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Authors

Chan, Shawna T
McCarthy, Michael J
Vawter, Marquis P

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Psychiatric drugs impact mitochondrial function in brain and other tissues

Shawna Chan[a,b], **Michael McCarthy**[c], **Marquis P. Vawter**[a,*]

[a]Functional Genomics Laboratory, Department of Human Behavior and Psychiatry, University of California, Irvine, United States of America

[b]School of Medicine University of California, Irvine, United States of America

[c]Psychiatry Service VA San Diego Healthcare System, Department of Psychiatry, University of California, San Diego, United States of America

Abstract

Mitochondria have been linked to the etiology of schizophrenia (SZ). However, studies of mitochondria in SZ might be confounded by the effects of pharmacological treatment with antipsychotic drugs (APDs) and other common medications. This review summarizes findings on relevant mitochondria mechanisms underlying SZ, and the potential impact of psychoactive drugs including primarily APDs, but also antidepressants and anxiolytics. The summarized data suggest that APDs impair mitochondria function by decreasing Complex I activity and ATP production and dissipation of the mitochondria membrane potential. At the same time, in the brains of patients with SZ, antipsychotic drug treatment normalizes gene expression modules enriched in mitochondrial genes that are decreased in SZ. This indicates that APDs may have both positive and negative effects on mitochondria. The available evidence suggests three conclusions i) alterations in mitochondria functions in SZ exist prior to APD treatment, ii) mitochondria alterations in SZ can be reversed by APD treatment, and iii) APDs directly cause impairment of mitochondria function. Overall, the mechanisms of action of psychiatric drugs on mitochondria are both direct and indirect; we conclude the effects of APDs on mitochondria may contribute to both their therapeutic and metabolic side effects. These studies support the hypothesis that neuronal mitochondria are an etiological factor in SZ. Moreover, APDs and other drugs must be considered in the evaluation of this pathophysiological role of mitochondria in SZ. Considering these effects, pharmacological actions on mitochondria may be a worthwhile target for further APD development.

[*]**Corresponding author:** Marquis P. Vawter, mvawter@uci.edu, Gillespie Neuroscience Research Facility, 829 Health Sciences Road, Irvine, CA 92697, Phone: 949-824-9014, Fax: 949-824-7012.

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1. Introduction

Schizophrenia (SZ) is a devastating psychiatric disorder characterized by recurrent psychosis leading to significantly impaired social and cognitive functioning. To date, there is no optimal treatment for patients with SZ, and the World Health Organization found that only about half of treated patients achieve favorable outcomes in terms of symptomology, employment, and Global Assessment of Functioning scores (Harrison et al. 2001). The pathogenesis of the disorder remains poorly understood, and the management of SZ is further complicated by the heterogeneous presentation and course of the illness. Antipsychotic drugs (APDs) are the first-line treatment for SZ, and because of psychiatric comorbidities including substance abuse, depression, and anxiety, polypharmacy is extremely common with psychotropic medications that have potentially harmful side effects and interactions. Suboptimal treatment of patients with SZ is often associated with medication discontinuation, and undesirable side effects lead to decreased treatment compliance. Together, these factors indicate that the current drugs and their targets do not lead to long periods of remission.

It has been proposed that in a subset of SZ patients there may be underlying mitochondria dysfunction. Whether this dysfunction is due to APD treatment or is part of the underlying pathophysiology of SZ has not been resolved. In seeking answers to this question of the role of mitochondria in etiology, APD treatment, and metabolic comorbidity of SZ, we review relevant literature in these areas.

1.1 Essential Biology of Mitochondria

In this section, the basic functions of mitochondria in cellular pathways are described (Figure 1).

The primary role of mitochondria is to provide energetic support to cells through the biosynthesis of ATP molecules through the Krebs cycle (2 ATP) and the electron transport chain (32 ATP), netting about 34 ATP molecules from each molecule of glucose (Lehninger, Nelson, and Cox 2013)’(Mitchell and Moyle 1965). In addition, mitochondria regulate apoptosis, calcium uptake, redox balance, and reactive oxygen species (ROS) production.

Mitochondria have a general role in cellular metabolism and signaling pathways, e.g. mitochondria are involved in basic metabolism of 17 amino acids (Guda, Guda, and Subramaniam 2007). Among the amino acids is glutamate which is interconverted into GABA in the mitochondria. The well-known neurotransmitter metabolic enzyme family (monoamine oxidases) is anchored to the mitochondria outer membrane and serves as a site for the oxidation of various neurotransmitters (serotonin, norepinephrine, epinephrine, and dopamine).

Mitochondria generate ROS as a byproduct of oxidative phosphorylation by transferring one electron to molecular oxygen O_2 to form a superoxide anion ($O_2^{\bullet-}$) (Murphy 2009). In this context, ROS functions as important signaling and regulatory molecule, and can also lead to toxic injury, cell death, and neurodegeneration when ROS levels become dysregulated (Angelova and Abramov 2018). ROS elevation occurs mainly in mitochondria via electron leakage and transfer of the electron to molecular oxygen transforming oxygen into a highly reactive free radical. Antioxidant scavenger proteins such as a mitochondria isoform of superoxide dismutase can accept electrons from ROS and shuttle those electrons to hydrogen peroxide (Murphy 2009). Chronic elevation of ROS can be caused by incremental damage to the mitochondria matrix. Initially, low production of ROS damages the mitochondria gradually causes further oxidative damage that ultimately exceeds the mitochondria's ability to transfer electrons from all of the surplus of ROS molecules generated. This overall chronic oxidative stress resulting from elevated ROS can be one of the causes of mitochondria dysfunction along a spiraling pathway. Reactive nitrogen species (RNS) can be formed from nitric oxide (NO) and reaction with superoxide ($O_2^{\bullet-}$) to form peroxynitrite ($ONOO^{\bullet-}$). In biological tissues, both ROS and RNS can oxidize lipids, proteins, and DNA damaging the efficacy of these biomolecules.

The increase in ROS and RNS damage to biomolecules within the mitochondria will cause decreased coupling of electron flow in the electron transport chain thereby decreasing the production of ATP. With this uncoupling, cellular metabolism will likely shift to less aerobic conditions, and glycolysis will become a more preferred pathway for energy production. This results in the accumulation of lactate in mitochondria, hence in some classical mitochondrial disorders, increased lactic acidosis as well as a decrease in extracellular pH, are pathognomonic signs of mitochondria metabolic defect. With the general reduction in electron coupling, the mitochondria membrane potential can be reduced, causing a failure of the charge gradient used by mitochondria to produce ATP. Thus, from the induction of ROS or RNS, this triggers cascades of mitochondrial processes that can ultimately result in the release of cytochrome c and triggering cellular apoptosis.

The essential roles of mitochondria in synaptic transmission and plasticity, the involvement of mitochondria for LTP induction and maintenance (Kocsis et al. 2014), and mitochondria transport in dendrites and axons have been described (Cheng, Hou, and Mattson 2010). Mitochondria can synthesize ATP for neurotransmission, buffer calcium in both pre- and post-synaptic compartments, synthesize glutamate, and regulate presynaptic vesicle release (Smith et al. 2016). For example, when mitochondria are present in presynaptic boutons, this effectively buffers calcium levels (Ruggiero et al. 2017) and influences the release of synaptic vesicles by correlation with the number and volume of mitochondria located in the presynaptic bouton. Neurotransmitter synthesis, glutamine → glutamate occurs in the mitochondria, packaging of glutamate into vesicles requires ATP, and the release of vesicles is ATP-dependent (Smith et al. 2016). Taken together, to maintain a structural LTP, local mitochondria are required (Fu et al. 2017). Without mitochondria tethered near an active presynaptic bouton, there will be decreased numbers of vesicles and a smaller area of postsynaptic density (Smith et al. 2016).

