Park et al., 2010). Furthermore, a splice variant of D-amino acid oxidase activator (DAOA), a candidate gene for schizophrenia and bipolar disorder susceptibility, encodes for a mitochondrial protein. Interestingly, its overexpression promotes mitochondrial fragmentation in mammalian cell lines and neurons and induces dendritic arborization in immature neurons (Kvajo et al., 2008).

6. The role of mitochondria in regulating social behaviours and autistic traits

Over the last years, increasing data have suggested a mitochondrial aetiology of autism spectrum disorder (ASD). Early evidence suggesting a possible link between autism and metabolism can be traced back to 1985 when Coleman and Blass described four autistic patients with signs of lactic acidosis. This study raised the possibility that some abnormalities in carbohydrates metabolism were occurring in autistic patients and might be secondary to respiratory chain defects or pyruvate dehydrogenase deficiency (Coleman and Blass, 1985). Few years later, Filipek et al. reported two cases of autistic children with an inverted duplication of the 15q11-q13 locus showing an hyperproliferation of mitochondria in the muscle, associated with a defective respiratory complex function (Filipek et al., 2003). Recently, the potential mitochondrial aetiology of autism has been further substantiated by several studies on mitochondrial genome that identified mutations in the mtDNA in patients with ASD (Giulivi et al., 2010; Napoli et al., 2013; Pons et al., 2004). Moreover, alterations in mtDNA copy number and pyruvate dehydrogenase as well as reduced activities of the electron transport chain complexes have been observed in the frontal cortex of subjects with ASD (Gu et al., 2013). Another study on autistic patients detected a range of mitochondrial dysregulations, including defects in proteins of the respiratory chain, decreased levels of antioxidant enzyme SOD2 and increased oxidative DNA damage in the temporal lobe. The same study also provided evidence for alterations in fusion/fission dynamics and mitochondrial membranes mass (Tang et al., 2013). A recent meta-analysis evidenced deregulations in mitochondrial biomarkers, including lactate, pyruvate, carnitine, and ubiquinone, in ASD patients with some of these markers correlating with the severity of the disease (Rossignol and Frye, 2012).

These human correlation studies were further supported by experimental evidence from animal models. A mouse model carrying a missense mutation in mtDNA complex I ND6 gene (ND6^{P25L}) exhibited deficits in social interaction and increased compulsive behaviour. These mutants also displayed increased anxiety and freezing behaviour. Notably, ND6^{P25L} mtDNA mutation could induce neuronal networks abnormalities with EEG alterations and increased susceptibility to seizures, consistently with the deficits observed in ASD patients (Yardeni et al., 2021).

Other lines of evidence have been supporting the idea that autism-linked genes may also play a role in mitochondrial function. For instance, in the previously mentioned mouse model of DiGeorge/22q11.2 deletion syndrome, associated with autism, Txnrd2 gene appears to be essential for ROS catabolism. Txnrd2 diminished dosage in 22q11.2 syndrome produces oxidative stress, thus resulting in a reduction of mitochondria in layer 2/3, synaptic vesicles, and pre-synaptic terminals, as well as mitochondrial morphological alterations. 22q11.2 deletion mice also showed deficits in the visual reversal learning task that could be restored by antioxidant therapy, consistently with the fact that cortico-cortical connectivity sustained by layer 2/3 projection neurons is crucially involved in the regulation of higher cognitive functions (Fernandez et al., 2019).

Additionally, recent research demonstrated that abnormalities in mitochondrial thermogenesis may contribute to Fragile X syndrome's phenotype, characterized by intellectual disability and autism. Forebrains isolated from Fmr1 KO mice at postnatal day 10 exhibited coenzyme Q10 deficiency and pathological opening of cyclosporin A-sensitive channel, resulting in excessive proton leak and inefficient thermogenesis. Remarkably, the administration of CoQ10 could rescue the spine density and some autistic traits in Fmr1 KO mice (Griffiths et al., 2020).

