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Postmortem studies on mitochondria in schizophrenia

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ABSTRACT

The aim of this paper is to provide a brief review of mitochondrial structure as it relates to function and then present abnormalities in mitochondria in postmortem schizophrenia with a focus on ultrastructure. Function, morphology, fusion, fission, motility, ΔΨmem, ATP production, mitochondrial derived vesicles, and mitochondria-associated ER membranes will be briefly covered. Pathology in mitochondria has long been implicated in schizophrenia, as shown by genetic, proteomic, enzymatic and anatomical abnormalities. The cortex and basal ganglia will be reviewed. In the anterior cingulate cortex, the number of mitochondria per neuronal somata in layers 5/6 in schizophrenia is decreased by 43%. There are also fewer mitochondria in terminals forming axospinous synapses. In the caudate and putamen the number of mitochondria is abnormal in both glial cells and neurons in schizophrenia subjects, the extent of which depends on treatment, response and predominant lifetime symptoms. Treatment-responsive schizophrenia subjects had about a 40% decrease in the number of mitochondria per synapse in the caudate nucleus and putamen, while treatment resistant cases had normal values. A decrease in mitochondrial density in the neuropil distinguishes paranoid from undifferentiated schizophrenia. The appearance, size and density of mitochondria were normal in the nucleus accumbens. In the substantia nigra, COX subunits were affected in rostral regions. Mitochondrial hyperplasia occurs within axon terminals that synapse onto dopamine neurons, but mitochondria in dopamine neuronal somata are similar in size and number. In schizophrenia, mitochondria are differentially affected depending on the brain region, cell type, subcellular location, treatment status, treatment response and symptoms.

1. Introduction

The aim of this paper is to provide a brief review of mitochondrial structure as it relates to function and then present abnormalities in mitochondria in schizophrenia with a focus on ultrastructure.

1.1. Normal mitochondrial function

Mitochondria are famous for producing 95% of cellular energy using the electron transport chain (Wong-Riley, 1989). In addition, they are necessary for other cellular functions including intracellular calcium buffering (Babcock and Hille, 1998; Duchen et al., 2008; Gunter et al., 1994), production of reactive oxygen species (Chang and Reynolds, 2006), regulation of apoptosis (Susin et al., 1999) and modulation of synaptic activity (Duchen et al., 2008; Li et al., 2004; Miller and Sheetz, 2004; Sheng and Cai, 2012). Mitochondria are plastic and dynamic organelles that can change shape, location, size and number in response to energy demands (Isaacs et al., 1992; Ligon and Steward, 2000; Mjaatvedt and Wong-Riley, 1988; Prince et al., 1999).

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1.2. The afterlife of mitochondria

Neuronal function in the brain requires energy in the form of ATP. To assess mitochondrial activity in human brain, investigators have previously utilized frozen postmortem brain tissue to analyze mitochondrial enzymatic activities (Devi et al., 2008), protein levels (Park et al., 2001), and DNA (Alam et al., 1997; Vila et al., 2008). However, there are several other vital indices that provide insight into brain mitochondrial activity which cannot be accomplished in frozen tissue samples. These include measurements of the mitochondrial membrane potential ($\Delta\Psi_{mem}$), ATP production, calcium buffering capacity, and respiration, which together give an overall assessment of mitochondrial health and activity. For example, the ΔΨmem, which is the electrochemical gradient across the inner mitochondrial membrane, serves as an important overall indicator of mitochondrial activity. It is also a fundamental component of respiring mitochondria. The ΔΨmem is linked to many crucial mitochondrial functions including ATP synthesis, calcium homeostasis, mitochondrial protein import, and mitochondrial metabolite transport (Hüttemann et al., 2008), all of which are typically analyzed in real-time measurements.

Although metabolic activity in the brain ceases at death, we have been able to measure the ΔΨmem and ATP production in mitochondria isolated from human postmortem brains with postmortem intervals of

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up to 8.5 h (Barksdale et al., 2010). Furthermore, postmortem brain mitochondria retain their ΔΨmem and ATP production capacities following cryopreservation, indicating that functional isolated mitochondria can be archived for future studies. The findings that ΔΨmem and ATP generation can be reinitiated in brain mitochondria hours after death indicates that postmortem brains can be an abundant source of viable mitochondria for the study of metabolic processes in health and disease, and it is also possible to archive these mitochondria for future studies (Barksdale et al., 2010).

1.3. Morphology

Mitochondria have different shapes; they can be round, elongated, blob-shaped, donut- shaped or have an elaborate configuration (Picard and McEwen, 2014). In most instances the overall shape of the mitochondrion has functional implications (Youle and van der Bliek, 2012; Ahmad et al., 2013). Take for example the relationship between the shape of mitochondria and the production of reactive oxygen species. In cell culture, mitochondrial stressors can induce the conversion of straight (i.e. rod-shaped) mitochondria to donut-shaped mitochondria, to blob-shaped mitochondria (Liu and Hajnóczky, 2011; Ahmad et al., 2013). Blob-shaped mitochondria generate the highest levels of reactive oxygen species, followed by donut shaped compared to straight mitochondria (Liu and Hajnóczky, 2011; Ahmad et al., 2013). While donut-shaped mitochondria can revert back to the straight configuration, blob-shaped mitochondria are unable to revert back to healthier configurations. In axon terminals, donut-shaped mitochondria are associated with shorter synapses and fewer docked vesicles; in the dorsolateral prefrontal cortex donut-shaped mitochondria are correlated with poor delayed response memory (Hara et al., 2014).

