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Mitochondrial dysfunction in schizophrenia: with a focus on postmortem studies

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Abstract

Among the many brain abnormalities in schizophrenia are those related to mitochondrial functions such as oxidative stress, energy metabolism and synaptic efficacy. The aim of this paper is to provide a brief review of mitochondrial structure and function and then to present abnormalities in mitochondria in postmortem brain in schizophrenia with a focus on anatomy. Deficits in expression of various mitochondrial genes have been found in multiple schizophrenia cohorts. Decreased activity of complexes I and IV are prominent as well as abnormal levels of individual subunits that comprise the complexes of the electron transport chain. Ultrastructural studies have shown layer, input and cell specific decreases in mitochondria. In cortex, there are fewer mitochondria in axon terminals, neuronal somata of pyramidal neurons and oligodendrocytes in both grey and white matter. In the caudate and putamen mitochondrial number is linked with symptoms and symptom severity. While there is a decrease in the number of mitochondria in astrocytes, mitochondria are smaller in oligodendrocytes. In the nucleus accumbens and substantia nigra, mitochondria are similar in density, size and structural integrity in schizophrenia compared to controls. Mitochondrial production of ATP and calcium buffering are essential in maintaining synaptic strength and abnormalities in these processes could lead to decreased metabolism and defective synaptic activity. Abnormalities in mitochondria in oligodendrocytes might contribute to myelin pathology and underlie dysconnectivity in the brain. In schizophrenia, mitochondria are affected differentially depending on the brain region, cell type in which they reside, subcellular location, treatment status, treatment response and predominant symptoms.

Keywords

psychosis; electron microscopy; neuropathology; cytochrome oxidase

The aim of this paper is to provide a brief introduction to schizophrenia, to review mitochondrial structure as it relates to function and then to present abnormalities in

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mitochondria that have been identified in postmortem brains of schizophrenia patients with a focus on anatomy and electron transport chain abnormalities.

Schizophrenia

Schizophrenia (SZ) is a biologically complex disease with several risk factors, a developmental and genetic basis, and neuropathology throughout the brain involving several transmitter systems. Briefly, SZ is a devastating mental illness that affects 1% of the world's population (DSM). In spite of decades of research the causes, prevention and effective treatments remain elusive. SZ typically manifests itself in early adulthood with hallucinations, delusions and disorganized thought and behavior. In addition, most patients suffer from cognitive impairments and a subset present enduring negative symptoms (for example poverty of thought and speech, loss of motivation and affect). Cognitive and negative symptoms usually precede the first floridly psychotic episode and have no effective treatments, with the exception of clozapine. Antipsychotic drugs (APDs) are used to treat psychotic symptoms, but are not effective in approximately one third of patients; in treatment responders there is a gradient of response (Meltzer, 1997; Sheitman and Lieberman, 1998). Pharmacological evidence indicates that the efficacy of APDs is directly related to their ability to block dopamine D_2 receptors, which are primarily located in the striatum (Creese 1976; Seeman et al., 1976). A preponderance of evidence shows that psychosis arises from an over-abundance of DA in the striatum, while cognitive and/or negative symptoms arise from an under-abundance of DA in the cortex (reviewed in Howes et al., 2012). Evidence from *in vivo* imaging, postmortem studies and animal models of schizophrenia implicate the glutamatergic system in schizophrenia as well (Coyle, 2006; Goff and Coyle, 2001; Javitt, 2004; Krystal, 2008), particularly in treatment resistant schizophrenia (Demjaha et al., 2014). The GABAergic system is impaired in schizophrenia, particularly in cortical and hippocampal interneurons (Lewis, 2014; Heckers and Konradi, 2015). Mitochondria are also affected in the illness, and mitochondrial defects will be discussed after a short introduction on normal mitochondrial function and anatomy.

Mitochondrial function

Mitochondria produce 95% of cellular ATP through oxidative phosphorylation, a process performed by complexes I through IV of the electron transport chain (ETC) (Wong-Riley, 1989; Huttemann et al., 2008). Mitochondria are also crucial for cellular functions such as calcium buffering (Gunter et al., 1994; Babcock and Hille, 1998; Duchen et al., 2008), modulation of synaptic activity (Li et al., 2004; Miller and Sheetz, 2004; Duchen et al., 2008; Sheng and Cai, 2012), regulation of apoptosis (Susin et al., 1999), and production of reactive oxygen species (Chang and Reynolds, 2006). Mitochondria are dynamic organelles that change intracellular location in response to energy demands (Ligon and Steward, 2000; O'Toole et al., 2008; Niescier et al., 2016). They are essential for normal formation of dendritic cytoarchitecture and dendritic spines (Li et al., 2004; Sheng and Cai, 2012), and are in part regulated by DISC1 for this particular function (Norkett et al., 2016). At the synaptic level, mitochondria provide the vast majority of energy for ionic homeostasis in axon terminals, synaptogenesis, synaptic transmission, synaptic vesicle recycling, and long-term potentiation (Mjaatvedt and Wong-Riley, 1988; Li et al., 2004; Change et al., 2006; Vos

et al., 2010; Sheng and Cai, 2012; Pathak et la., 2015). The production of ATP and calcium buffering are essential in maintaining synaptic strength and abnormalities in these processes could lead to decreased metabolism and defective synaptic activity (Ben-Shachar and Laifenfeld, 2004; Chang and Reynolds, 2006; Duchen et al., 2008).

Cellular function and proper energy generation requires the tricarboxylic acid (TCA) cycle, which is located in the mitochondrial matrix. The enzymes of the TCA cycle (also known as the citric acid cycle or the Krebs cycle) produce the reducing equivalents NADH and $FADH_2$, which in turn deliver electrons to complexes of electron transport chain (ETC), which drives ATP production. Optimal cellular function requires proper functioning of the ETC, which is comprised of four enzymes located within the inner mitochondrial membrane. These enzymes create a proton gradient used to power the enzyme ATP synthase (sometimes referred to as Complex V), which produces ATP. Each complex of the ETC is comprised of several subunits encoded either by nuclear or mitochondrial DNA (70 and 13 subunits, respectively). Abnormalities in a single enzyme of the electron transport chain are sufficient to cause disruption of cellular metabolism. Complexes I, II/III and IV of the electron transport chain can be measured to assess mitochondrial function (Wong-Riley, 1989). The evidence that Complex IV (cytochrome c oxidase, COX) is coupled to neuronal energy demands is derived from studies in which changes in COX activity can be induced by experimental interventions that alter neuronal activity.

