Schizophrenia Research xxx (2017) xxx–xxx

Contents lists available at ScienceDirect

Schizophrenia Research

journal homepage: www.elsevier.com/locate/schres

An emerging role for mitochondrial dynamics in schizophrenia

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ARTICLE INFO

Article history:
Received 30 January 2017
Received in revised form 25 April 2017
Accepted 1 May 2017
Available online xxxx

Keywords:
Mitochondria
Mitochondrial dynamics
Axonal transport
Mitochondrial fission
Mitochondrial fusion
Bioenergetics

ABSTRACT

Abnormal brain development has long been thought to contribute to the pathophysiology of schizophrenia. Impaired dendritic arborization, synaptogenesis, and long term potentiation and memory have been demonstrated in animal models of schizophrenia. In addition to aberrant nervous system development, altered brain metabolism and mitochondrial function has long been observed in schizophrenic patients. Single nucleotide polymorphisms in the mitochondrial genome as well as impaired mitochondrial function have both been associated with increased risk for developing schizophrenia. Mitochondrial function in neurons is highly dependent on fission, fusion, and transport of the organelle, collectively referred to as mitochondrial dynamics. Indeed, there is mounting evidence that mitochondrial dynamics strongly influences neuron development and synaptic transmission. While there are a few studies describing altered mitochondrial shape in schizophrenic patients, as well as in animal and *in vitro* models of schizophrenia, the precise role of mitochondrial dynamics in the pathophysiology of schizophrenia is all but unexplored. Here we discuss the influence of mitochondrial dynamics and mitochondrial function on nervous system development, and highlight recent work suggesting a link between aberrant mitochondrial dynamics and schizophrenia.

1. Introduction

Despite schizophrenia affecting ~1% of the world population we lack any concrete understanding of its etiology (Saha et al., 2005). Consequently, safe and effective therapeutic options are limited. While antipsychotic pharmaceuticals serve as the first-line of therapy for schizophrenia, they are not effective in treating the negative symptoms of schizophrenia, and improve positive symptoms in only 50% of patients (van Os and Kapur, 2009). Moreover, many schizophrenic patients helped by anti-psychotic drugs experience extrapyramidal side effects decreasing rates of compliance (Tenback et al., 2010; Barry et al., 2012). The first symptoms of schizophrenia commonly do not manifest until late adolescence or early adulthood, suggesting preventative therapies may be possible as long as biomarkers are identified. Many lines of evidence suggest the pathology of schizophrenia is related to impaired brain development and connectivity (Rajasekaran et al., 2015). Additionally, several clinical studies have linked mitochondrial dysfunction with increased risk of developing schizophrenia (Park and Park, 2012; Rajasekaran et al., 2015). Recent work also suggests aberrant mitochondrial dynamics may contribute to abnormal connectivity in the brains of schizophrenic patients (Millar et al., 2005; Devine et al., 2016; Norkett et al., 2016). While mitochondrial dynamics regulate nervous system development and are associated with numerous human neurological disorders (Flippo and Strack, 2017), whether mitochondrial dynamics plays a role in the pathology of schizophrenia remains relatively unexplored. Here we review the influence of mitochondrial dynamics on nervous system development and suggest a potential role for mitochondrial dynamics in the pathology of schizophrenia based on recent studies implicating schizophrenia risk genes in mitochondrial dynamics.

2. Mitochondrial dynamics in nervous system development

2.1. Mitochondrial transport

In compartmentalized cells like neurons, mitochondrial localization plays a crucial role in determining local energy supply. Mitochondria are highly concentrated in energy demanding compartments of neurons such as the pre-synaptic terminals and the nodes of Ranvier in axons (Bogan and Cabot, 1991; Fabricius et al., 1993; Mutsaers and Carroll, 1998; Shepherd and Harris, 1998). Interestingly, ~60% of synaptic terminals in the CA1 region of the hippocampus lack mitochondria, which poses still relatively unexplored questions about the precise role of mitochondria at the synapse (Shepherd and Harris, 1998). Regardless, mitochondrial localization throughout the cell is mostly a result of mitochondrial transport as the majority of mitochondrial biogenesis occurs in the soma of the neuron, but evidence suggests limited biogenesis can occur in axons as well (Amiri and Hollenbeck, 2008; Saxton and Hollenbeck, 2012). Mitochondria can be transported bi-directionally throughout neuronal arbors and axons along microtubule tracks until they dock at a particular cellular location.