Apart from autism spectrum disorder, recent studies on animal models pointed out that mitochondrial metabolism may also underlie complex social behaviours. For instance, a rat model of high trait anxiety, that predisposes to social subordination, exhibited reduced protein levels of mitochondrial complex I and II into the NAc, as well as lower ATP production and increased oxidative stress. Notably, intra-accumbal infusion of complex I and complex II inhibitors could per se reduce social dominance. Conversely, boosting mitochondrial respiration by nicotinamide treatment could abolish social disadvantage in high anxious rats (Hollis et al., 2015). As a further evidence, social dominance in high anxious rats could be ameliorated by diazepam treatment directly infused into the VTA. This mechanism seems to be mediated by a D1-dependent enhancement of the mitochondrial function in the NAc. (van der Kooij et al., 2018). Alternative approaches based on dietary supplementation have been also used and further support the role of energy metabolism in social behaviours. In a recent paper, rats fed with a medium chain triglycerides (MCT)-based diet showed increased social competitiveness and reduced anxiety. The effects of this dietary regimen were due to a specific decrease in mitochondrial respiration in the PFC, observed in high anxious animals, along with a reduction of mitochondrial complex I levels and a modulation of the glutamate reuptake (Hollis et al., 2018).

Another study employed C57/Bl6J male mice cohabitating in the same cage for 7 weeks. Mice identified as dominant and subordinated using the social confrontation tube test were then subjected to chronic social defeat. This paper demonstrated that subordinate mice showed lower levels of energy-related metabolites which increased following chronic social defeat to confer more capability to cope with stress. Interestingly, no changes in energy-related metabolites were observed in dominant males which were indeed more susceptible to chronic social defeat (Larrieu et al., 2017).

Based on these lines of evidence, it is reasonable to hypothesise that stress-induced changes in mitochondrial functions could effectively alter neuronal transmission and synaptic plasticity. To elucidate the molecular mechanisms linking mitochondrial functions to the development of stress-related psychopathologies, several rodent models have been employed in recent years.

Stressful experiences such as reductions in maternal care, changes in diet and exposure to aversive stimuli, are known to lead to long lasting epigenetic modifications in the degree of DNA methylation/ demethylation or histone post-translational modifications such as acetylation (Zovkic et al., 2013; Zovkic and Sweatt, 2013).

All together, these findings are potentially relevant also for human psychopathology and could open new avenues for treatment. Individuals with trait anxiety are indeed more prone to adopt submissive behaviours and their self-confidence becomes compromised in a stressful environment, that may impact on the social rank. Importantly, lower social status and the constant striving in a competitive environment are believed to be crucial factors that increase vulnerability to depression, anxiety, and self-harm (Gilbert et al., 2009; Goette et al., 2015). Nevertheless, despite the emerging experimental evidence strongly supporting the role of mitochondria in these processes, it has yet to be determined how mitochondrial functions can affect the specific neuronal networks behind social behaviours.

It must be noted that most studies on either stress-related disorders or social cognition used stressors to induce some pathological endophenotypes. However, these behavioural paradigms may not be able to fully recapitulate other human conditions, for example those triggered by highly competitive social environments. A possible pathological manifestation induced by enhanced social competition is the antisocial personality disorder (APD), which accounts for a significant proportion of violent crimes in our society.