Mitochondrial function declines in the aging brain (Bornstein et al., 2020), due in part to the accumulation of oxidative damage (Shigenaga et al., 1994). In the aging nervous system, there are reports of fewer mitochondria, but they are larger in size (Shigenaga et al., 1994; Martinelli et al., 2006; Soghomonian et al., 2010). Functionally, 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).

Mitochondrial structure

Mitochondria are structurally complex, dynamic organelles that fuse, divide, change shape and move around the cell (Isaacs et al., 1992; Hollenbeck, 1996; Legros et al., 2002; Hollenbeck and Saxton, 2005; MacAskill et al., 2010; Otera et al., 2010; Loson et al., 2013; Bertholet et al., 2016; Ploumi et al., 2017) (Figure 1A). Mitochondria can assume different shapes (Picard and McEwen, 2014), which in most cases have functional implications (Youle and van der Bliek, 2012; Ahmad et al., 2013) (Figure 1B). For example, round and rod shapes reflect healthy mitochondria, while blob and donut shapes indicate diseased states (Liu and Hajnóczky, 2011; Ahmad et al., 2013; Picard and McEwen, 2014; Hara et al., 2014). Moreover, there is a relationship between the shape of mitochondria and the production of reactive oxygen species. In cell culture, mitochondrial stressors can induce the sequential conversion of mitochondria from rod-shaped to donut-shaped, to blob-shaped (Liu and Hajnóczky, 2011; Ahmad et al., 2013) (Figure 1C). 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 to the straight configuration, blob-shaped mitochondria are unable to revert to healthier configurations. In axon terminals in the dorsolateral prefrontal

cortex of non-human primates, donut-shaped mitochondria are associated with shorter synapses, fewer docked vesicles and are correlated with poor delayed response memory (Hara et al., 2014). This finding could be relevant for schizophrenia pathophysiology as there is a robust decline in prefrontal cortical cognitive abilities in the illness (Goldman-Rakic, 1999).

The morphology of the cristae, matrix and inner mitochondrial membrane correspond to the activity of the electron transport chain (Hackenbrock, 1968). The orthodox configuration of mitochondria, which is typically illustrated in electron micrographs (Figure 1A), corresponds to higher energy producing states (Hackenbrock, 1968). The condensed configuration corresponds to low energy producing states. The morphological features of the condensed configuration include a small and dense matrix, an irregularly organized inner membrane with few cristae, and an enlarged space between inner and outer membranes (Figure 1D). Thus, examining the size and shape of mitochondria can reveal important information about their functionality.

Mitochondrial abnormalities in schizophrenia

Among the many brain abnormalities in schizophrenia are those related to mitochondrial functions such as oxidative stress, energy metabolism and synaptic efficacy (see reviews by Shao et al., 2008; Clay et al., 2011; Martins-de-Souza et al., 2011; Anglin et al., 2012; Manji et al., 2012; Hjelm et al., 2015; Ni and Chung, 2020). Indeed, mitochondrial pathology is a frequent finding in schizophrenia, as shown by various techniques in patients, postmortem samples, cell lines and animal models. That said there are many non-replications in the literature, which is a common plague in schizophrenia research. Part of the problem in reconciling the literature on mitochondria in schizophrenia are the differences between studies in techniques, brain areas, and patient characteristics. In addition, it is difficult to compare many findings because different things were being studied, such as different subunits of a given complex. The present review will concentrate on findings, particularly anatomical, derived from postmortem studies (Tables II–IV).

Genetics

Deficits in expression of various mitochondrial genes have been found in multiple schizophrenia cohorts (Table II). Most of the brain regions studied have been cortical regions (Mulcrone et al., 1995; Whatley et al., 1996; Middleton et al., 2002; Prabakaran et al., 2004; Iwamoto et al., 2005; Rollins et al., 2009; Nagaoka et al., 2020) or the hippocampus (Altar et al., 2005). While not all studies of the same brain region identify similar genes, it is clear that mitochondrial genes are affected in the illness. A recent review (Hjelm et al., 2015) identified 57 mitochondrial genes that were found to be dysregulated (mostly downregulated) in at least two independent studies. Reductions in expression in genes include those involved in proline metabolism (Nagaoka et al., 2020), the mitochondrial malate shuttle system, the tricarboxylic acid cycle and the electron transport chain (Middleton et al., 2002; Altar et al., 2005). Proteomics studies showed decreases in gene expression involved in energy metabolism and oxidative stress in 90% of the schizophrenia cohort examined (Prabakaran et al., 2004). Mitochondrial gene expression is affected by pH,

with more genes affected in subjects with prolonged agonal status and low pH (Iwamoto et al., 2005; Vawter et al., 2006). Therefore, pH and agonal status are important considerations when evaluating or planning studies in schizophrenia, and inconsistencies in attention to these details may account for different reports in the literature.

