Journal of Medical Genetics and Genomics Vol. 3(5), pp. 84 - 94, May 2011
Available online http://www.academicjournals.org/jmgg
ISSN 2141-2278 ©2011 Academic Journals

Review

The effects of mitochondrial dysfunction in schizophrenia

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Accepted 28 March, 2011

Mitochondria are unique and important organelles in terms of energy production for the eukaryotic cell. Through complexes of the electron transport chain embedded in the mitochondrial membrane, the cell is able produce large amounts of ATP. Mitochondria posses their own genome, some of which encodes for the subunits of these protein complexes. From the comorbidity of psychotic symptoms seen in those with mitochondrial disorders, the change in efficiency of cellular respiration has started to emerge as a target for research for understanding the mechanisms and potential therapeutic approaches in mental disorders. Schizophrenia is the hallmark of psychotic diseases and its diverse symptoms have been implicated to have its primary effects in the mesolimbic and mesocortical pathways in the brain. Mitochondrial concentrations in these areas and mutations within the mitochondrial genome are an active area of research. Additionally, the effects of mood stabilizers and antipsychotics in terms of oxidative phosphorylation have been examined in proteomics, DNA and RNA microarray technology, and neuroimaging to name a few. In this article, we make an attempt to discuss and analyze the effects of mutations in the mitochondrial genome with respect to electron transport chain and cellular respiration in individuals affected with schizophrenia.

Key words: Mitochondria, schizophrenia, electron transport chain, antipsychotics, mood stabilizers.

INTRODUCTION

Mitochondria are the powerhouse (Maurer et al., 2001) energy producing organelles of every eukaryotic cell. Through the metabolic pathway of oxidative phosphorylation (OXPHOS), these endosymbionts produce large amounts of ATP. Additionally, they are involved in a range processes including regulation of the cell cycle, cell signaling, apoptosis, and calcium buffering. With the mitochondria possessing their own genome and being maternally inherited (Shimizu et al., 1987), the study of disease in terms of genetic vulnerability has shifted from the nuclear genome to the mitochondrial DNA (mtDNA). In the inner most membrane of the double membrane-bound organelle, a respiratory chain of proteins called the electron transport chain (ETC) create a proton gradient for the production of ATP through ATP synthase. Due to the large amounts of energy produced by the mitochondria, it is clear that a mutation in mitochondrial DNA would cause deleterious effects especially in tissues that have the highest metabolic activity, examples including the brain, cardiac, and muscle tissue (Orth and Schapira, 2001; Boekema and Braun, 2007). The comorbidity in the psychotic symptoms seen in both mitochondrial and psychiatric diseases is what triggered an interest in the effects of mutations of mtDNA and psychological disorders (Kato, 2001; Fattal et al., 2006).

Furthermore, considering that the research for the emergence and etiology of psychiatric disorders is focused primarily on malfunctions within specific brain pathways, and the brain relying exclusively on glycolysis and oxidative phosphorylation (OXPHOS) for its energy (Orth and Schapira, 2001; Marchbanks et al., 2003), mitochondrial mutations are becoming a priority for experimentation and treatment possibilities (Kato, 2001; Ben-Shachar, 2002; Kerry et al., 2004; Konradi et al.,

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2004; Rezin et al., 2008; Rollins et al., 2009; Clay et al., 2010; Scaglia, 2010; Verge et al., 2011). Dysfunction associated with cellular respiration not only reduces the amount of energy in the brain, but it also has been shown to cause neuronal depolarization, alterations in plasticity and circuitry, and an increase in cellular calcium levels which can ultimately lead to a slow neuronal death (Maurer et al., 2001; Ben-Shachar and Karry, 2004).

One of the most severe psychiatric disorders is schizophrenia. It has a prevalence of 1.1% in the world population over the age of eighteen (NIMH). In the United States alone, there are over 300,000 acute schizophrenic episodes annually. 25 to 50% of these patients attempt suicide, 10% succeed causing schizophrenia to have one the highest mortality rates (Stalh, 2008). A combination of environmental factors and genetic predisposition is the accepted theory amongst researchers regarding the development of the disorder (Karsgodt et al., 2008; Burmeister et al., 2008). It is clear that the pathology and genetics of the disease is diverse and there are multiple hypotheses that describe the possible etiologies. However, studies conducting microanalysis including proteomic, metabolomics and genomics, have come to the conclusion that mitochondrial dysfunction and its effects on OXPHOS maybe the primary origin in the disorder. Alterations in mitochondrial function were found in the prefrontal cortex of post mortem schizophrenics (Middleton et al., 2002; Prabakaran et al., 2004). The pre-frontal cortex is especially important with schizophrenia because it is part of both the mesolimbic and mesocortical pathways in the brain. These pathways have implications in the emergence of positive and negative symptoms respectively of the disorder (Stahl, 2008). This paper will focus primarily on the effects of mutations within mtDNA of these specific pathways, with respect to the ETC and cellular respiration in individuals affected with schizophrenia.