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http://dx.doi.org/10.1016/j.schres.2017.05.003
0920-9964/

The actin and microtubule cytoskeleton can serve as anchors for mitochondrial docking in neurons with mitochondria accumulating in regions that experience frequent calcium transients (Sheng and Cai, 2012). Mitochondrial transport arrest is mediated by the outer mitochondrial membrane (OMM) localized Ca^{2+} sensitive GTPase Miro and is believed to satisfy energy demands for Ca^{2+} extrusion (Cai and Sheng, 2009). Retrograde mitochondrial transport was thought to be required for degradation of damaged mitochondria, as the cell body contains most of the degradation machinery however, recent evidence indicates that while the neuronal cell body is the major site of mitochondrial autophagy (mitophagy), mitophagy does occur in axons (Maday, 2016).

Multi-subunit complexes of adaptor and motor proteins mediate mitochondrial transport (Saxton and Hollenbeck, 2012; Schwarz, 2013). Two large families of motor proteins interact with microtubules to move cargo in opposite directions, utilizing ATP as a power source. The kinesins mediate anterograde transport, while the dyneins are responsible for retrograde transport (Hirokawa et al., 2010). Mitochondria interact with motor proteins through various adaptor proteins that dictate the direction of mitochondrial transport and ultimately localization to specific sub-cellular locales. Milton, a well characterized adaptor protein in *D. melanogaster* interacts with the kinesin heavy chain KIF5, while associating with mitochondria through an additional interaction with Miro (Stowers et al., 2002; Glater et al., 2006). TRAK2, a mammalian orthologue of Milton also interacts with KIF5 and Miro to form a functional mitochondrial transport complex (Brickley et al., 2005; Fransson et al., 2006; Smith et al., 2006; MacAskill et al., 2009).

2.2. Mitochondrial transport proteins in nervous system development

Mammalian KIF5 is encoded by three genes (*KIF5A-C*), all of which are highly expressed in the nervous system (MacAskill and Kittler, 2010). Disruption of KIF5C mediated transport in rat primary hippocampal cultures impairs mitochondrial transport and promotes formation of small punctate mitochondria (Iworima et al., 2016). Furthermore, evidence suggests KIF5C is important for human nervous system development as a *de novo* mutation was reported in a patient presenting with intellectual disability, epilepsy, and CNS malformations (Willemsen et al., 2014). Additionally, a germline mosaic mutation in KIF5C was identified in a family in which all members carrying the mutation presented with impaired cortical development and microcephaly (Poirier et al., 2013). The neuron-specific kinesin heavy chain KIF5A is also critical, since missense mutations in this gene cause autosomal dominant spastic paraplegia type 10, a disorder that can present with a variety of both central and peripheral neurological problems, including cognitive decline, peripheral neuropathy, distal upper limb amyotrophy, as well as ALS-like symptoms (Goizet et al., 2009; Fink, 2013; Jerath et al., 2015; Lopez et al., 2015; Kaji et al., 2016). Additionally, a *de novo* mutation in KIF5A was described in a patient presenting with progressive neonatal degeneration of myelin and myoclonic seizures (Rydzanicz et al., 2016). KIF5-family proteins can both homo- and heterodimerize allowing for complex regulation of organelle transport (Kanai et al., 2000). Supporting a dominant-negative mechanism in which mutant KIF5A forms inactive complexes with wild-type KIF5 proteins, expression of mutant KIF5A in zebrafish was shown to interfere with axonal transport of mitochondria while promoting axonal degeneration and aberrant synaptic transmission (Campbell et al., 2014). Additionally, impaired ETC activity and developmental delay are observed in patients harboring mutations in KIF5A (Duis et al., 2016). While KIF5A is clearly important for nervous system development and function, the extent to which impaired mitochondrial transport contributes to the etiology of disease symptoms associated with mutations in KIF5A is uncertain given its role in transporting other cellular cargo.