The mtDNA common deletion is a somatic 4,977 base pair deletion of the mitochondrial genome (Soong et al., 1992). Several findings regarding the common deletion are very well replicated in normal brains. The common deletion is found in adult but not fetal tissue suggesting that it accumulates with age. The amount of the common deletion varies greatly depending on the brain region. Levels o f the deletion are highest in dopamine containing nuclei and projection sites (Soong et al., 1992). There are several reports on the levels of the mtDNA common deletion in schizophrenia, but most of the results show no change. Sequeria et al., (2012) found an increase in the common deletion with age especially in the dopamine rich areas, such as the SN and dorsal striatum, but no change in schizophrenia. In addition, no changes were detected in the common deletion in several cortical areas, striatum, limbic system and thalamus (Sequeria et al., 2012). Others have also shown no changes in the common deletion in the frontal cortex or caudate nucleus (Cavelier et al., 1995; Kakiuchi et al., 2005; Sabunciyan et al., 2007; Fuke et al., 2008; Shao et al., 2008). In contrast, Mamdani et al., (2014) reported a decrease in the common deletion in schizophrenia with the largest abnormalities in dopaminergic regions including the ventral midbrain. The common deletion contains genes encoding subunits of cytochrome oxidase, NADH dehydrogenase and ATP synthase (Samuels et al., 2004; Verge et al., 2011). Oxidative stress mechanisms related to dopamine metabolism might be involved in the accumulation of the common deletion suggesting that mitochondrial function is impaired in dopaminergic nuclei and projection sites. While these are key areas affected in schizophrenia, if the common deletion plays a role in the pathology of schizophrenia, one would expect an increase in accumulation of the common deletion in key brain areas already in late teens and young adulthood when the disease first manifests itself. Since there is no evidence that this happens, it appears that the common deletion does not play a role in the pathogenesis of schizophrenia.

Activity of the electron transport chain

Some of the most thoroughly studied metabolic abnormalities in schizophrenia indicate disruptions in oxidative phosphorylation in various cortical regions and the basal ganglia (Table III). The results in cortex are mixed. Some have found decreased activity of complex I (Cavelier et al., 1995; Maurer et al., 2001) and a decreased protein levels in complex I subunits (Holper et al., 2019), while Andreazza et al., (2010) found no change in activity of complex I or of complexes III and IV. In addition, decreases in COX subunit II mRNA were found (Whatley et al., 1996; Clark et al 1999; Maurer et al., 2001; Andreazza et al., 2010). Several studies have shown mitochondrial abnormalities in the striatum in subjects with schizophrenia such as decreases in complex I and III and IV activity, protein and/or mRNA levels (Cavelier et al., 1995; Prince et al., 1999, 2000; Maurer et al., 2001; Ben-Shachar and Karry, 2008; Ben-Shachar, 2017). The activity of the complexes do not necessarily change in the same direction in all nuclei. For instance, there is a decrease in COX (complex IV) activity in the caudate and an increase in COX and succinate dehydrogenase (complex II) in

the putamen and nucleus accumbens in postmortem tissue from schizophrenia patients (Prince, et al., 1999). Interestingly, COX and complex II have been shown to correlate with the severity of symptoms in the putamen (Prince et al., 2000), linking symptoms with mitochondrial dysfunction. Most of the changes to complex I appear to be caused by antipsychotic drugs (APDs) (Burkhardt et. al., 1993; Maurer and Moller, 1997; Prince et al., 1997; Balijepalli et al., 1999, 2001; Karry et al., 2004; Streck et al., 2007; Rosenfeld et al., 2011), while COX appears to be less affected (Whatley et al., 1996).

In one of our previous studies, COX activity and the protein expression of key subunits for its assembly were measured in postmortem substantia nigra/ventral tegmental area (SN/VTA) (Rice et al., 2014). While overall COX activity was similar between schizophrenia patients and controls, there were decreases in the protein expression of two of the COX subunits (II and IV-I) in schizophrenia in samples containing rostral regions of the SN/VTA. These changes in the schizophrenia group probably were not caused by medication because samples containing only the middle to caudal portions of the SN/VTA were unaffected as were the SN/VTA from rats chronically treated with antipsychotic drugs (Rice et al., 2014).

Subunit IV of the COX enzyme is crucial for the proper functioning of the COX complex as a whole (Nijtmans et al., 1998; Clark et al., 1999; Rahman et al., 1999). COX subunit II is responsible for the binding of cytochrome c and the subsequent electron transfer to subunit I of the COX enzyme (Taanman, 1997). Interestingly, decreases in complex IV-II mRNA expression in the frontal cortex in schizophrenia have not resulted in significant changes in overall COX activity (Clark et al., 1999), suggesting that there might be some compensatory mechanisms involved that restores overall COX activity to normal in spite of a deficit in COX-II. However, suppression of subunit IV has been linked to a reduced function in overall COX activity and an increased susceptibility to apoptosis (Huttemann et al., 2001; Li et al., 2006). Thus, deficits in COX-IV subunit protein expression may lead to a faulty assembly of the COX enzyme and a greater vulnerability to metabolic insult in a region specific manner in the SN/VTA.

Tricarboxylic acid cycle

A thorough discussion of all of the intricacies of the TCA cycle as it related to schizophrenia is outside of the scope of this review. Briefly, two recent meta-analyses of postmortem and imaging studies strongly suggest that schizophrenia is associated with increased lactate and decreased pH in the brain (Hagihara et al., 2018; Pruett and Meador-Woodruff, 2020). Pruett and Meador-Woodruff (2020) discuss that the consequence of this could lead to a shift away from the TCA cycle and oxidative phosphorylation toward increased glycolysis for energy production. Pyruvate dehydrogenase (PDH), the enzyme that converts pyruvate to acetyl-CoA in order for it to enter the TCA cycle, is downregulated in the brain of schizophrenia patients (Dean et al., 2016; Prabakaran et al., 2004), supporting this hypothesis. Functionally, this indicates decreased energy production, increased lactate, and decreased pH, which is linked to cognitive and emotional impairments (Rae et al., 1996; Shioiri et al., 1997; Rowland et al., 2016).

Anatomy

Interestingly, much of the anatomical studies on mitochondria in schizophrenia have been performed at the electron microscopic level by my laboratory and Uranova's group (Table IV). This is striking because ultrastructural studies, especially quantitative ultrastructural studies with or without combined immunohistochemistry, are rare in postmortem schizophrenia research due to practical issues such as needing brains with very short postmortem intervals. We have both published extensively on ultrastructural differences in multiple brain regions and for the most part our results are compatible when we have studied the same cell type or brain region.