COMORBIDITY OF MITOCHONDRIAL DISEASES AND PSYCHOTIC SYMPTOMS

Mitochondrial disorders can be either inherited maternally (Shimizu et al., 1987) or can be a result of spontaneous mutation (Orth and Schapira, 2001). These disorders display a phenomenon known as heteroplasmy, where one cell can have multiple mitochondrial genomes. The ratio of mutant mtDNA to non-mutant mtDNA is what determines the ultimate physical expression of the effected cell. This proportion is usually determined once the embryo is formed and this variation between each individual is called somatic mosaicism (Youssoufian and Pyeritz, 2002; Marchbanks et al., 2003). Mitochondrial dysfunction can affect any organ system in the body and therefore mitochondrial diseases display a wide variety of symptoms. Because the brain, skeletal muscle, and cardiac muscles have a higher metabolic demand, an increased amount of mitochondria are found in these areas causing these systems to be more vulnerable to changes in function of the organelle (Orth and Schapira, 2001; Boekema and Braun, 2007). Diseases such as mitochondrial encephalomyopathy lactic acidosis and strokelike episodes (MELAS) (Spellberg et al., 2000; Udea et al., 2004; Kaufmann et al., 2009), mitochondrial myopathy (Gardner et al., 2003), and mitochondrial encephalomyopathy (Amemiya et al., 2000) are a few disorders that exhibit this conclusion (Fattal et al., 2006).

Although mitochondrial diseases manifest themselves in largely physical symptoms, it has been reported that individuals with these disorders display a high prevalence of psychiatric symptoms including auditory and visual hallucinations, delusions, erratic behavior, and depression. Some patients have been diagnosed with psychosis and schizophrenia (Kato, 2001; Fattal et al., 2006), others have found that the diagnosis of the psychiatric disease actually obscured the additional diagnosis of mitochondrial disorders for up to a decade (Fattal et al., 2006; Kaufmann et al., 2009). Interestingly, the effects of mitochondrial dysfunction were not limited to those diagnosed. Relatives of MELAS, patients have been shown to demonstrate neurobehavioral symptoms such as irritability, distraction, and frustration. Additionally, one third of the carriers are diagnosed with depression (Kaufmann et al., 2009). This further solidifies the connection between mitochondrial dysfunction and psychiatric conditions.

MITOCHONDRIAL GENETICS AND PHYSIOLOGY

Mitochondria are encircled by a double-membrane, both of which are made of phospholipid bilayers. Between these two layers, the inner and outer membrane is the intermembrane space. The space enclosed by the inner membrane is called the mitochondrial matrix. The matrix is important because this is where the oxidation of fatty acids and pyruvate as well as the Kreb's cycle takes place. Additionally, the inner membrane space is where the ETC for cellular respiration is located (Figure 1). It is well accepted that the higher metabolic need of the tissue, the higher the mitochondrial concentration is found and therefore, the nervous, muscular, and cardiac systems are more susceptible to aerobic respiratory damage (Orth and Schapira, 2001; Boekema and Braun, 2007).

The ETC is located in the mitochondria's inner membrane and contains five complex's including four oxidoreductase complexes: The NADH dehydrogenase (complex I), the succinate dehydrogenase (complex II), the cytochrome bc1 (complex III), and the cytochrome c oxidase (complex IV). The last complex is the ATP synthase (complex V) (Wallace, 2005; Boekema and