Mitochondria play dynamic roles during brain development. There are key differences in the migration of interneurons depending on levels of mitochondria dysfunction (Lin-Hendel et al. 2016). The migratory distance of interneurons is dependent on levels of oxidative phosphorylation, while migration of projection neurons from the ventricular zone are not influenced. This would suggest that differences in inhibitory and excitatory neurons will be altered by mitochondria dysfunction occurring early in the wiring of brain circuitry. Healthy mitochondria respond to signals by increasing copy number, changing shape, size, motility, cellular location. The mitochondria copy number in the brain responds to aging and environment by nuclear genes involved in mitochondria transport (Lewis et al. 2018)'(Reddy 2011), mitochondria biogenesis (Nisoli et al. 2004), fission and mitophagy (Pryde et al. 2016)'(Cummins et al. 2019). A host of key molecules involved in the movement of mitochondria in axons, dendrites have been identified and are associated with Parkinson's disease (Bose and Beal 2016) and Alzheimer's disease (Cummins and Gotz 2018), but have not been studied in models of SZ.

1.2 Is there an etiological role for mitochondria in SZ?

As the brain is the most metabolically demanding organ of the body and the most functionally intricate and complex, imbalances in mitochondrial function may lead to severe downstream effects on neuronal processes and brain circuitry (Kim *et al.* 2019). The roles of mitochondria subserve a wide variety of functions beyond the energy-producing requirement of brain cells and have been studied as risk factors in psychiatric disorders including SZ (Somerville, Conley, and Roberts 2011; Robicsek et al. 2013; Rosenfeld et al. 2011b; Ben-Shachar 2002; Goncalves et al. 2018; Hagen et al. 2018; Mamdani et al. 2014; Rollins et al. 2018b), bipolar disorder (BD) (Kato 2006; Kato and Kato 2000; Kim *et al.* 2019), depression (Kim et al. 2018; Rollins et al. 2009; Karabatsiakis et al. 2014), and autism (Anitha et al. 2012; Schwede et al. 2018; Pei and Wallace 2018).

Classical mitochondria diseases often involve Complex I, making Complex I deficiency a hallmark of mitochondrial diseases, and there is support for Complex I dysfunction in SZ (Bergman and Ben-Shachar 2016; Rollins et al. 2018b). There are other classical signs of mitochondria dysfunction, reminiscent of mitochondria disorders, in SZ such as oxidative damage, increased brain lactate, altered copy number, and altered mitochondrial DNA (mtDNA) gene levels. Metabolic syndrome might also be associated with classical mitochondria disorders and SZ. Abnormal glucose metabolism has been reported in patients with SZ (Holmes et al. 2006; Fernandez-Egea et al. 2009) while CSF lactate concentrations were significantly higher in BD and SZ, 34% and 23% higher compared to control group, respectively (Regenold et al. 2009). The difference persisted after adjusting for CSF glucose which correlated positively with CSF lactate concentration (Regenold et al. 2009). This further evidence of subtle mitochondria imbalance of metabolism suggests that some patients may have a mitochondria dysfunction and could be identified and treated.

The expression of mtDNA encoded genes (Rollins et al. 2009; Hjelm et al. 2015) and protein alterations in mitochondrial pathways (Martins-de-Souza, Guest, Harris, et al. 2012; Martins-de-Souza, Maccarrone, *et al.* 2010; Martins-De-Souza, Dias-Neto, *et al.* 2010) have been associated with SZ. One highlighted example was the discovery that the expression of

11 mtDNA encoded genes is decreased in SZ in the dorsolateral prefrontal cortex (Shao et al. 2008).

Genetic association studies of mitochondria DNA variants with schizophrenia have been reviewed recently (Schulmann et al. 2019). In some studies of common mtDNA variants, those variants are ethnic defining polymorphisms where a spontaneous mutation arose in the ancestral population and was maternally transmitted. These mtDNA variants can define mitochondria haplogroup branches. Additional mutations could arise on the same ancestral line so that further sub haplogroup branches could be defined based on the distinct mutations. Further, during recent migrations over the past 5,000 – 20,000 years these mtDNA mutations were selected due to climatic adaptation and metabolic advantages in certain nuclear ancestry backgrounds. Since mtDNA does not recombine with other strands of mtDNA, it is incorrect to think of linkage disequilibrium of nuclear haplotypes as applicable to mitochondria genetics. However, heteroplasmy of mtDNA does occur, such that multiple variants at the same mtDNA position coexist within the brain and other tissues (Rollins et al. 2009).

A summary of recent evidence supports the association of mtDNA polymorphisms and SZ (Schulmann et al. 2019). Examples of common variants association in mtDNA and SZ were A15218G polymorphism in meta-analysis of four independent studies (total N = 47, 451, adjusted p-value of 2.15E-03). There was also a meta-analysis of T16519C showing association with schizophrenia (pooled OR = 0.894, 95% CI upper-lower: 0.80–0.98, p = 0.027). In a third example, T195C was also significantly associated with SZ and BD (pooled total N = 8,559). These variants can be ethnic defining polymorphisms, especially A15218G for haplogroup G, while T16519C and T195C occur sporadically across multiple haplogroups. Nevertheless, the distribution of common mitochondrial haplogroups can be geographically stratified within a population sample. Compounding the issue of common mitochondrial haplogroups being stratified by country or ethnic group, there are nuclear ancestry differences between different mtDNA haplogroups. These layers of potential dependence in certain combinations of mtDNA and nuclear SNPs (mitochondria - nuclear crosstalk, ethnic stratification of mtDNA defining alleles, nuclear ancestry, population admixture) could have co-evolved or been subject to recent immigration and geographic isolation. This relationship can be called a mitonuclear dependence, mitonuclear interaction, or bi-genome interaction (Hagen et al. 2018; (Sloan, Fields, and Havird 2015; Hill et al. 2019). Careful research into the putative association of common variants with SZ shows that when the variants are not equally distributed in a geographic location, this could confound the outcome due to stratification. In a study of Danes with schizophrenia, there was no difference in the overall mtDNA haplogroup distribution or nuclear ancestry distribution between cases and controls overall. The association of A15218G and SZ was significant in an analysis that corrected for nuclear ancestry stratification by using clusters defined by ADMIXTURE results. The association was not significant when the analysis was conducted by mtDNA haplogroup stratification (Hagen et al. 2018).