Recently, Shaw and colleagues (Shaw et al., 2020) (Fig. 2) proposed a novel paradigm, referred to as "Negative Enrichment", with the aim to recapitulate APD-like phenotypes in mice. The negative enrichment consisted in three different manipulations (introduction of female pheromones, predator pheromones and overcrowding as housing condition) aimed to increase social competition. The authors demonstrated that the negatively enriched group showed a more competitive behaviour in the tube test and when interacting with an oestrous female.
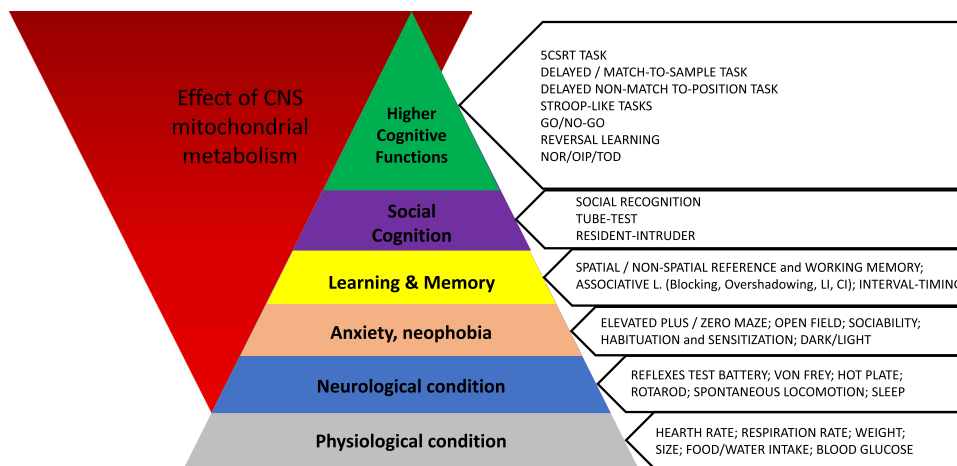
Fig. 1. : The effect of CNS mitochondrial metabolism is directly proportional to the behavioural and cognitive task complexity and attention demand. A working model of the potential impact of CNS mitochondrial metabolism on each of the components of a given behavioural response. Depicted the general CNS functions in the triangle (centre) and specific tests to measure them on the right. The more complex and more attention demanding task the more the brain mitochondrial metabolism plays a greater role (left). Hence the tasks listed on the top are more sensitive to smaller metabolic alterations.
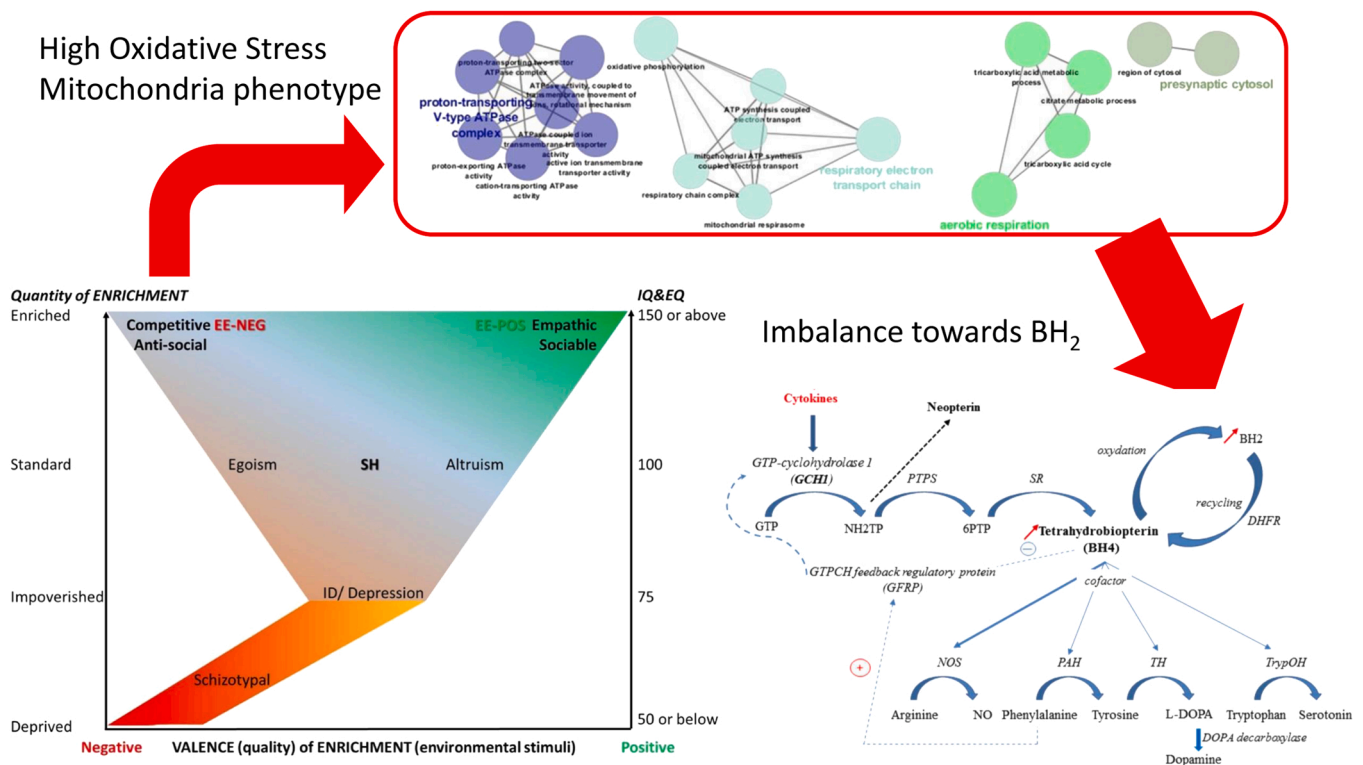
Fig. 2. : A highly competitive environment generates a high oxidative stress mitochondrial phenotype. This mitochondrial phenotype is believed to alter the BH4: BH2 ratio pushing it towards BH2 and so affecting the production of dopamine and serotonin. Pictures collated and edited from Shaw et al. (2020) and Vancassel et al. (2018).