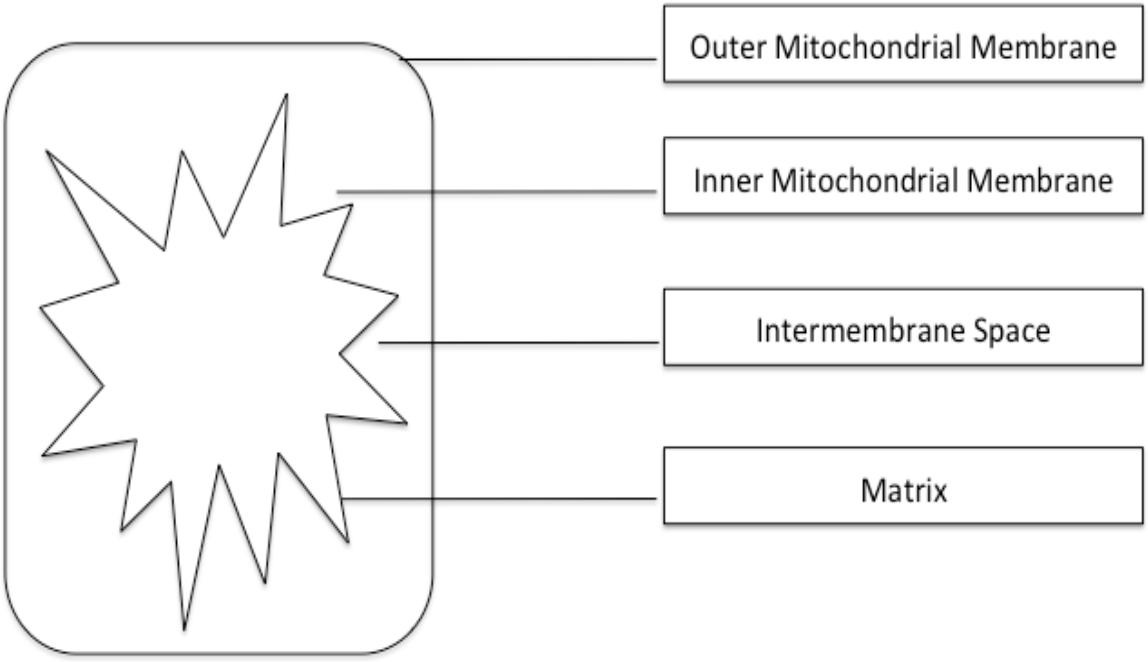

Figure 1. Anatomy of mitochondria.

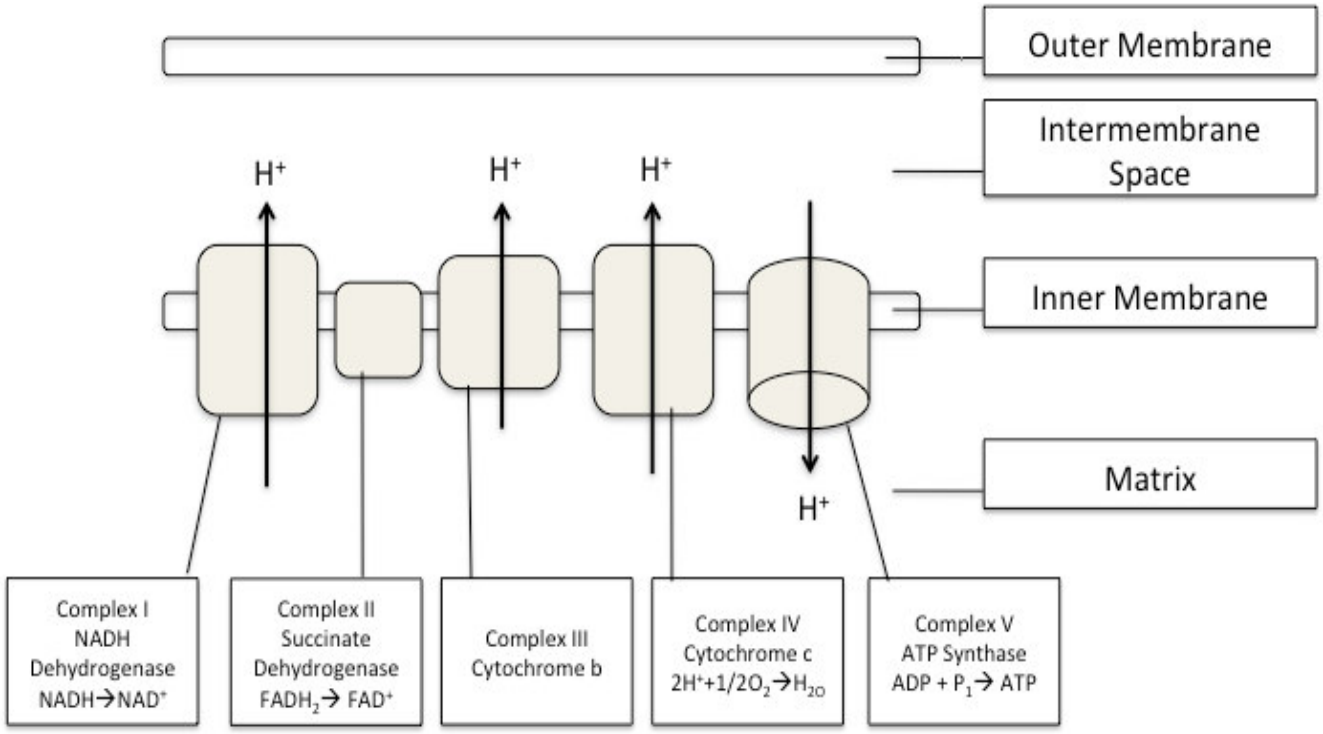

Figure 2. Mitochondrial electron transport chain.