In addition to shape, the morphology of the cristae, matrix and inner mitochondrial membrane correspond to the activity of the electron transport chain (Hackenbrock, 1968). At the ultrastructural level, mitochondria have an orthodox or condensed configuration, which corresponds to high or low energy producing states, respectively (Hackenbrock, 1968). In the condensed configuration, the matrix is smaller and denser, the inner membrane is irregularly organized and forms few cristae, and the space between inner and outer membranes is increased. The orthodox configuration is what is usually illustrated in electron micrographs (Figs. 1 and 2).

In the aging nervous system, there are reports of fewer mitochondria, but they are larger in size (Shigenaga et al., 1994; Soghomonian et al., 2010; Martinelli et al., 2006). Perhaps enlargement of the mitochondria is a compensatory mechanism to deal with the decreased number. However, fewer bigger mitochondria are able to meet short energy demands, but sustained energy demands are not met (Shigenaga et al., 1994; Soghomonian et al., 2010; Martinelli et al., 2006). Thus, the examination of size and shape of mitochondria will reveal important information about their functionality.

1.4. Fission and fusion

Mitochondria function as a dynamic network constantly undergoing fission and fusion, the balance of which is important in maintaining their structural integrity and function (Legros et al., 2002). Proteins that cause mitochondrial fusion include mitofusin-1, mitofusion-2 and Opa1 (Koshiba et al., 2004). Although they are critical for mitochondrial fusion, they are necessary for other functions as well. For example, besides its role in mitochondrial fusion, mitofusin-2 contributes to the maintenance and operation of the mitochondrial network (Bach et al., 2003). Mitofusin 2 is also necessary for transporting mitochondria and

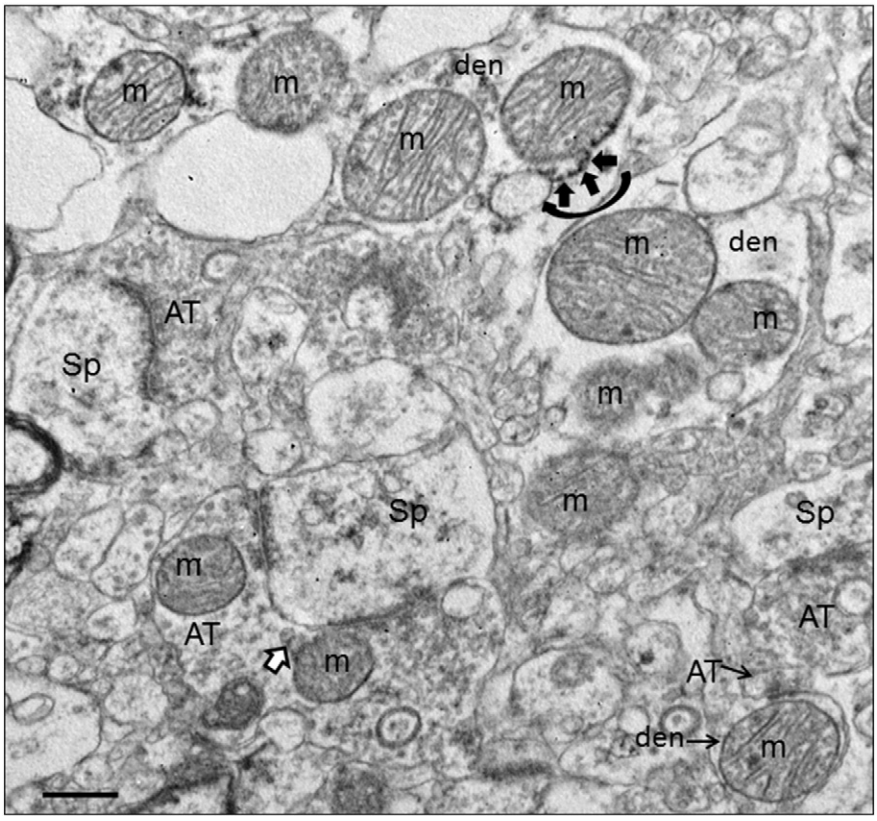

Fig. 1. Electron micrograph of human striatum. Mitochondria (m) are shown in various subcellular locations. In the dendrite (den) at the top of the field, mitochondrial associated ER (MAM) is shown (curved black arrow) with ER (short black arrows) connecting to the adjacent mitochondrion. In the terminal (AT) synapsing on a spine (Sp) in the lower part of the field, mitochondrial derived vesicles (MDVs) are shown (white arrow with black outline) budding off of a mitochondrion. Scale bars = 0.5 μm. Figure is modified from Fig. 2a in Somerville et al., 2011b.