Intracellular Abnormalities:

Mitochondria have structural appendages called mitochondria derived vesicles (MDVs) and mitochondria-associated endoplasmic reticulum membranes (MAMs) (Hayashi et al., 2009). MDVs are structures that bud off mitochondria and transport damaged cargo to peroxisomes or lysosomes (Neuspiel et al., 2080) (Figure 1A). MDVs are stimulated by various forms of stress, and the vesicles incorporate cargo, whose composition depends upon the type of stress (Soubannier et al., 2012). MDVs have not been studied in schizophrenia but could be a fertile field of study considering their function.

Mitochondria are connected to the endoplasmic reticulum via MAMs (Hayashi et al., 2009) (Figure 1A). MAMs are enriched in cholesterol, anionic phospholipids, (Hayashi and Fujimoto, 2010) and proteins related to the control of mitochondrial division (Friedman et al., 2011) and dynamics (Schon and Area-Gomez, 2013). MAMs are involved in a number of key metabolic functions, including phospholipid and cholesterol metabolism (Hayashi et al., 2009). Mitofusin 2 tethers mitochondria to the endoplasmic reticulum (de Brito and Scorrano, 2008). Mitochondria move within neurons along microtubules via kinesin and adaptors for anterograde transport and via dynein and adaptors for retrograde transport; they also can be anchored via actin and neurofilaments (reviewed by Lin and Sheng, 2015).

Disrupted in Schizophrenia 1 (DISC1) is a scaffold protein that is involved in intracellular functions and abnormalities in DISC1 are linked to cognitive and emotional deficits in schizophrenia (see review by Roberts, 2007 and references therein). DISC1 is predominantly localized to mitochondria (James et al., 2004) and in particular to MAMs (Park et al., 2017). At the MAM, DISC1 modulates the transfer of calcium from endoplasmic reticulum to the mitochondria. Disrupted DISC1 causes increased calcium transfer leading to increased calcium accumulation in mitochondria following oxidative stress, which impairs mitochondrial functions. (Park et al., 2017).

Cortex:

The anterior cingulate cortex, a structurally and functionally diverse region, is one of several brain regions that is abnormal in schizophrenia (Fornito et al., 2009). Mitofusion-2 is a mitochondrial fusion protein (Koshiba et al., 2004) that is also necessary for the maintenance and operation of the mitochondrial network (Bach et al., 2003) and transporting mitochondria to their proper location in axons and dendrites (Misko et al., 2010; Sheng and

Cai, 2012). Protein levels of mitofusin-2 were normal in schizophrenia cases; moreover, there were no effects of antipsychotic treatment or treatment response (Barksdale et al., 2014). Normal protein levels suggest that mitochondrial fusion, maintenance and operation of the mitochondrial network may be intact. However, while protein levels of mitofusin 2 are unaffected, there are many other mitochondrial proteins involved in these functions that might be abnormal.

In an ultrastructural study, the numbers of mitochondria per neuronal somata and per axon terminal were decreased in a layer and input specific manner (Aganova and Uranova, 1992; Roberts et al., 2015). Excitatory synapses in superficial layers, likely arising from the medial dorsal thalamus and contralateral cortex (see Hoftman et al., 2016), had fewer mitochondria per axon terminal (Aganova and Uranova, 1992; Roberts et al., 2015). Synapses characteristically made by inhibitory interneurons and/or dopaminergic inputs (Kubota et al., 2016) had fewer mitochondria per axon terminal in deep layers (Roberts et al., 2015). Fewer mitochondria in axon terminals suggest a decrease in efficacy of synaptic transmission (Brodin et al., 1999; Verstreken et al., 2005; Hall et al., 2012), and in the case of the anterior cingulate cortex this abnormality affects both excitatory and inhibitory connections. Pyramidal neurons in the deep layers, which project to the striatum, brainstem, or thalamus (Goldman and Nauta, 1977), had fewer mitochondria per soma, suggesting compromised metabolism in one or more of those pathways (Roberts et al., 2015). There were no structural differences and no obvious blob or donut shaped mitochondria. This is somewhat surprising considering the observed increase in reactive oxygen species in schizophrenia (Wang et al., 2009; Madireddy and Madireddy, 2020) that are produced at a higher rates in mitochondria with those shapes (Liu and Hajnóczky, 2011; Ahmad et al., 2013). However, it is possible that upstream biochemical pathways, such as the pentose phosphate shuttle, may be responsible for the increase in reactive oxygen species (Koo et al., 2018). The layer specific location of the mitochondrial abnormalities suggests multiple connections are affected that might impact the cortex as well as several downstream pathways. Madireddy

Fewer mitochondria may be a primary deficit of the disease, or mitochondria may die as an epiphenomenon of the disease. Alternatively, mitochondria may be sequestered in neuronal somata located either extrinsic to the region studied. An inability of mitochondria to move into axon terminals or dendrites could account for a decreased number of mitochondria in these structures. Since mitochondria move around the neuron along microtubules between the soma and processes, damage to cytoskeletal elements might lead to a failure of proper mitochondrial movement. In the cingulum bundle, but not the arcuate fasciculus or the corpus callosum, we found abnormally high protein levels of αlpha-tubulin, a component of microtubules, in off drug schizophrenia, which was normalized by APD treatment (Schoonover et al., 2018). Moreover, in the schizophrenia cohort correlations between alpha-tubulin and other markers of white matter integrity (neurofilament heavy, myelin basic protein, and the autophagosome marker LC3) were opposite to controls in the cingulum bundle. These data suggest there is a dysregulation of the relationship between α-tubulin and the other markers of white matter integrity in the cingulum bundle in schizophrenia. Taken together, cytoskeletal abnormalities that could lead to faulty transport of mitochondria in a regionally specific manner.