Braun, 2007) (Figure 2). Glucose is broken down into pyruvate through glycolysis in the cells cytoplasm. The pyruvate is then reduced to carbon dioxide in the citric acid cycle located in the mitochondrial matrix.

The reduction of pyruvate in turn makes the electron carriers NADH and $FADH_2$ from NAD^+ and FAD^+.[1] The electrons from NADH and $FADH_2$ are then transferred from complex I and II to ubiquinone, an oil-soluble vitamin like substance, which moves freely through the mitochondrial membrane. Electrons then pass from ubiquinol to complex III and complex IV. Three of these complexes couple the transfer of electrons with the movement of protons into the intermembrane space of the mitochondria. The build up of protons causes an electrochemical gradient to form. Protons then pass from the intermembrane space through complex V, leading to the synthesis of ATP from ADP (Wallace, 2005; Boekema and Braun, 2007; Clay et al., 2010).

Mitochondria possess its own genome, and it encodes for the 12S and 16S rRNAs, 22 tRNAs, and 13 polypeptides involved in the structural aspects of the enzymes involved in OXPHOS and ETC. The rest of the subunits of the enzymes are encoded in nuclear DNA, which are transcribed and transferred to the mitochondria through unique mechanisms. The subunits include 7 out of the 46 of complex I, 1 out of the 11 for complex III, the three largest subunits out of 13 for complex IV, and 2 out of the 16 for complex V. The nuclear DNA encodes for the rest of the subunits in complex II as well as the mitochondrial DNA polymerase γ (Wallace, 1994; Wallace, 2005). A change in the structure of these complexes directly affects the amount of energy produced for proper cell function. Mitochondrial dysfunction has been found to have a direct effect on disorders that involve organs with a high metabolic demand, most notably the brain.

BRAIN PATHWAYS AND EFFECTS OF MITOCHONDRIAL CONCENTRATION

In terms of todays research and treatment plans for psychotic disorders, most of the focus is exclusively on the brain. The brain consists of several different structures, areas, systems, and pathways that have distinguishing functions. There are two main categories of symptoms when it comes to schizophrenia, positive and negative symptoms. Positive symptoms are dramatic, can happen without warning, and tend to exaggerate behavior; examples include delusions, hallucinations, agitation, and disorganized speech and behavior. Negative symptoms are classified as a reduction of normal function; examples include blunted affect, emotional withdrawal, lack of spontaneity, and sociality (Thaker and Carpenter, 2001; Stahl, 2008). The positive and negative symptoms of schizophrenia are generally associated with two separate pathways in the brain. Although this categorization is oversimplified, it proves advantageous when associating specific symptoms with certain areas of the brain specifically regarding the research and clinical treatment of the disorder. This can assist with optimizing individual treatment plans considering many patients have different combinations of symptoms. Additionally, mutations in specific genes associated with those particular areas can be identified and could be used for the integration of gene therapy into treatment.

Positive symptoms are identified with malfunctions regarding the mesolimbic circuit, which is directly associated with the neurotransmitter dopamine (DA) and secondary regulatory neurotransmitters including serotonin (Hoyer et al., 2002), gamma-aminobutyric acid (GABA) (Floresco et al., 2001; Lecourtier et al., 2010), and glutamate. It has dopaminergic cell bodies in the ventral tegmentum area in the brain stem to one of the terminal axons located particularly in nucleus accumbens in the ventral striatum. It is mostly associated with functioning of reward, motivation, and pleasure. DA has been traditionally been associated with schizophrenia. For several years, it has been shown that drugs administered chronically that increase the amount of the neurotransmitter in the limbic areas of the brain, such as cocaine and amphetamine, produce nearly identical symptoms to the positive symptoms in schizophrenia (Murray et al., 2008). The confirmation of this mechanism evolved with the administration of antipsychotic drugs, which block D2 DA receptors, in order to alleviate positive symptoms (Stahl, 2008). Evidence for negative symptoms has been categorized with the mesocortical circuit. Once again, dopamernergic cell bodies residing the ventral tegmentum area in the brain stem have projections into the dorsolateral prefrontal cortex and the ventromedial prefrontal cortex. However, differing from the mesolimbic system, a deficit in DA is seen with the appearance of negative symptoms. The prefrontal cortex is associated with cognitive and executive functions and the continued degeneration of these circuits could explain the increase of severity of the deficits seen in negative symptoms (Stahl, 2008; Medalia and Brekke, 2010).