Notably, proteomic analysis revealed that 47 proteins related to the mitochondrial processes of the Krebs cycle and the electron transport chain were significantly increased in the frontal pole of negatively enriched mice. These pathophysiological changes in mitochondrial metabolism are associated with increased levels of reactive oxygen species (ROS), perturbations in redox signalling, and the onset of oxidative stress (OS). Tetrahydrobiopterin (BH_4) is a cofactor required for nitric oxide (NO) production and neurotransmitter synthesis but has also recently been shown to be a central mitochondrial redox signalling hub. The brain is particularly susceptible to redox changes and the onset of OS. OS causes a decrease in BH_4 availability (via reduction to BH_2), which in turn is known to impair the production of NO and catecholamines such as Serotonin and L- DOPA (Vancassel et al., 2018). See Fig. 2 for a depiction of how an environmentally triggered high

oxidative stress mitochondria phenotype might affect CNS neurotransmitters biosynthesis.

Ethologically relevant paradigms of social behaviours have been used recently by Kanellopoulos et al. in Drosophila models with CYFIP1 haploinsufficiency, a genetic variant associated with increased risk for schizophrenia and a candidate risk factor for ASD. These mutants displayed deficits in courtship behaviour and food competition that were associated with increased mitochondrial size and excessive Krebs cycle, resulting in GABA to be sequestered into the mitochondria via Aralar transporter. Social deficits could be restored by pharmacological and genetic approaches targeting mitochondria (Kanellopoulos et al., 2020).

7. Conclusions

The evidence presented here suggests that alterations in mitochondrial function do impact on cognitive processes and may be causative linked to the onset of psychiatric disorders such as anxiety, stress related disorders as well as social interaction deficits in the domain of autism and antisocial personality disorder. In the context of mood disorders and schizophrenia, more research is needed to determine the disease-specificity of mitochondrial dysfunctions. In addition, it has yet to be determined whether the observed alterations in brain metabolism are primary etiological factors or they just increase the vulnerability to other disease-specific factors. It is also possible that mitochondrial dysfunctions result from co-occurring lifestyle factors often observed in psychiatric patients, such as altered sleep patterns, disturbed eating as well as smoking and substance abuse.

Given the enormous importance that mitochondria have on brain metabolism and function it seems reasonable to hypothesise that challenging cognitive tasks will require a higher demand from neuronal and astrocytic mitochondria. We have depicted this in Fig. 1. Furthermore, stress burden, sleep deprivation and social challenges associated with the modern lifestyle may predispose some individuals to neuropsychiatric disorders due to their inability to cope with the increased energetic demand. This might at least partially explain the epidemic of stress-related disorders in the modern populations.

There have been already several reports of a strict link between mitochondria and brain metabolism with specific behavioural effects such as a marked effect on working memory due to ablation of mitochondrial fission (Oettinghaus et al., 2016) or general mitochondrial function (Zweig et al., 2020).

Moreover, other studies focussed on more demanding executive functions' performance, either in obesity with methyl donor supplementation (McKee et al., 2017) or due to ROS increase induced by ageing (Brawek et al., 2010; Harper et al., 2016) cast support to the hypothesis aforementioned.

Mitochondria seem to be one of the key players to act upon in both ageing and pathology. This might already be the unintended target of many nootropic substances currently under investigation increasing BDNF levels (Lauterborn et al., 2016; Mishra et al., 2021; Zhang et al., 2018).

However, a more detailed investigation to link mitochondrial function and dysfunction to specific cognitive processes is necessary. The current major limitation hampering a detailed analysis of the molecular and cellular mechanisms of cognition is given by the relatively limited physiological and behavioural tests employed. We proposed, as depicted in Fig. 1, a pipeline of tests addressing the different aspects of cognitive functions including high-energy demand sustained attention and executive functions.

Understanding the connections between mitochondria and cognitive functions could pave the way to next generation approaches targeting mitochondria to alleviate neuropsychiatric conditions, ageing and cognitive decline in general. Nevertheless, a lot has yet to be discovered and future work will be necessary to effectively translate this knowledge into the clinic.

Data Availability

No data was used for the research described in the article.

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