Striatum:

Previous ultrastructural studies of striatal neuropil in schizophrenia have shown similar numbers (Somerville et al., 2011a) and size (Kung and Roberts, 1999) of mitochondria. However, decreases in the number of mitochondria per synapse were detected in both the caudate and putamen in schizophrenia. Since the majority of mitochondria are in dendrites, fewer mitochondria in axon terminals might have been overlooked in overall neuropil counts. Further analysis showed that subjects divided by treatment status into off drug, atypical APD or typical APD, all showed significant decreases in the putamen compared to controls (Somerville et al., 2011a). Since the patients on APD had similar decreases in mitochondrial number compared to the off-drug subjects, this result may not be an APD effect. Moreover, it seems unlikely that APDs would affect the putamen but not the caudate. However, haloperidol, a typical APD, does reduce the number of mitochondria in striatal neuropil of chronically treated rats (Roberts et al., 1995).

Mitochondrial pathology is linked with symptoms and symptom severity.— Symptoms of schizophrenia can vary markedly between patients, and similar symptoms may be related to shared pathophysiology. For example, a relationship between symptoms and mitochondrial pathology is evident in blood. Lymphocytes analyzed from paranoid schizophrenia patients showed less mitochondrial volume than in controls (Uranova et al., 2007). Moreover, the severity of the mitochondrial deficit was positively correlated with symptom severity, linking the severity of paranoid symptoms with mitochondrial impairment, albeit in blood (Uranova et al., 2007). Also, lower levels of COX and complex II activity correlate with increased severity of emotional and cognitive impairment in the putamen, but not other basal ganglia regions (Prince et al., 2000), again linking symptoms with mitochondrial dysfunction in a region specific way.

In an ultrastructural study of the striatum, decreases in the density of mitochondria were observed in the neuropil in chronic paranoid subjects compared to both controls and the chronic undifferentiated group (Somerville et al., 2012). In addition, the number of mitochondria in axon terminals in the putamen was decreased selectively in chronic paranoid subjects compared to controls and chronic undifferentiated patients. The number of mitochondria per synapse showed similar decreases compared to controls in both subgroups in the putamen, and a similar albeit insignificant pattern in the caudate. These deficits were found only in the matrix compartment, and not in the striosomes; cognition and memory are processed through the matrix, while limbic information is processed through the patches (Graybiel and Ragsdale, 1978; Flaherty and Graybiel, 1993; Eblen and Graybiel, 1995; Goldman-Rakic, 1999). Thus, it could be expected that decreased numbers of mitochondria in the striatal matrix in schizophrenia could impact cognitive skills.

Given the period of sample collection, the schizophrenia subjects in that study were diagnosed in accordance with the DSM-III and DSM-IV criteria, which define prominent symptomology at the time of death (Deep-Soboslay et al., 2005). In contrast, the DSM-V recognizes that predominant symptoms may fluctuate over the course of the illness, and that the diagnosis initially given may not reflect symptomology at the time of death. Importantly, in this study, all paranoid schizophrenia subjects were given a lifetime diagnosis of chronic

paranoid schizophrenia with no history of formal thought disorder. Taken together, fewer mitochondria than normal in blood and the striatum could be associated with the symptoms of paranoia and/or could represent a protective mechanism against some of the symptoms that are less pronounced in this subtype than in the undifferentiated subgroup, such as formal though disorder.

One third of patients with schizophrenia do not respond to medication and remain psychotic (Meltzer, 1997). The patients that do respond, do so on a continuum, but only respond to positive symptoms. Cognitive and negative symptoms are poorly treated in all people with schizophrenia. Although treatment response and resistance have a biological basis (Sheitman and Lieberman, 1998), all studies conducted outside of our own work have been imaging live people. In a cohort of subjects rated for treatment response or resistance, treatment-responsive schizophrenia subjects had a large decrease in the number of mitochondria per synapse in the caudate nucleus and putamen compared to controls. In the putamen, treatment-responsive subjects also had decreases in this measure compared to treatment-resistant subjects (Somerville et al., 2011b). These results provide further support for a biological distinction between treatment response and treatment resistance in schizophrenia. Because treatment-resistant subjects had normal levels of mitochondria per synapse, but treatment responders had fewer mitochondria per synapse than controls, fewer mitochondria per synapse may be related to treatment response.

Fewer mitochondria per synapse were observed in a combined cohort of subjects and does not appear to be caused by APDs. This change was confined to treatment responders, and was not observed in treatment resistant subjects. A decrease in mitochondrial density in the neuropil distinguishes the paranoid from the undifferentiated schizophrenia subgroup. Fewer mitochondria may contribute to the pathophysiology of the illness, may be a medication effect, or an adaptive response to normalize overactive neurotransmission that may occur from the higher than normal number of excitatory striatal synapses previously found (Roberts et al., 2005a,b, 2008, 2012).

Nucleus Accumbens:

Given the report of increased COX and succinate dehydrogenase activity in the nucleus accumbens in schizophrenia compared to controls (Prince, et al., 1999), the observation that the structural integrity and general appearance of mitochondria were normal in the schizophrenia group in this same structure was surprising (McCollum et al., 2015). Moreover, the density of mitochondria in the neuropil, the average diameter, and the number of calcium deposits per mitochondrion were similar between controls and schizophrenia in both the core and shell. Taken together, alterations in mitochondrial function may not be detected with morphology.

Substantia Nigra:

In spite of the fact that the substantia nigra (SN) and ventral tegmental area (VTA) house the largest proportion of dopamine neurons in the brain and that antipsychotic medication works by blocking dopamine receptors (Creese et al., 1976), there have been very few studies of the SN/VTA in schizophrenia. At the ultrastructural level, mitochondrial hyperplasia has

been observed within axon terminals that synapse onto dopamine neurons in a qualitative study of a small cohort of schizophrenia subjects (Kolomeets and Uranova, 1999); however, there were no comments on the number of mitochondria per terminal. In one of our recent studies, we quantified the number of mitochondria per terminal and found no difference in the number of mitochondria in all terminals or in subsets of excitatory or inhibitory terminals (Mabry et al., 2019); qualitatively, we did not observe any differences in the size of the mitochondria, so we did not measure them. Moreover, we found that mitochondria in dopamine neuronal somata were similar in size, density and structural integrity between schizophrenia patients and controls (Walker et al., 2018). From a structural standpoint, mitochondria do not appear to be affected in the substantia nigra in schizophrenia.