The neurotransmitter glutamate and the hypofunction of the N-methyl-D-asparate (NMDA) receptors and its affects on DA concentration in the mesolimbic and mesocortical circuits regarding schizophrenic symptoms have been studied extensively. It was found that NMDA receptor is antagonist to phencyclidine (PCP) and ketamine has severe symptoms like those of schizophrenia. The descending glutamatergic pathway projections from the brainstem are very important in the regulation of the release of neurotransmitters such as DA, serotonin, and norepinephrine. Specifically, regarding DA, in the mesolimibic pathway (positive symptoms), glutamate from the brainstem stimulates the NMDA receptors on the interneuron that projects into the ventral tegmental area. The interneuron releases GABA

[1]NADH is also formed in glycolysis

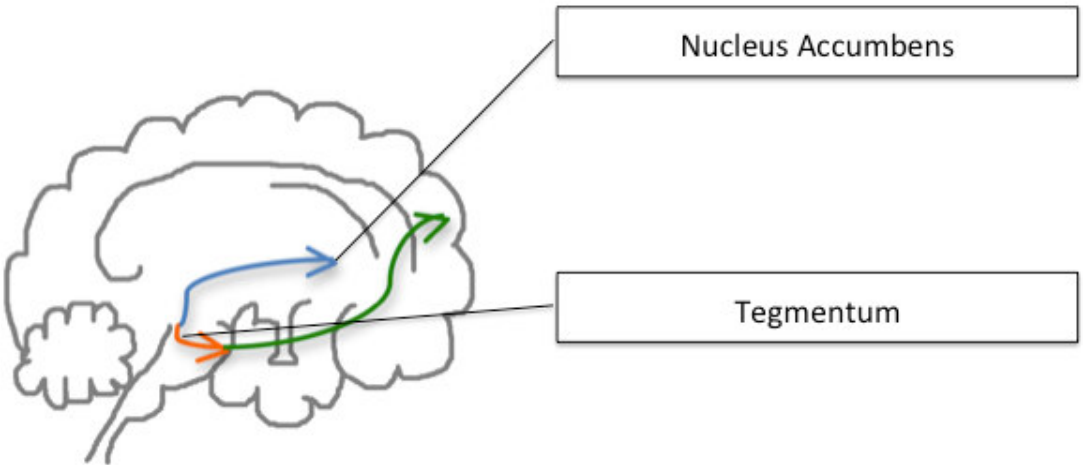

Figure 3. Mesolimbic pathway DA, GABA and GLU neuronal connection. Blue = *DA neurons; Green = GLU neurons; Orange = GABA interneuron.*

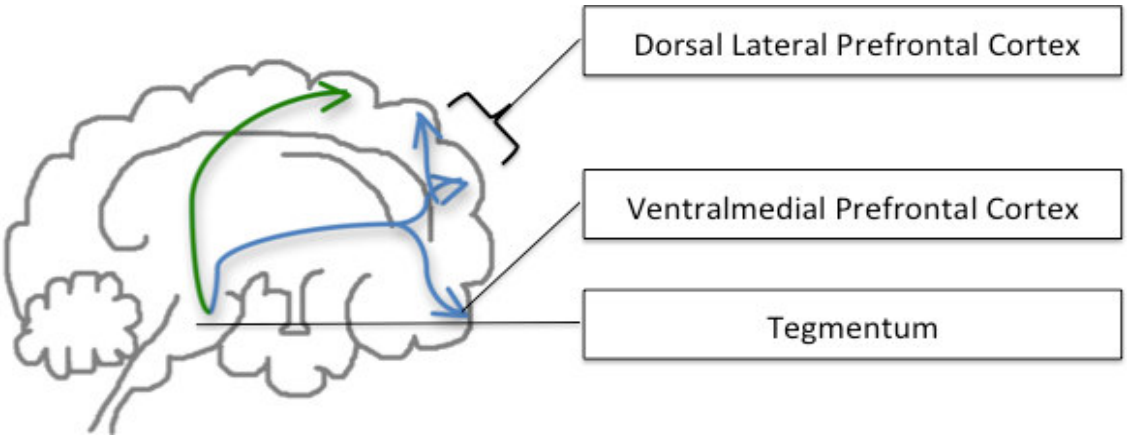

Figure 4. Mesocortical pathway DA and GLU neuronal connection. Blue = DA neurons; Green = GLU neurons.

therefore inhibiting DA release along the mesolimbic pathway. Hypoactivity of NMDA receptors could cause an unregulated increase of DA throughout mesolimbic structures. At the same time, glutamate projections from the brainstem into the mesocortical (negative symptoms) DA neurons usually increase the release of DA. However, if once again, NMDA receptors are hypoactive, this regulatory mechanism is gone, causing a deficit of DA concentration in the mesocortical pathway. This "integrated" hypothesis of the actions of multiple neurotransmitters on brain function in these particular pathways is becoming key for understanding the emergence of both positive and negative symptoms seen in schizophrenia (Stahl, 2008) (Figures 3 and 4).