This question of how to analyze the mitonuclear relationship in genetic studies remains at the forefront of mtDNA genetic research into SZ Mismatches between the mitochondria and nuclear genomes could lead to mitochondria dysfunction while mtDNA mutations may be

dependent upon the nuclear background as shown in different model approaches (Zaidi and Makova 2019; Kenney et al. 2014). An example of a mismatch between mtDNA haplogroups is the alteration of electron transport respiration rates seen in cybrids from the same nuclear background but different mtDNA haplogroups (Kenney et al. 2014). Another example of nuclear mismatch with mtDNA is a study of two mice lines with identical nuclear DNA background, one line had a different mtDNA inserted into the oocyte, causing life-long changes in metabolism and healthy aging (Latorre-Pellicer et al. 2016). This is unequivocal evidence that pairings of nuclear DNA with different mtDNA will have profound influence across multiple tissues and physiological processes (mtDNA copy number (Zaidi and Makova 2019), telomere length, O_2 consumption, ATP production, lifespan, weight, ROS production, mitochondria biogenesis, and mitochondria oxidative protein response) (Latorre-Pellicer et al. 2016). These examples illustrate the dependence of two-way signaling between mitochondria and nuclear genes and that a mismatch between these two genomes could lead to an imbalance in mitochondria regulation (Kenney et al. 2014).

Recently, mitonuclear interactions in SZ were calculated, there was a suggestive association between the mtDNA and nuclear DNA variants in a GWAS of SZ (Schulmann et al. 2019). This recent study implicated mitonuclear gene pair associations in pathways such as neuron projection development, cell morphogenesis involved in neuron differentiation, excitatory synapse, and other specific neurodevelopmental pathways (Schulmann et al. 2019). A pioneering mitonuclear interaction study of BD also showed suggestive associations to mitonuclear gene pairs (Ryu et al. 2018). Both of these epistatic studies require larger sample sizes to determine if this joint interaction of mtDNA and nuclear DNA approach will yield credible associations.

Another mitochondria dysfunction occurring in mitochondria disorders is large somatic mtDNA mutations of mtDNA, which can accumulate in brain tissue (Rollins et al. 2009). These large deletions (> 1kb) usually do not involve 100% of the mtDNA copies in the brain, however, accumulation of large mutations could play an etiological role as large deletions have been associated with increased ROS and mitochondria dysfunction. However, the age-related large common deletion of mitochondria (Mamdani et al. 2014) shows a significant reduction in SZ compared to age-matched controls across 10 brain regions. This common deletion is only one of scores of somatic mtDNA large deletions occurring in brain tissue, thus screening for mtDNA deletions in the brain is underway (Hjelm et al. 2019).

Taken together, mtDNA copy number, somatic deletions, and mtDNA SNPs are relevant factors to consider in the etiology of SZ. A simplified hypothesis of mitochondria dysfunction in SZ is that the propagation of mtDNA errors can lead to an accumulation of oxidative stress and generation of small amounts of (ROS/RNS) with downstream consequences. The mitochondria lack histones to protect against oxidation, as well as error correction, resulting in propagation of mtDNA deletions in vulnerable neurocircuitry (Kasahara et al. 2017). This vicious cycle continues until loss of mitochondria function becomes apparent in neuronal functions such as firing rate, LTP, mitochondria movement, mitophagy, mitochondria biogenesis, and mitochondria fusion/fission events. Recent GWAS studies suggest an association of common mtDNA variants with SZ notwithstanding that

some variants might be subject to mitonuclear dependence in studies (Schulmann et al. 2019; Hagen et al. 2018). The neurobiology of mitochondria in brain and psychiatric disorders is logical and compelling, and in animal models are an unequivocal causative factor in learning and memory deficits (Sharpley et al. 2012) and neurodegeneration.

2 Antipsychotic drugs

2.1 Impairment of mitochondria

First-generation APDs antagonize pre and postsynaptic dopamine D_2 receptors with high affinity with variable effects on 5-HT2A, alpha-1 adrenergic, histaminergic, and muscarinic receptors. Most second-generation APDs antagonize both 5-HT2A and D_2 receptors with additional activity at D_3, D_4, alpha-1 adrenergic, histaminergic, and muscarinic receptors. There are some unique exceptions of dopamine receptor partial agonism for medications such as aripiprazole, which has been referred to as a third-generation APD (Mailman and Murthy 2010). The diverse binding affinities of second-generation APDs lead to various side effects including metabolic syndrome, anticholinergic toxicity, cardiovascular toxicity, and hyperprolactinemia, but overall less occurrences of movement disorders and extrapyramidal effects.

An overview of pharmacological mechanisms of action on mitochondria function shows three different scenarios influencing mitochondria function that are not mutually exclusive: i) Receptor occupancy of drug causes alterations in ionic permeability of Ca^{++}, K+, Zn^{++}, or Cl^{-} altering proton-motive force and mitochondria membrane potential. ii) Second messenger signaling pathways are altered by GPCR occupancy; those changes profoundly alter PKA and PKC levels which can bind to the mitochondria at specific A-kinase anchoring proteins. iii) Direct drug binding to mitochondria, presuming the drug is translocated across cellular membrane, at proteins such as TSPO, MAO, and Complex I. Drugs can compete with native ligands, such as neurotransmitters, in agonist or antagonist manner. Studies of isolated mitochondria might yield clues about potential binding to mitochondria; however, results of studies of isolated mitochondria, cells, and tissues may differ.

Both first- and second-generation APDs have been associated with mitochondrial impairment in multiple prior studies; as both classes share activity at dopamine (DA) receptors, these have been suggested to be responsible. For example, DA was found to inhibit Complex I activity, and closely related DA compounds (L-3,4-dihydroxyphenylalanine (L-DOPA), 3,4-dihydroxyphenylaceticacid (DOPAC), 6-hydroxydopamine (6-OHDA)) also inhibited the Complex I activity to a lesser extent than DA (Ben-Shachar et al. 2004). These findings were supported in a subsequent study in which DA dissipated mitochondrial membrane potential (MMP) without affecting cell viability, yet bypassing Complex I prevented DA-induced MMP depolarization, hence the interaction between DA and mitochondrial impairment likely involved Complex I (Brenner-Lavie et al. 2008).

While mitochondrial dysfunction has been found to be associated with SZ in various studies, the directionality of the mitochondrial defect is less well understood, i.e. whether the

mitochondrial dysfunction precedes the development of SZ or whether mitochondrial dysfunction follows treatment of SZ with APDs. Some reports of mitochondria alterations at the proteomic, transcriptomic, and metabolomic levels of analyses in the brain found that these changes do not appear to be related to treatment with antipsychotic drugs in SZ (Prabakaran et al. 2004a; Middleton et al. 2002; Shao and Vawter 2008) or BD (Shao and Vawter 2008; Chen et al. 2013). Human studies in first episode psychosis subjects reported mitochondrial changes that were present prior to exposure to APDs that may be linked to differential expression of proteins involved in metabolic pathways (Martins-de-Souza, Guest, Mann, et al. 2012; Martins-de-Souza, Harris, et al. 2010) and altered levels of circulating insulin-related peptides and other neuroendocrine hormones (Guest et al. 2011). Gene-expression and proteomic studies in non-human primates treated with APDs helped determine the effects of APDs on mitochondrial gene expression (Mirnics et al. 2000; Middleton et al. 2002; Sweet et al. 2009). A microarray study of primate frontal cortex following chronic treatment with haloperidol and olanzapine did not show significant impact of APD treatment upon mitochondrial-related gene expression (Martin et al. 2015). Interestingly, upon reanalysis of the same dataset, a significant negative overlap was found between the transcriptomic alterations following treatment with APDs versus treatment with the psychotomimetic drug phencyclidine, which recapitulates the disease signature of SZ. One potential conclusion is rather than driving mitochondrial alterations, APDs may serve to normalize the mitochondrial dysfunction of SZ (Gandal et al. 2018). Thus, the direction of alteration on mitochondria functioning by chronic administration of APDs might compensate for decreased mitochondria function.