Medication effects:

The effects of antipsychotic drugs (APDs) on mitochondrial function is a vast topic beyond the scope of this review. However, an excellent recent review (Chan et al., 2020) addresses this complex issue. The authors conclude a complicated relationship between APDs and mitochondrial function with several scenarios: 1) mitochondrial damage precedes the onset of schizophrenia, 2) can be reversed by APDs, but 3) can also be caused by APD treatment. The general consensus is that antipsychotic drugs can alter mitochondrial function, number and size (for reviews see Carboni and Domenici, 2016; Roberts 2017; Chan et al., 2020). Antipsychotic drugs have differential effects on mitochondrial structure and function depending on brain location, type of antipsychotic drug, length of use, length of withdrawal period, dose and route of administration (for some examples see Takeichi and Sato, 1987; Uranova et al., 1991; Roberts et al., 1995; Prince et al., 1999; Streck et al., 2007). For instance, there are more striatal mitochondria after 3 weeks of haloperidol treatment (Uranova et al., 1991), but less after 6 months (Roberts et al., 1995). The majority of evidence is in agreement that complex I and succinate dehydrogenase appear to be adversely affected by antipsychotic drugs, however COX may not be as vulnerable (Burkhardt, et al., 1993; Balijepalli et al., 1999, 2001; Karry et al., 2004; Rosenfeld et al., 2011; Maurer and Moller, 1997; Prince et al., 1997; Streck et al., 2007).

Mitochondrial abnormalities in glial cells:

Mitochondrial abnormalities have been observed in glial cells in various brain regions. In the cortex, Uranova and colleagues have found fewer and smaller mitochondria in oligodendrocytes in both gray and white matter (Uranova et al., 2007; Vikhreva et al., 2016), suggesting that oligodendrocytes have less available energy, which may have an impact on proper myelination. In recent studies, Uranova and colleagues found a decrease in the number and size of mitochondria in oligodendrocytes adjacent to microglia in both grey (Uranova et al., 2020) and white matter (Uranova et al., 2018) in the prefrontal cortex. They concluded that oligodendrocyte dystrophy is not associated with microglial activation in white matter, but that microglial dystrophy might contribute to oligodendrocyte dystrophy in grey matter.

In the caudate nucleus, there are fewer mitochondria in astrocytes (Uranova et. al. 1996), and mitochondria are smaller in oligodendrocytes (Uranova et al., 2001). Either of these results could compromise the function of these cell types as discussed above.

Conclusions:

In the brains of subjects with schizophrenia, mitochondria are differentially affected depending on the brain region, cell type, and subcellular location in which they are located. Moreover, mitochondrial abnormalities differ depending on treatment status, treatment response and symptoms. While certain morphological configurations definitely correspond to energy capacity and other functions, it appears that mitochondria can appear intact, while being functionally compromised. Decreases in functional measures may be reflected by decreased number of mitochondria rather than decreased size or structural configuration.

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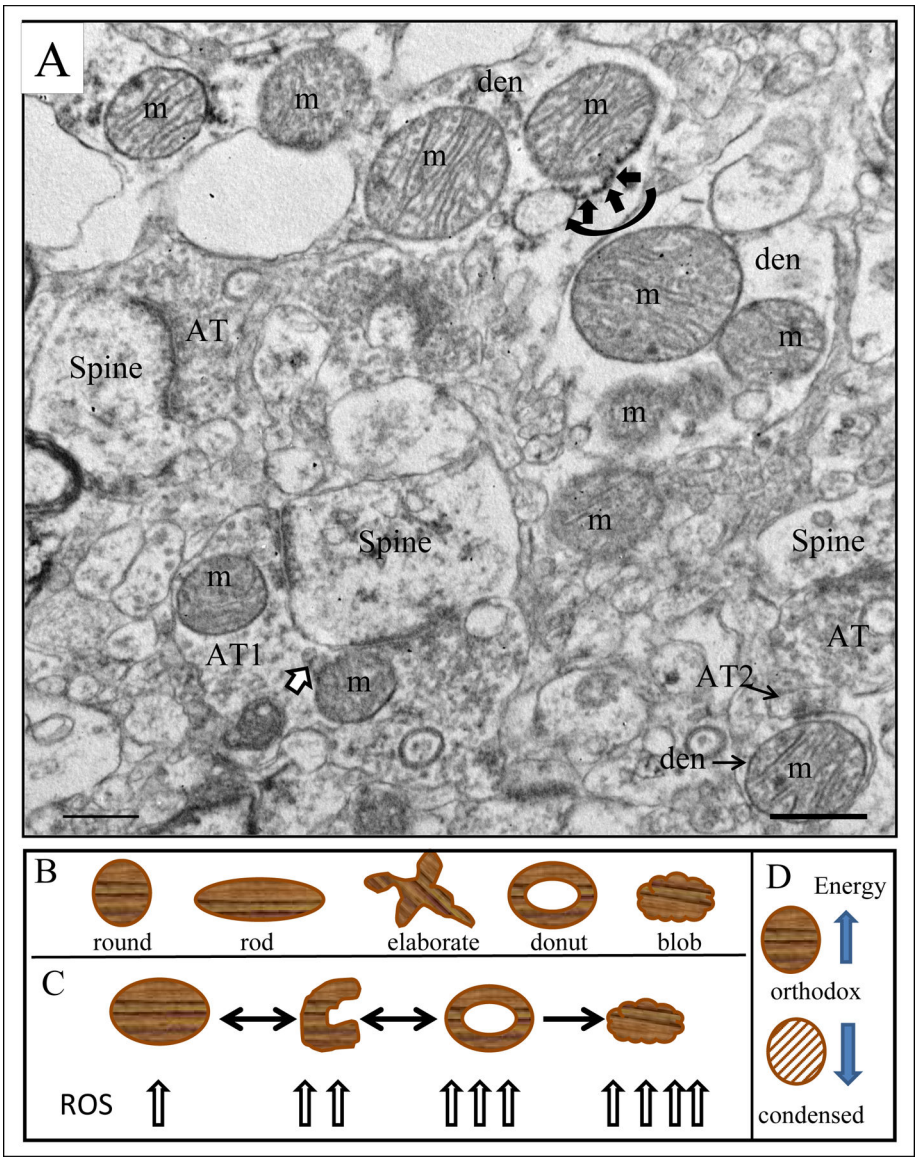

Figure 1.