An overall depletion of mitochondrial concentration within brain tissue of the mesolimbic and mesocortical pathways has been reported (Inuwa et al., 2005). A comparison of the striatum's of un-medicated schizophrenic brains to controls found a decrease in mitochondrial concentration per axon (Kung and Roberts, 1999; Fattal et al., 2006). Supporting this find, a decreased number of mitochondria per synapse was found in the putamen and caudate nucleus, which are the two sectors of the striatum, of post mortem schizophrenic brains (Somerville et al., 2011), indicating a loss of efficiency due to mitochondrial dysfunction. A defor-mation and decreased concentration in the anterior limbic cortex was also found (Uranova and Aganova, 1989). Additionally, a reduction in mitochondrial concentration was seen in the olgiodendrocytes surrounding caudate nucleus and prefrontal cortex (Uranova et al., 2001). NMR spectroscopy studies indicate a reduction of ATP concentration in the frontal and temporal lobes of schizophrenics when compared to controls, indicating either a decrease in concentration or dysfunction of mitochondria in those areas (Volz et al., 2000).

GENES EFFECTING MITOCHONDRIAL FUNCTION AND mtDNA MUTATIONS IN ETC COMPLEXES

It had been reported that a “common deletion” of roughly 5000 bp in mtDNA, associated in general with mental disorders, has been demonstrated to show cellular abnormality and even lead to apoptosis. This deletion has been widely reported on to have a major role in bipolar disorder (Kato, 2001; Frahm et al., 2005). Whether it plays a pivotal role in schizophrenia has yet to be determined. Some research says that the minor amount of the mutation found in schizophrenic brains is indicative of the lack of its influence (Rezin et al., 2009; Scaglia, 2010). On the other hand, others say that this deletion causes the increased release of reactive oxygen species (ROS). This increase could be due do the increase in glutamate activity as a compensation for the detection of hypoactive NMDA receptors. Glutamate stimulates the NMDA receptor channels to open allowing calcium to enter into the neuron. Neurons are extremely sensitive to small changes in calcium concentration. Too much calcium within the neuron triggers the activations of intracellular enzymes that form ROS. ROS destroys the membranes of critical organelles such as the mitochondria (Stalh, 2008). Although the full effect of ROS within cells is not known, studies point to the increase in ROS to be directly correlated to decreased ETC function and ultimately cell death due to ecitotoxicity (Prakbaran et al., 2004; Clay et al., 2010).

The DISC-1 (disrupted in schizophrenia-1) gene has been connected in subtle molecular changes in terms of neurogenesis and migration (Ishizuha et al., 2006; Clay et al., 2010; Park et al., 2010; Atkin et al., 2011). Stahl 2008 implicated that a mutation within this gene could cause weak synapses to form at critical junctions such as glutamate NMDA receptors. Failure to strengthen these connections could lead to an early onset of schizophrenia in adolescence. Although the mechanism of the DISC-1 protein is not known, it has been implicated in the formation of the cytoskeletal structures made for mitochondrial migration particularly in the synaptic area of the neuron (Ishizuha et al., 2006). A shRNA sequence used to decrease of DISC-1 expression caused a significant reduction of motile mitochondria, whereas an elevation in DISC-1 expression caused a significant increase of mitochondrial movement towards the neuronal axons (Atkin et al., 2011). Park et al. (2010) suggested that the DISC-1 protein formed a complex with the mitofilin complex acting as interacting partners and regulate several mitochondrial functions including calcium-buffering dynamics. Additionally, it was found that cells that were deficient in both the DISC-1 protein and mitofilin complex caused a significant decrease in complex I or NADH dehydrogenase function and ATP levels.

Although a significant decline in metabolic activity is well documented in the dorsal prefrontal cortex of schizophrenic patients (Andreasen et al., 1992; Buchsbaum et al., 1992), a difference in the protein and mRNA levels, the genes encoding for the complexes in the ETC, and the concentration of mitochondria in specific areas of the brain is inconsistent within the literature. Parkbaran et al. (2004) found a significant down regulation of nuclear genes encoding for the subunits of complex I, III, and IV in the prefrontal cortex of schizophrenic patients. Additionally, a proteomic analysis showed a significant decrease in subunits for complex I and III and a lower transcription level for complex IV. Reduced protein and mRNA levels were found in two of the three subunits tested of complex I in the prefrontal cortex, both of which were encoded by mtDNA (Karry et al., 2004). Maurer et al. (2001) found that specific enzyme activities for complex IV were reduced by 62% when compared to controls in the frontal cortex. Yet differences in enzyme activity of complex I and III were significant only when the results had been adjusted for the heteroplasmy of the organelle. Furthermore, they also found that the structure of the protein complex’s in the ETC as the reason for the lower metabolic rates seen as opposed to a decrease in the amount of mitochondria per neuron. Either way, the reduction in the rate of enzyme activity specifically in complex I and IV suggests damage to mtDNA.