Conversely, there is a long history of reports showing mitochondrial impairment by APDs and dopamine agonists, *in vitro,* often measured in Complex I (Bachmann and Zbinden 1979; Sagara 1998; Whatley et al. 1998; Casademont et al. 2007; Balijepalli, Boyd, and Ravindranath 1999; Balijepalli et al. 2001; Robicsek et al. 2013; Rosenfeld et al. 2011a; Brenner-Lavie, Klein, and Ben-Shachar 2009b; Ben-Shachar and Karry 2008; Karry, Klein, and Ben Shachar 2004; Ben-Shachar and Laifenfeld 2004; Dror et al. 2002; Ben-Shachar 2002; Ben-Shachar et al. 1999; Holper, Ben-Shachar, and Mann 2019). Consistent data show that therapeutic levels of APD have long term effects on mitochondrial protein in synaptosomal preparations (Farrelly et al. 2014). APD use has been associated with mitochondrial dysfunction through depolarization of mitochondrial membranes (Babich et al. 2016), impairing gene and protein expression in glycolytic and oxidative phosphorylation pathways (Schubert et al. 2016; Farrelly et al. 2014; Prabakaran et al. 2004b; Scaini et al. 2018), and antipsychotic-induced metabolic syndrome (Mittal et al. 2017; Parsons et al. 2009). Some reports of an apparent lack of APD effects on mitochondria gene expression findings (Fatemi et al. 2012; Fatemi et al. 2006; Rice et al. 2014) are from brain homogenate which contradicts studies focusing on cells and subcellular compartments.

In a proteomic analysis of rat mitochondria from the cerebral cortex and hippocampus, Ji *et al* (Ji et al. 2009) found that following treatment with an APD, either chlorpromazine, clozapine, and quetiapine, 14 proteins showed significant changes in quantity, 6 proteins were involved in the electron transport chain, and ultimately inhibited the efficiency of the electron transport chain (ETC). Notably, 3 of the ETC member proteins, NDUFV1, NDUFV2, and NADH dehydrogenase (ubiquinone) Fe-S protein 1, 75 kDa (NADH-

coenzyme Q reductase) (NDUFS1) are subunits that form Complex I and the other 3 ETC member proteins were subunits of ATP synthase. While this study provided compelling data that mitochondrial components were altered following treatment with APDs, the cerebral cortex and hippocampus are heterogeneous brain regions with different cell types that have different binding-specificities. It may be that some cell types are more or less vulnerable to the effects of the APDs on mitochondrial function. An investigation of specific cell types would be helpful in elucidating the mechanism of APD-induced mitochondrial impairment.

Although both first- and second-generation APDs have been associated with mitochondrial impairment, they may impair mitochondria in different ways. Compared to atypical APDs, typical APDs inhibit mitochondria to a greater extent and cause more oxidative damage, as evaluated by disruption of MMP (Shinoda et al. 2016; Eftekhari et al. 2016), inhibition of electron transport chain complex activities (Burkhardt et al. 1993; Balijepalli, Boyd, and Ravindranath 1999), and reduction of NADH-coenzyme Q reductase level, both in rat and human studies (Casademont et al. 2007; Modica-Napolitano et al. 2003). In hepatocytes of postmortem patients with SZ, haloperidol, phenothiazines, olanzapine, and risperidone were found to differentially regulate gene expression profiles. Typical neuroleptics affected genes associated with nuclear protein, stress response, and phosphorylation, while atypical APDs affected genes associated with Golgi apparatus, endoplasmic reticulum, and cytoplasmic transport (Choi et al. 2009). Additionally, Choi *et al* found that genes involved with lipid metabolism were found to be downregulated by typical APDs compared to atypical APDs, and genes related to mitochondrial function were differentially regulated by typical vs. atypical APDs. Mitochondria genes (SOD2, PDK1, and NAPG) were upregulated by the typical APDs vs. atypical APDs, and 11 mitochondria-related genes including BDH1, ACAMD, C14orf68, and NAGS were downregulated in typical vs. atypical APDs. The typical APD phenothiazine especially affected genes related to stress responses and increased expression of C-reactive protein in hepatocytes, a marker of inflammation, which may ultimately lead to increased risk of liver toxicity in patients treated with phenothiazines such as chlorpromazine, fluphenazine, and thioridazine. It has also been reported that supratherapeutic doses of haloperidol reduced ROS production and oxygen consumption in lymphoblastoid cell lines (Hjelm et al. 2015). Although the experiments above utilized nonneuronal cell lines, the results consistently demonstrate mitochondrial hypofunction following APD treatment.

As a further example of the complex relationship of medications and mitochondria, the activity of Complex I of the ETC was significantly decreased in patients with detectable psychotropic medications in pooled cases (both SZ and bipolar disorder (Rollins et al. 2018a). The direction of Complex I activity compared to controls was opposite depending on the stratification of patients, where Complex I activity decreased in a subclass of patients with both medication and younger age of onset, while Complex I activity was increased in older onset non-medicated patients compared to controls. Although the medications that appeared in the toxicological analysis of brain samples were mixtures of classes (APD, anxiolytics, sedatives, and antidepressants), patients without any medications had elevated levels Complex I activity. The data suggest there might be a subgroup of more affected patients with mitochondria dysfunction characterized by a younger age of onset.

In summary, significant evidence exists for a relationship between APDs, mitochondrial dysfunction, and the pathogenesis of SZ, although the exact directionality and mechanisms are not completely understood. Additional studies of mitochondria copy number, mitochondrial motility, mitochondria membrane potential, and intra neuronal localization conducted in conjunction with APDs and dopamine agonists may provide helpful data and open the door for the development of novel pharmacological targets and treatments to increase mitochondrial function in neurons in patients with SZ.

2.2 Metabolic syndrome

The constellation of metabolic side effects associated with the use of APDs such as weight gain, central obesity, insulin resistance, dyslipidemia, and hypertension make up metabolic syndrome. Baseline data from the Clinical Antipsychotic Trials of Intervention Effectiveness (CATIE) SZ Trial showed the prevalence of metabolic syndrome to range from 36% to 54% in patients with SZ treated with APDs (McEvoy et al. 2005; Meyer et al. 2005). While atypical APDs have lower risk of EPS than typical APDs, they are associated with a greater risk of developing metabolic syndrome (Henderson et al. 2015; Newcomer 2005; Brooks, Chang, and Krasnykh 2009). Among the atypical APDs, clozapine and olanzapine carry the highest risk (Leslie and Rosenheck 2004; Rummel-Kluge et al. 2010) and risperidone and quetiapine carry a moderate risk (Lieberman et al. 2005). While lurasidone, ziprasidone, and aripiprazole carry the lowest risk for metabolic syndrome, studies have shown that even these drugs may cause insulin resistance and other metabolic side effects in some people (Brooks, Chang, and Krasnykh 2009; Parsons et al. 2009; Newcomer 2005; Komossa et al. 2009; Fleischhacker et al. 2013). While the mechanism of metabolic syndrome is not completely understood, previous studies suggest that i) neurotransmitter systems, including histamine H1 (Kim et al. 2007; Deng, Weston-Green, and Huang 2010; Masaki et al. 2004), muscarinic (Bymaster et al. 2003), dopamine D_2 (Lencz et al. 2010; Volkow et al. 2008), and serotonin 5HT2C (Kirk et al. 2009) blockade; ii) satiety and energy homeostasis signaling via regulatory peptides adiponectin (Hanssens et al. 2008; Bai et al. 2009), leptin (Ragguett et al. 2017; Sentissi et al. 2008; Chen et al. 2018), and other inflammatory cytokines (Mori, McEvoy, and Miller 2015; Beumer et al. 2012); iii) genetic polymorphisms and gene-drug interactions that predispose to metabolic side effects (Malan-Muller et al. 2016; Roffeei et al. 2014; Risselada et al. 2012; Nsaiba et al. 2015) and/or lead to gene-drug interactions (Huang et al. 2014; Reynolds et al. 2013; Lett et al. 2012) may be involved in the development of metabolic syndrome.