A) Electron micrograph of human striatum. Mitochondria (m) are indicated in various subcellular locations. In the dendrite (den) at the top of the field, a mitochondrial associated ER (MAM) is shown (curved black arrow) with ER (short black arrows) connecting to the adjacent mitochondrion. Axon terminal (AT1) forms an excitatory synapse on a spine in the lower part of the field; mitochondrial derived vesicles (MDVs) are shown (white arrow with black outline) budding off of a mitochondrion in the terminal. Axon terminal AT2 forms an inhibitory synapse on the dendrite (den). Scale bar = 0.5 μm. Figure is modified from Figure 2a in Somerville et al., 2011b and Figure 1 in Roberts, 2017). B) Drawings of different shaped mitochondria. C) Transformation of a mitochondrion from round/rod to curved to donut to blob shape and the corresponding amount of reactive oxygen species each produces. Arrows are bidirectional between round and curved and donut shaped mitochondria indicating the ability to change shape in either direction. Once a

mitochondrion has assumed a blob shape, it cannot recover healthier configurations, thus the unidirectional arrow. D) Depiction of the orthodox and condensed form of mitochondria. Orthodox configuration is high energy producing, while condensed configuration is low energy producing, indicated by the directionality of the arrows.

Table I.

List of abbreviations

Abbreviations and aliases	
ALDH4A1	aldehyde dehydrogenase 4 family, member A1
APD	antipsychotic drugs
ATP	adenosine triphosphate
Complex I	NADH-CoQ oxidoreductase
Complex II	succinate dehydrogenase
Complex III	cytochrome bc complex
Complex IV	cytochrome c oxidase (COX)
Complex V	ATP synthase
DLPFC	dorsal lateral prefrontal cortex
DOI	duration of illness
ETC	electron transport chain
mtDNA	mitochondrial DNA
NAcc	nucleus accumbens
NADH	nicotinamide adenine dinucleotide
NDUFS7	a subunit of complex I
OFC	olfactory cortex
OxPhos	oxidative phosphorylation
PFC	prefrontal cortex
ROS	reactive oxygen species
SN	substantia nigra
TCA cycle	tricarboxylic acid cycle
VTA	ventral tegmental area

Table II:

Genetics

finding	Brain area	comments	reference
↓ in four mitochondrial rRNA three encode parts of the 16s rRNA	PFC		Mulcrone, et al., 1995 Whatley, et al., 1996
↓ in malate shuttle & TCA genes	PFC		Middleton et al., 2002
↓ mitochondrial genes related to energy metabolism and oxidative stress	DLPFC	↓ transcript levels of pyruvate dehydrogenase APD effects ruled out	Prabakaran et al., 2004
Δ expression of 11% of mitochondria-related genes 82% of those were ↓	DLPFC	Findings held up when controlled for pH, might be APD effect	Iwamoto et al., 2005
synonymous base pair substitutions in the coding regions of the mtDNA genome was 22% higher in SZ	DLPFC	pH sensitive, PMI independent	Rollins et al, 2009
Genetic polymorphisms in molecules associated with proline metabolism	BA10 & superior temporal gyrus	Genetic data showing abnormal metabolism of proline.	Nagaoka et al., 2020
↓ in mitochondrial genes mitochondrial oxidative energy metabolism (isocitrate, lactate, malate, NADH, complexes II, IV, ATP synthase)	Hippocampus, laser captured granule cells	Data derived from multiple cohorts	Altar et al., 2005
Review cites 57 mitochondrial genes changed in SZ in at least 2 studies		data support that SZ has many dysregulated mitochondrial genes	Hjelm et al., 2015
↓ in mitochondrial genes with QPCR confirmation	DLPFC	Layer 3 pyramidal neurons, controlled for APD effects	Arion et al., 2015
No Δ mtDNA common deletion	Frontal cortex		Cavelier et al.,, 1995; Kakiuchi et al., 2005; Sabunciyan et al., 2007; Fuke et al., 2008; Shao et al.,2008
No Δ mtDNA common deletion in schizophrenia ↑mtDNA common deletion with age, not diagnosis mtDNA common deletion very variable across brain areas	DLPFC ACC, OFC, amygdala hippocampus caudate, NAcc putamen, SN, thalamus, cerebellum	↑mtDNA common deletion in striatum, NAcc and amygdala with age ↑mtDNA common deletion SN> putamen, NAcc & Caudate vs other brain areas	Sequeria et al., 2012
↓ brain mtDNA common deletion in DA rich areas when corrected for age, sex, PMI and pH	DLPFC, ACC, OFC, amygdala hippocampus caudate, NAcc putamen, SN, thalamus	Common deletion has genes encoding sub-units of COX, NADH-d and ATP synthase, affecting mitochondrial function in DA areas.	Mamdani et al., 2014

The table is organized by the brain area from cortex to subcortical regions. Abbreviations are in Table I.