There are several studies examining specific mutations in mtDNA (Iwamoto et al., 2004). A 22% increase of synonymous substitutions were found when comparing dorsal lateral prefrontal cortex of schizophrenics to controls. Furthermore, the ratio of transition to transversion mutations increased 2.25 fold in the genes encoding for complex I in the ETC (Rollins et al., 2009; Bamne et al., 2008). There have been studies on specific single nucleotide polymorphisms (SNP) in mtDNA. An up-regulation of the 3243A>G mutation was found in schizophrenic brains (Munakata et al., 2005) and a sequence variant m.12027T>C in the ND4 subunit of complex I was also reported (Marchbanks et al., 2003). All of these studies point to conformational changes ETC protein complexes as evidence for the emergence of schizophrenic symptoms.

EFFECTS OF ANTIPSYCHOTICS AND MOOD STABILIZERS ON MITOCHONDRIAL FUNCTION

The common treatment of schizophrenia often involves mood stabilizers and antipsychotics. Despite the extensive research done on the effects of these drugs, the exact mechanism is not known. An enhancement of mitochondrial function has been seen through the administration of mood stabilizers such as lithium (commonly used in the treatment of bipolar disorder which can include episodes of mania and depression)

and valproate (VPA) (epilepsy, bipolar disorder and less commonly in depression). Bachmann et al. (2009) found that *in vivo* VPA and lithium increased the rate of cellular respiration after administration of methamphetamine. The drugs additionally attenuated the methamphetamine-induced reduction of complex IV. Bachmann et al. (2009) also found that VPA and lithium caused a greater than 300% increase in the Bcl-2 gene levels in the mitochondria. The presence of the Bcl-2 gene was found when therapeutic levels of lithium and VPA were administered to rats (Chen et al., 1999). Although the exact mechanisms for the genes protective effects such as increasing calcium uptake by the mitochondria, preventing apoptosis, and producing antioxidant effects is not clear (Adams and Cory, 1998; Chen et al., 1999); it is now accepted that the Bcl-2 gene enhances cellular respiration (Glantz et al., 2005). The increase of gene expression during the administration of mood stabilizers demonstrates the Bcl-2 gene is crucial in the regulation of mitochondrial function (Quiroz et al., 2008; Bachmann et al., 2009; Clay et al., 2010) and should be researched further with regards to schizophrenia and other mental disorders.

Antipsychotics are another type of drug used in the treatment of mental disorders. There are two types of antipsychotics, typical and atypical. Typical anti-psychotics are DA antagonists and block D2 receptors in all dopamine pathways. Although effective, they have a debilitating side affects including extrapyramidal symptoms (restlessness, involuntary movement, uncontrollable speech) and tardive dyskinesia, both of which can become permanent even after the medication as stopped. This presents a problem in terms of treatment because many patients choose not to have permanent symptoms and end up relapsing and living the "revolving door" lifestyle. Atypical antipsychotics on the other hand in addition to having D2 antagonistic properties, they have a 5-HT2A receptor antagonistic effect. The 5-HT2A, a postsynaptic receptor inhibits DA release in the striatum by acting on the GABA interneuron in the substantia nigra. Administration of an atypical antipsychotic increases DA release through the medications 5-$HT2^{A}$ antagonistic effect in mesolimbic pathways, and at the same time decreases DA release in mesocortical pathways by their D2 receptor antagonist effect. Therefore both the negative and positive symptoms of schizophrenia can be reduced without unwanted side effects seen in typical antipsychotics (Stahl, 2008) (Figure 5). However, with the numerous amounts of 5-HT receptors such as the 5-HT_{1A} and 5-HT_{1B} autoreceptors, this effect can be quickly reversed by the brains own regulating mechanisms. Taking into account the numerous amounts of medications available, their various receptor antagonist/agonist effects, and the regulation mechanisms of the brain, the pharmokinetics used in the treatment of psychotic disorders is an emerging field.

Typical and atypical antipsychotics have been shown to directly inhibit complex I of the ETC of the frontal cortex and striatum (Burkhardt et al., 1993; Maurer and Möller 1997; Ben-Shachar 2002; Baohu et al., 2008) and the subunits of the complex V (Baohu et al., 2008). Even though these drugs alleviate symptoms of psychosis, structural changes implicate a depletion of the supply of ATP leading to a decrease in mitochondrial function, which ultimately effects higher-level brain function.