More recently, mitochondrial interactions with APDs have been identified as a potential driver of metabolic syndrome, which is supported by the vital role of mitochondria in energy metabolism and homeostasis. In a study of cultured mouse neuroblasts, myoblasts, adipocytes, hepatocytes, and monocytes, treatment with clozapine was associated with altered mitochondrial morphology with increased mitochondrial volume, mitochondrial membrane depolarization, and reduced ATP levels in all cell lines (Contreras-Shannon et al. 2013). The authors also found increased production of pro inflammatory cytokines following clozapine treatment, suggesting perhaps inflammatory signaling pathways are linked with cellular dysfunction at the level of mitochondria. Inhibition of complex I activity by APDs (Ben-Shachar et al. 2004; Brenner-Lavie, Klein, and Ben-Shachar 2009a) may be an

additional mechanism leading to mitochondrial dysfunction and subsequent metabolic syndrome, although the finding that typical APDs inhibit Complex I activity more than atypical APDs (olanzapine and clozapine are atypical APDs (Casademont et al. 2007; Modica-Napolitano et al. 2003) suggests a more complex interaction.

These findings are further supported by human studies. In a study of patients with SZ treated with APDs with different metabolic risk profiles, patients treated with high-risk APDs (olanzapine and clozapine) showed decreased mRNA levels of complex III and IV subunit genes, and patients treated with high- and medium-risk APDs (quetiapine and risperidone) showed decreased expression of nuclear-encoded mitochondrial complex I and II. Additionally, mitochondrial oxygen consumption and ATP production were reduced in lymphoblastoid cell lines from patients compared to healthy controls, and cells subsequently treated with high-risk APDs showed the most significant decreases in functional parameters of mitochondrial oxygen consumption and as well as ATP production (Scaini et al. 2018). Hence, treatment with APDs most strongly associated with metabolic syndrome resulted in the greatest downregulation of mitochondrial dynamic and repression of oxidative metabolism, which may explain the increased prevalence of metabolic syndrome in patients taking olanzapine and clozapine. In patients taking risperidone, quetiapine, and olanzapine from the CATIE sample, SNPs in thirty nuclear-encoded mitochondrial genes were associated with weight gain, of which three (CLPB, PARL, and ACAD10) were replicated in an independent prospectively assessed sample (Mittal et al. 2017). While no association was observed between mtDNA variants and weight gain, the studies to date are underpowered and may have missed effects that were not very large. Replication in larger samples may be warranted to further explore this preliminary data.

Taken together, there appear to be APD effects in both CNS tissue and non-CNS tissues on mitochondria function that could be directly related to metabolic syndrome. The development of metabolic syndrome has been linked with increased medical comorbidity (Mitchell et al. 2013), cardiovascular risk factors (Sanchez-Martinez et al. 2018), and somatic preoccupation (Meyer et al. 2005), and patient dissatisfaction side effects may lead to drug switching or discontinuation (Stroup et al. 2011). Therefore, patients treated with medium- and high-risk APDs may benefit from pharmacologic and/or behavioral interventions, and a better understanding of the still elusive pathway between APDs and metabolic syndrome is crucial to the development of successful interventions.

3 Antidepressants and other psychoactive compounds

Prior studies have found that psychotropic medications in addition to APDs lead to impairment of Complex I activity (Corena-McLeod et al. 2013; Hroudova and Fisar 2012; Abdel-Razaq, Kendall, and Bates 2011; Adzic et al. 2016; Holper, Ben-Shachar, and Mann 2019), and patients with SZ often receive concomitant treatment with antidepressants, anxiolytics, and other psychoactive drugs. The interactions between polypharmacy and mitochondrial activity may be clinically relevant in patients treated with APDs.

3.1 Antidepressants

Many patients with SZ are also treated for mood symptoms. Indeed, while distinct, there is overlap in polygenic risk for major depressive disorder, bipolar disorder and SZ (Schulze et al. 2014). Protein components of the oxidative phosphorylation pathway were found to be upregulated in patients with MDD (Martins-de-Souza, Guest, Harris, et al. 2012); these proteins were downregulated in patients with SZ (Martins-de-Souza *et al.* 2011) as well as patients with psychotic depression (Martins-de-Souza, Guest, Harris, et al. 2012). Mitochondrial dysfunction is thought to play role in mood disorders by impairing neuroplasticity and hippocampal neurogenesis ultimately leading to depression (Caruncho et al. 2016; Allen et al. 2018), and antidepressant medications have been found to modulate mitochondrial activity at the cellular, proteomic, and genomic levels.

Existing studies on antidepressant drugs and effects on mitochondria are discordant with respect to whether antidepressants facilitate or inhibit mitochondrial activity, largely depending on different measures of mitochondria function. In rat hippocampus, fluoxetine, an antidepressant of the selective serotonergic receptor inhibitor (SSRI) class, has been found to differentially regulate 63 nonsynaptic mitochondrial proteins related to metabolic processes such as ATP synthesis and transduction, oxidative phosphorylation, and pyruvate and glutamate metabolism, with the effect of directing energy metabolism toward the Krebs cycle and oxidative phosphorylation (Filipovic et al. 2017). Acute treatment with fluoxetine increased citrate synthase, a proxy of mitochondria number in the striatum and increased complex I activity in the hippocampus in Wistar rats. Chronic treatment showed no change in citrate synthase activity in the prefrontal cortex, hippocampus, and striatum (Agostinho, Reus, Stringari, Ribeiro, Ferraro, *et al.* 2011) but decreased complex IV activity in the hippocampus (Agostinho, Reus, Stringari, Ribeiro, Ferreira, *et al.* 2011). Interestingly, fluoxetine in combination with olanzapine increased alterations in mitochondrial activity, where increased citrate synthase activity was seen in the prefrontal cortex and hippocampus in addition to the striatum (Agostinho, Reus, Stringari, Ribeiro, Ferraro, *et al.* 2011) and where increased complex II-IV activity was seen with acute treatment, and complex I activity remained increased with chronic treatment (Agostinho, Reus, Stringari, Ribeiro, Ferreira, *et al.* 2011). These studies illustrate how the effects of antidepressants in combination with antipsychotics (often seen in clinical practice) upon mitochondrial metabolism can be exceedingly complex and dependent on a number of variables such as treatment regimen, duration of treatment, brain area, and drug concentration. In summary, prior *in vivo* studies suggest that antidepressants generally lead to upregulation of mitochondrial activity in various metabolic pathways with acute treatment while chronic treatment leads to decreased or no change in mitochondrial activity. In combination with APDs, however, both acute and chronic treatment with antidepressants increased mitochondrial activity.