Table III:

Mitochondrial enzymes and proteins

finding	Brain area	comments	reference
↓ COX subunit II mRNA expression but no Δ in COX activity	Frontal cortex	This can happen without any changes in COX activity.	Whatley et al., 1996; Clark et al., 1999
↓ complex IV activity	frontal & temporal cortex, basal ganglia	Deficit in OxPhos in cortex may contribute to deficits in energy generation	Maurer et al., 2001
↓ complex I, III activity	temporal cortex, basal ganglia		
No Δ in levels of NDUFS7, a subunit of complex I, & complex I activity	prefrontal cortex	Complex I in PFC is unaffected	Andreazza et al., 2010
Δ in enzymes of TCA cycle	DLPFC	Abnormalities in energy metabolism could contribute to brain pathology in SZ.	Bubber et al., 2011
↑ ALDH4A1 detected with IHC Genetic polymorphisms in molecules associated with proline metabolism. ALDH4A1 is step in the metabolism of proline to glutamate, which occurs in mitochondria.	frontal cortex (BA10) & superior temporal gyrus	Genetic and anatomical data shows abnormal metabolism of proline, which may affect glutamate neurotransmission.	Nagaoka et al., 2020
↑ levels of a marker of oxidative stress	anterior cingulate cortex	Oxidative damage may contribute in part to brain pathology in SZ.	Wang et al., 2009
No Δ in protein levels of mitofusin2	anterior cingulate cortex	No difference in SZ, no effect of treatment, or treatment response.	Barksdale et al., 2014
↓ in mitochodrial proteins in synaptosomes	Primary auditory cortex		MacDonald et al., 2019
↓ COX activity	frontal cortex caudate,	Could lead to abnormalities in energy metabolism	Cavelier et al., 1995
Meta analysis: variable Δ in complex I subunits; ↓ COX activity in cortex, but ↑ in striatum	frontal cortex, striatum		Holper et al., 2019
↓ protein levels of pyruvate dehydrogenase	frontal cortex	shift away from the TCA cycle toward glycolysis	Prabakaran et al., 2004
↓ β subunit of pyruvate dehydrogenase; ↑ pyruvate, glucose, lactate	striatum	Impaired glucose metabolism; shift away from the TCA cycle toward glycolysis	Dean et al., 2016
↓ COX activity	caudate	↓ COX activity can lead to ↑ susceptibility to apoptosis	Prince et al., 1999
↑ COX complex II activity	putamen	Negative correlation with the severity of symptoms	Prince et al, 1999
↓ protein levels of ARF1, a mitochondrial protein, in synaptosomes	ventromedial caudate	↓ ARF1 especially in glutamatergic synapses may compromise excitatory synaptic function	Ramos-Miguel et al., 2019
No Δ in COX activity ↓protein levels of COX subunits II and IV-I	rostral substantia nigra ventral tegmental area	Faulty assembly of COX enzyme could lead to greater vulnerability to metabolic insult.	Rice et al., 2014
No Δ in complex I, III or IV	cerebellum	Cerebellum is not affected.	Maurer et al., 2001

The table is organized by the brain area from cortex to subcortical regions. Abbreviations are in Table I.

Table IV:

Mitochondrial number, structure, and localization

finding	brain area	comments	reference
↓ # mitochondria in axon terminals	ACC	↓ synaptic efficacy	Aganova & Uranova 1992
Layer III: ↓#mitochondria at excitatory synapses Layer V/VI: ↓#mitochondria at inhibitory synapses and in soma. Structure & size normal.	ACC	↓ synaptic efficacy of thalamic inputs ↓ synaptic efficacy of DA input and/or interneuron connections ↓ energy capacity in projection neurons	Roberts et al., 2015
↓ # and size of mitochondria in oligodendrocytes	Prefrontal cortex	Abnormalities in oligodendrocyte energy might disturb myelin, axonal integrity and thus circuitry.	Uranova et al., 2007
↓ # and size of mitochondria in oligodendrocytes	Frontal cortex white matter		Vikhreva et al., 2016
↓ # and size of mitochondria in oligodendrocytes adjacent to microglia	Frontal cortex white matter	oligodendrocyte dystrophy is not associated with microglial activation	Uranova et al., 2018
↓ # and size of mitochondria in oligodendrocytes adjacent to microglia	Frontal cortex grey matter	Microglial dystrophy might contribute to oligodendrocyte dystrophy in SZ during relapse of positive symptoms	Uranova et al., 2020
↓ # and area of mitochondria in astrocytes in SZ with DOI >20 years vs NCs and SZ with DOI<20yrs	hippocampus	Decreased energy of astrocytes with DOI	Kolomeets et al., 2010
↓ # mitochondria in astrocytes	caudate	Decreased energy available in astrocytes	Uranova et al., 1996
↓ size mitochondria in oligodendrocytes	caudate	Compromised function in oligodendrocytes	Uranova et al., 2001
No Δ in mitochondrial size in the neuropil	caudate putamen	No obvious morphological abnormalities	Kung & Roberts 1999
↓ # mitochondria in neuropil	caudate putamen	Treatment responders and paranoid SZ may be able to decrease number of mitochondria and thus lower energy capabilities in the hyperactive glutamate system. This could translate into better outcomes than in treatment resistant or CUT SZ.	Somerville et al., 2012a
↓ # mitochondria in axon terminals in treatment responders, but not treatment resistant SZ	caudate putamen		Somerville et al., 2011
↓ # mitochondria in axon terminals in chronic paranoid SZ, but not chronic undifferentiated SZ	putamen		Somerville et al., 2012b
mitochondria appearance, density, and size are normal in dopaminergic axon terminals	nucleus accumbens	Normal number and morphology of mitochondria in dopaminergic inputs to the nucleus accumbens.	McCollum et al., 2015
Hyperplasia of mitochondria in axon terminals synapsing onto dopamine neurons	substantia nigra	Unmet energy requirements in terminals synapsing onto dopamine neurons	Kolomeets et al., 1999
= density, size & structure of mitochondria in dopamine neurons	substantia nigra	Normal number and morphology of mitochondria in dopaminergic neurons and in axon terminals in the substantia nigra	Walker et al., 2018
= density, size & structure of mitochondria in axon terminals	substantia nigra		Mabry et al., 2019

The table is organized by the brain area from cortex to subcortical regions. Abbreviations are in Table I.