While no human mutations have been described in mitochondrial adaptor proteins for the transport machinery, animal and *in vitro* models provide evidence for a role of Miro and TRAK proteins in nervous system development. Global M*iro1* KO mice die from asphyxia shortly after birth, because of loss of motor neurons innervating the diaphragm (Nguyen et al., 2014). Neuron-specific deletion of *miro1* was shown to have a milder phenotype, impairing retrograde axonal mitochondrial transport, neuromuscular function, and leading to death around 40 days of age (Nguyen et al., 2014). The kinesin adaptors of the Milton family, TRAK1 and TRAK2 also play vital roles in mitochondrial transport as genetic inhibition of either impairs mitochondrial transport in primary hippocampal neuron cultures (van Spronsen et al., 2013; Loss and Stephenson, 2015). Predominant localization of TRAK1 to axons and TRAK2 to dendrites likely accounts for the finding that knockdown of TRAK1 selectively impairs axonal transport of mitochondria and axonal outgrowth, whereas TRAK2 knockdown inhibits dendritic mitochondrial transport and dendritic development (van Spronsen et al., 2013; Loss and Stephenson, 2015).

2.3. Mitochondrial fission and fusion

Mitochondria perform numerous essential functions including ATP synthesis, Ca^{2+} buffering, ROS production/sequestration, and apoptosis (Gautheron, 1984; Wang and Youle, 2009; Glancy and Balaban, 2012; Zorov et al., 2014). Regulation of these processes is partly accomplished through the opposing processes of mitochondrial fission and fusion (Kasahara and Scorrano, 2014). Nuclear encoded dynamin-related GTPases catalyze mitochondrial fission and fusion, with Mitofusins 1 and 2 (Mfn1/2) and optic atrophy 1 (Opa1) coordinating fusion of the OMM and inner mitochondrial membrane (IMM), respectively (Ishihara et al., 2013; Schrepfer and Scorrano, 2016). While precise mechanisms are unknown, Opa1 and Mfn1/2 form complexes both within and across membranes, tethering them closely akin to vesicle fusion proteins of the SNARE family. Oppositely, dynamin-related protein 1 (Drp1) is necessary for fission of the mitochondrial membranes (Otera et al., 2013). Drp1 is also important for peroxisomal fission and proliferation (Koch et al., 2003). However, this aspect of Drp1's function is far less well characterized and the effect of impaired peroxisomal fission on neuronal development is unclear. Primarily a cytosolic enzyme, Drp1 translocates to the OMM when activated (Chang and Blackstone, 2007; Cribbs and Strack, 2007; Cereghetti et al., 2008; Cribbs and Strack, 2009). Recruited by mitochondria-anchored adaptor proteins, Drp1 assembles into spirals around the mitochondrion, which constrict and ultimately divide the organelle in two (Fig. 1). Preceding Drp1 assembly, close apposition of tubular endoplasmic reticulum and localized actin polymerization are also necessary for mitochondrial fission (Friedman et al., 2011; Hatch et al., 2014; Prudent and McBride, 2016), while dynamin-2 was recently shown to catalyze the final membrane scission event (Lee et al., 2016).

2.4. Mitochondrial fusion enzymes in nervous system development and function

The importance of mitochondrial fission and fusion in nervous system development and function is evidenced by findings that mutations of the ubiquitously expressed mitochondrial fission and fusion enzymes have predominantly neurological phenotypes. Mutations in the OMM-fusion enzyme Mfn2 cause Charcot Marie Tooth Disease Type 2A (CMT2A), a severe and early onset motor and sensory peripheral neuropathy with autosomal dominant inheritance (Zuchner et al., 2004; Kijima et al., 2005). Mfn2 mutations are thought to be dominant-negative, inhibiting mitochondrial fusion by complexing with wild-type Mfn1 and Mfn2 (Cartoni and Martinou, 2009). Acting by a similar dominant-negative mechanism, hypomorphic mutations in the IMM-fusion enzyme Opa1 cause dominant optic atrophy (DOA, or Kyer's optic atrophy), the most common cause of hereditary blindness. DOA is characterized by early-onset loss of retinal ganglion cells and degeneration of the optic nerve (Lenaers et al., 2012). 20% of DOA patients present symptoms of multi-system neurological disorders, including deafness,

Please cite this article as: Flippo, K.H., Strack, S., An emerging role for mitochondrial dynamics in schizophrenia, Schizophr. Res. (2017), http://dx.doi.org/10.1016/j.schres.2017.05.003