In contrast, *in vitro* studies in mitochondrial fractions extracted from pig brains found that antidepressants (amitriptyline, fluoxetine, tianeptine) were potent inhibitors of mitochondrial respiration, primarily at complex I and II, while mood stabilizers (lithium, valproate) had negligible effects (Hroudova and Fisar 2012). However, the tested drug concentrations were much higher than therapeutically active plasma concentrations used *in vivo,* therefore these

findings may have limited clinical applicability. The antidepressants, clomipramine, desipramine, and norfluoxetine (active metabolite of fluoxetine) caused apoptosis in a Chinese hamster ovary cell line as indicated by morphological changes and increases in caspase-3 activity (Abdel-Razaq, Kendall, and Bates 2011). Furthermore, clomipramine and norfluoxetine both reduced MMP in mitochondria isolated from rat hearts while there was no effect of tianeptine on MMP. Decreased complex II-IV activity was seen with 1 μM treatment with both tricyclic antidepressants (clomipramine, desipramine), while complex I activity was inhibited at concentrations > 20 μM, with the greatest inhibition by norfluoxetine (Abdel-Razaq, Kendall, and Bates 2011). Of note, while these drug concentrations are 2- to 40-fold greater than serum drug concentrations *in vivo* (Risch, Huey, and Janowsky 1979; Nelson 2017), they were lower than those used by Hroudova *et al* (Hroudova and Fisar 2012). The authors (Abdel-Razaq, Kendall, and Bates 2011) postulated that binding of mitochondrial complexes by antidepressants may lead to the production of ROS that disrupts the MMP resulting in decreased mitochondrial respiration; this may ultimately promote changes in transcription regulation that upregulate neuroprotection and adaptation in patients treated with antidepressants. Chronic tianeptine treatment in a prenatal stress model of depression increased a key component of the mitochondria proteome, isocitrate dehydrogenase (Glombik et al. 2017). This upregulation of the Krebs cycle enzyme indicates a positive change in mitochondria function by increasing the oxidative decarboxylation of 2-oxoglutarate, which generates energy in the form of NADH. In summary, *in vitro* studies have found that antidepressants may initially inhibit mitochondrial complex activity and cause disruption of MMP, although the downstream effects of this have the potential to be therapeutic for patients with mood disorders.

A similar relationship between ROS production and MMP disruption was described in an early study evaluating the effects of imipramine, clomipramine, and citalopram in human acute myeloid leukemia cells, where treatment with all three compounds activated apoptosis, with the generation of ROS preceding the loss of MMP. In response, the myeloid leukemia cells upregulated antiapoptotic proteins Bcl-2 and Bcl-X_L, this prevented antidepressant-induced apoptosis and MMP uncoupling but did not prevent ROS production (Xia et al. 1999). Although myeloid leukemia cells are quite distinct from brain cells, psychoactive drugs may also exert effects at the systemic level, as mentioned, and this study demonstrates that cells have self-regulatory mechanisms to respond to and thrive in the presence of drug-induced oxidative stress. Other antidepressants associated with increased ROS production and decreased MMP include selegiline, a monoamine oxidase inhibitor (Simon et al. 2005), amitriptyline (Villanueva-Paz et al. 2016), fluoxetine, sertraline (Elmorsy et al. 2017), and bupropion (Luethi, Liechti, and Krahenbuhl 2017). Nefazodone, an atypical antidepressant, was also found to induce MMP collapse in human hepatocellular carcinoma cell lines, although the authors were unable to analyze the relationship between MMP collapse and mitochondrial ROS levels (Silva et al. 2016).

To address the contradictory data on antidepressant effects on mitochondria and more deeply understand the mitochondrial mechanisms of SSRIs at the molecular level, a sub-cellular study was performed to evaluate protein activity in mitochondrial metabolic pathways in presynaptic light mitochondria (LM), heavy mitochondria (HM) (intra-synaptic), and post-synaptic free mitochondria (FM) (non-synaptic) isolated from rat hippocampus. Following

sub-chronic 21-day pharmacologic treatment, only desipramine but not fluoxetine increased malate dehydrogenase and decreased enzymatic activity in the ETC complexes in LM and HM, while both desipramine and fluoxetine enhanced cytochrome oxidase and glutamate dehydrogenase in FM (Villa et al. 2017). This study utilized a novel proteomic approach to localize drug effects within the micro-heterogeneity of brain mitochondria; however, the resolution of findings would be improved if the receptor-binding specificities (e.g. 5-HT vs. DA) of the isolated synapses were accounted for in the analysis.

Serotonin and dopamine receptor signaling appears to regulate mitochondrial trafficking through pre-synaptic and post-synaptic compartments. Serotonin (5-HT) via 5-HT1A receptors, promotes axonal transport through increased Akt activity. On the other hand, D_1 antagonism and D_2 agonism decrease Akt activity and may block the stimulatory effect of 5-HT on axonal transport (Chen, Owens, and Edelman 2008). Therefore by understanding the presence and ratios of 5-HT vs. DA binding cell types it may have helped determine the distribution of energy sources in neurons to further localize changes in mitochondrial enzymatic activities with antidepressant treatment in the study by Villa *et al* (Villa et al. 2017).

The effects of antidepressant treatment on energy balance in neural tissue reflect both increased and decreased energy production, causing alterations in MMP, ROS, apoptosis, and gene expression among many diverse effects. There is some evidence that polypharmacy with antidepressants and antipsychotics perturbs mitochondria differently than treatment with antidepressants alone. However, this interaction will require further study to quantify mitochondrial changes as increased versus decreased activity will not suffice to deduce the diverse nature of their interactions. Additionally, variability in intracellular processes likely participates in interindividual differences of the response to treatment with antidepressant or in drug resistance (Del Campo et al. 2018). Further studies of the effects of mood disorders, antidepressants and mood stabilizers on the molecular level are necessary to understand their roles in signaling pathways and influences on energy metabolism of neurons. They are expected to be helpful both in the search for biological markers of mood disorders or predictors of efficiency of the treatment with antidepressants and in the search of new psychotropic treatments.

3.2 Other psychoactive compounds

Benzodiazepines, opioids, and amphetamines are additional prescribed medications and drugs that patients with SZ often take concurrently with antipsychotics and/or antidepressants. Current studies suggest that benzodiazepines may have neuroprotective effects by reducing the production of free radicals and maintaining mitochondrial functions under metabolic (Baez et al. 2017) and acute physical stress (Mendez-Cuesta et al. 2011), increasing antioxidant activity (Arbo et al. 2017) and reducing neuronal excitotoxic injury. Additionally, JM-20, a benzodiazepine-dihydropyridine hybrid molecule whose dihydropyridine moiety does not interfere with its GABAergic properties, has been shown to prevent calcium-induced mitochondrial swelling, MMP dissipation, and release of the pro-apoptotic protein cytochrome c (Nunez-Figueredo et al. 2014), while PK11195 (isoquinoline carboxamide), a peripheral benzodiazepine receptor antagonist, caused mitochondrial

swelling, cytochrome c release, and mitochondrial uncoupling (Li, Wang, and Zeng 2007). Overall, benzodiazepines appear to have a neuroprotective role, particularly under conditions of metabolic stress such as glucose deprivation and hypoxia. Interestingly, clozapine was found to increase the binding of the translocator protein formerly known as the benzodiazepine receptor in rat brain and peripheral steroidogenic tissues, suggesting a possible interaction between certain classes of APDs, benzodiazepines, and neural and metabolic activity (Del Campo et al. 2018).

Meanwhile, opioids have been found to impair neural activity possibly through mitochondrial dysfunction. Tramadol, a partial opioid agonist, has been shown to inhibit mitochondrial complex I, II, and IV (Mohamed, Ghaffar, and El Husseiny 2015) and increase ROS and mitochondrial swelling and induce MMP collapse in brain cells of male rats (Mehdizadeh et al. 2017). However, inhibition of mitochondrial complexes only occurred at very high doses that exceeded the maximum recommended daily therapeutic doses for adult humans. Fentanyl, a full mu receptor opioid agonist, slightly reduced mitochondrial complex-specific respiration and cellular ATP content without changing cell morphology and mitochondrial permeability in human hepatocytes (Djafarzadeh et al. 2016), and concurrent morphine administration with transactivator of transcription (Tat) exacerbated the excitotoxic synapto-dendritic injury by disrupting calcium homeostasis and increasing MMP instability (Fitting et al. 2014). Amphetamine abuse has been associated with cognitive impairment (Wang et al. 2017; Scott et al. 2007), and chronic, but not acute amphetamine treatment increased ROS production in the submitochondrial particles of the prefrontal cortex and hippocampus in male Wistar rats (Frey et al. 2006). It is important to note that these drugs in varying combinations may interact at the level of mitochondria function with significant downstream effects. Please refer to Table 1 for a summary of psychotropic medication-induced changes in mitochondrial structure and function.

4 Conclusion and future directions

Both pharmacotherapy and psychiatric illness in schizophrenia are reported to modulate mitochondria; these overlaps are seen in respiratory chain activity declines and alterations in ROS and MMP. It is challenging to delineate whether mitochondrial dysfunction occurs secondary to pharmaceutical treatment or whether it is a result of the underlying disease process itself. While the MMP is important for ATP production, maintenance of calcium regulation, and homeostasis of synaptic functions, perhaps transient perturbations of MMP can lead to positive downstream effects. For example, a hypermetabolic (mitochondria) state may interfere with mtDNA transcription regulation, leading to the accumulation of mtDNA deletions and copy number alterations.

Due to varying degrees of polypharmacy, the mitochondrial effects are unknown, however, it is important to note that polypharmacy likely interacts at the level of mitochondria with significant downstream effects in multiple tissues leading to the potential for metabolic syndrome. The direction and mechanism of these downstream effects may differ for each class of drug and cell surface receptors, resulting in a myriad of pro- and anti-energetic phenomenon at the level of mitochondria metabolism and mitogenesis. Development of new

drugs that can alter the mitochondria defects found in aging, mood disorders, and first-episode subjects should be explored for potential therapeutic benefit.

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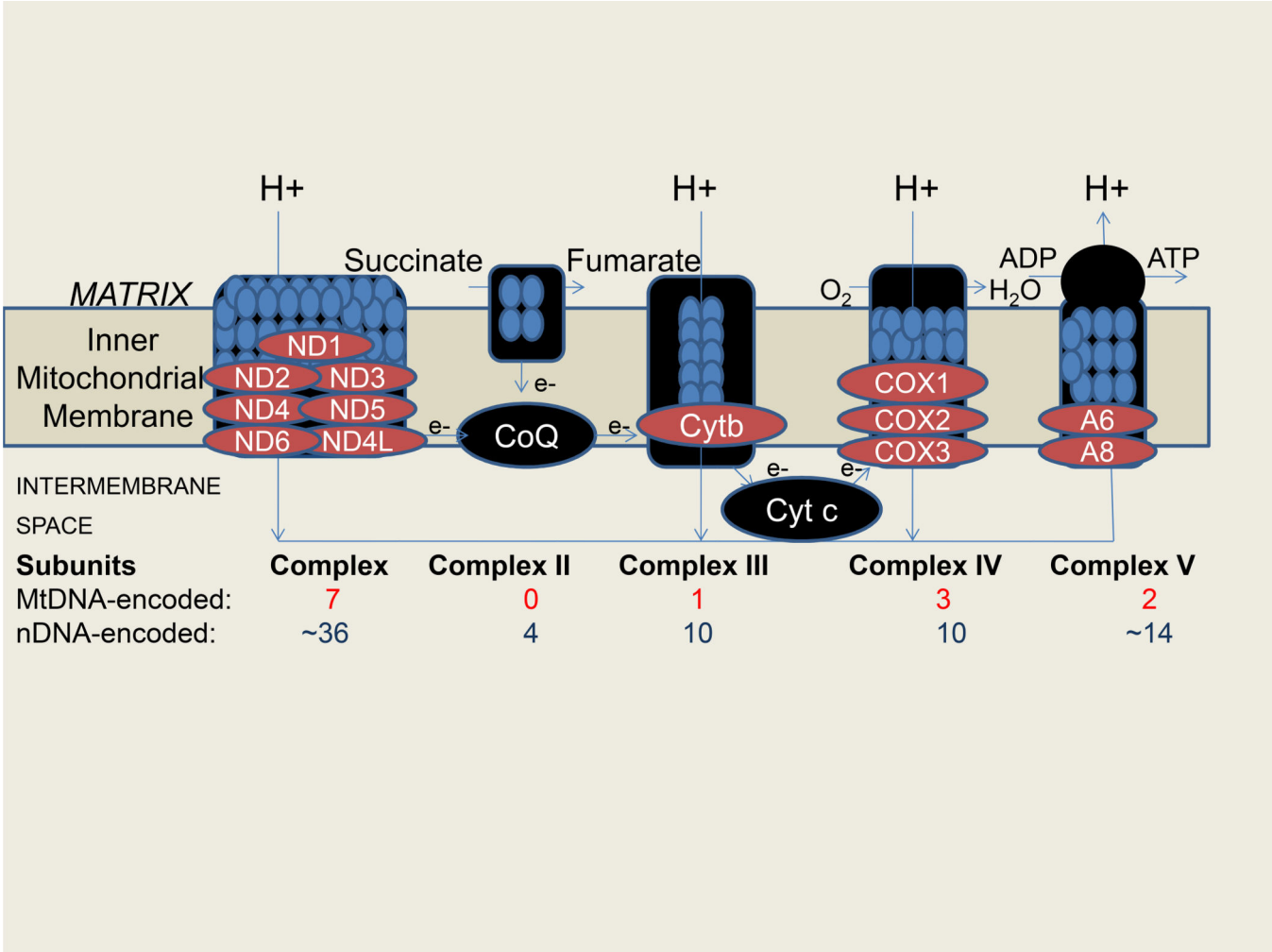

Figure 1.

Energy production, metabolism of carbohydrates, fatty acids and amino acids, and regulation of neurotransmitter degradation are important facets of mitochondria biochemistry.

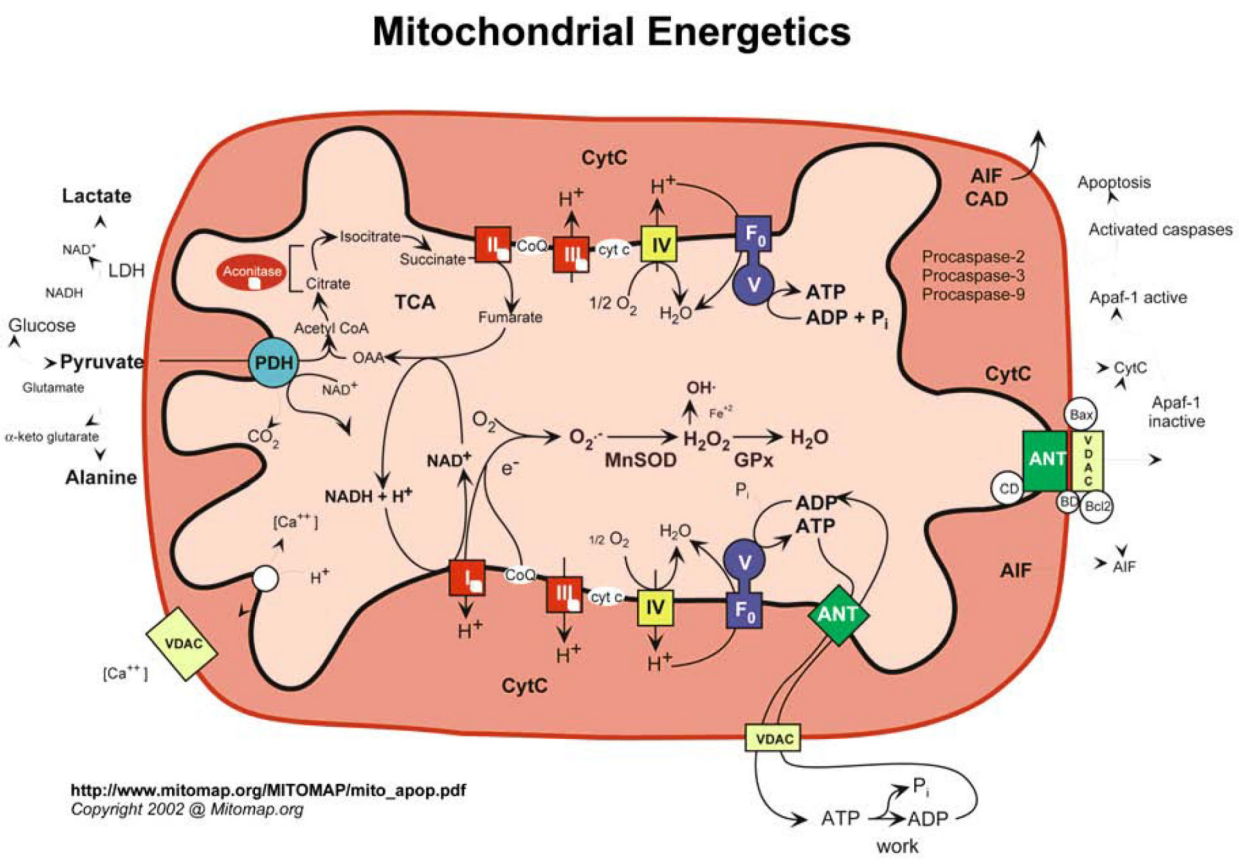

Diagram of the mammalian mitochondrion showing the relationship between energy production, ROS generation, and regulation of apoptosis.

Figure 2,

adapted from (Shao *et al.* 2008). The mitochondria genome is a circular double stranded DNA with 37 genes: 13 protein-coding genes in Complexes I, III, V; 22 tRNA genes, and 2 rRNA genes. A detailed map of each locus is found at www.mitomap.org. There are over 1,200 nuclear proteins imported into each mitochondria for functions described in Figures 1 and 2, a comprehensive list of those genes can be obtained from Mitocarta (Calvo, Clauser, and Mootha 2016) and Mitominer (Smith and Robinson 2019).

Table 1.

Summary of psychotropic medication-induced changes in mitochondrial structure and function.

Psychotropic Medication(s)	Effect on Mitochondrial Structure and Function	References
	Antipsychotics	
Aripiprazole, Chlorpromazine, Clozapine, Fluphenazine, Haloperidol, Olanzapine, Quetiapine, Risperidone	Inhibition of Complex I activity	Casademont *et al.* 2007, Balijepalli *et al.* 2001, Holper, Ben-Shachar, and Mann 2019
Haloperidol, Olanzapine, Trifluoperazine	Depolarization of mitochondrial membranes with disruption of mitochondrial membrane potential	Shinoda *et al.* 2016, Eftekhari *et al.* 2016, Babich *et al.* 2016
Chlorpromazine, Clozapine, Haloperidol, Olanzapine, Quetiapine, Risperidone	Impairment of gene and protein expression in glycolytic and oxidative phosphorylation pathways	Schubert *et al.* 2016, Farrelly *et al.* 2014, Scaini *et al.* 2018, Ji *et al.* 2009
Haloperidol, Olanzapine, Phenothiazine, Risperidone	Dysregulation of gene expression profiles in lipid metabolism, mitochondrial genes, and inflammatory pathways	Choi *et al.* 2009
Clozapine, Olanzapine, Quetiapine, Risperidone	Increased mitochondrial volume, mitochondrial membrane depolarization, downregulation of mitochondrial oxidative phosphorylation genes, and activation of pro-inflammatory signaling pathways as drivers of metabolic syndrome	Contreras-Shannon *et al.* 2013, Scaini *et al.* 2018
	Antidepressants	
Fluoxetine	Acute treatment leads to upregulation of mitochondrial activity in various metabolic pathways including Krebs cycle and oxidative phosphorylation; chronic treatment leads to decreased or no change in mitochondrial activity	Filipovic *et al.* 2017
Amitriptyline, Fluoxetine, Tianeptine	Inhibition of mitochondrial respiration, primarily at Complex I and II	Hroudova and Fisar 2012
Clomipramine, Desipramine, Norfluoxetine	Reduction of mitochondrial membrane potential, inhibition of Complex II-IV activity	Abdel-Razaq, Kendall, and Bates 2011
Amitriptyline, Bupropion, Imipramine, Clomipramine, Citalopram, Fluoxetine, Selegiline, Sertraline	Generation of reactive oxygen species preceding loss of mitochondrial membrane potential	(Villanueva-Paz et al. 2016, Luethi, Liechti, and Krahenbuhl 2017, Xia *et al.* 1999, Elmorsy et al. 2017, Simon *et al.* 2005
	Other Psychoactive Compounds	
4′-chlorodiazepam, Diazepam	Reduction of free radical production, increased antioxidant activity	Baez *et al.* 2017, Mendez-Cuesta *et al.* 2001, Arbo *et al.* 2017
Tramadol	Inhibition of Complex I, II, and IV	Mohamed, Ghaffar, and El Husseiny 2015
Tramadol	Increase reactive oxygen species production, induce mitochondrial membrane potential collapse	Mehdizadeh *et al.* 2017
Fentanyl	Reduction of mitochondrial complex-specific respiration and cellular ATP content	Djafarzadeh *et al.* 2016
Amphetamine	Chronic treatment increased reactive oxygen species production	Frey *et al.* 2006