Interestingly, Konradi et al. (2004) suggested that the lack of down regulation of mitochondrial genes seen in the brains of schizophrenics could be due to the administration of antipsychotics (Prince et al., 1997; Konradi et al., 2004). These varied findings suggest that the exact effects of antipsychotics are not known. Although they are used to alleviate psychotic symptoms, the possibility of inhibiting OXPHOS and reducing the functioning of the ETC could explain the high rate of relapse when patients are weaned off of the medication. Additionally, the timing, duration, and amount of drug taken, and if other medications are being taken at the same time, all could contribute to these varied findings. Furthermore, environmental influences such as tobacco intake (addition of nitric oxide), alcohol consumption (prolonged ethanol exposure) and calorie intake, all have the possibility of not only affecting cellular respiration on their own, but they could interact with these powerful drugs and enhance the deleterious effects seen in some cases (Yao et al., 2001).

GENE-ENVIRONMENT INTERACTION

The fact that both genes and the environment play roles in the manifestation of metal disorders is well accepted with the evidence presented in familial, twin, and adoption studies. Nature, or the genetic vulnerability of an individual, has been researched extensively in twin studies. Specifically for schizophrenia, in monozygotic twins, there is an estimated risk of 50%, dizygotic twins carry a 15% risk, making the total heritable vulnerability around 68% (Tsuang et al., 2004; Roth et al., 2009). However, these studies also demonstrated that identical genetic codes do not result in the manifestation of the disorder. Focus has now shifted to how and to what degree do genes and the environment interact to produce symptoms associated with schizophrenia. This is a difficult path to take considering changes in the amount of polymorphisms within the population and that every individual has different experiences. Furthermore epigenetics, which is when changes in the environment can influence the amount a gene is expressed, has to be taken into account (Tsuang et al., 2004; Roth et al., 2009; van Os et al., 2010).

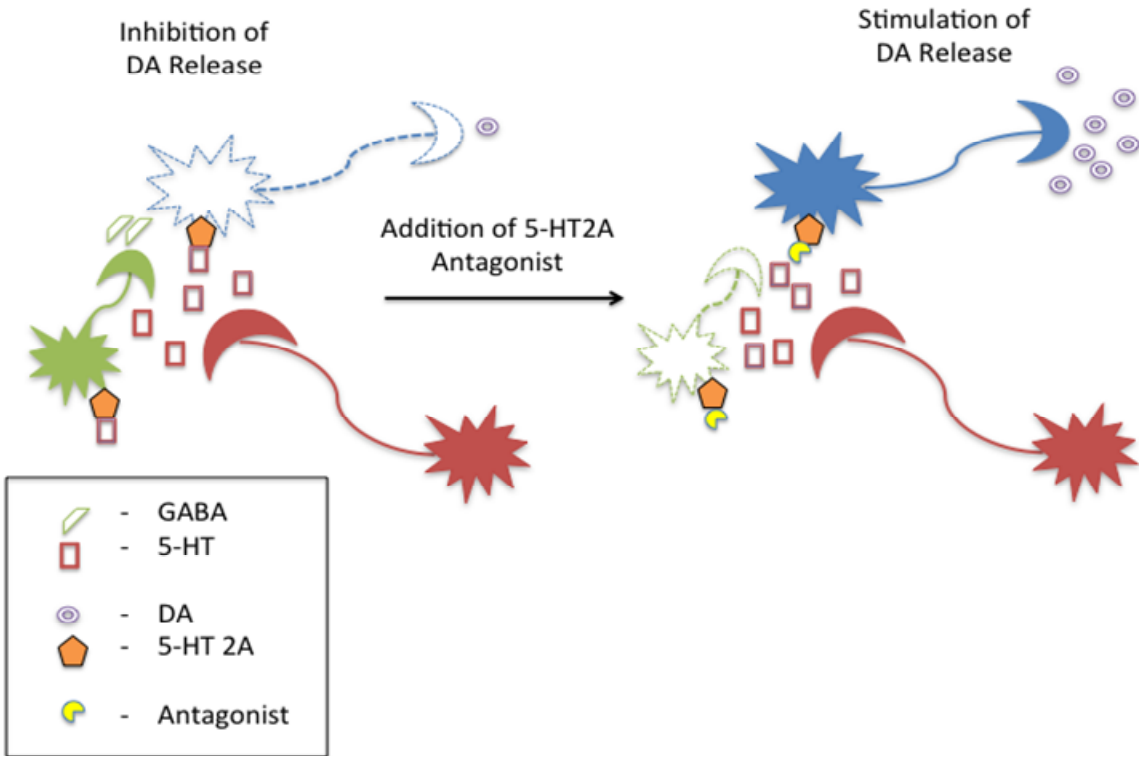

Figure 5. Mechanism of 5HT-2A antagonists. Dashed line, Inhibited: solid line = Activated neuron. Blue = DA neuron; Green = GABA neuron; Red = 5-HT neuron.

Epigenetics occurs when there is a change in the amount a gene is expressed by methylation of the DNA or altering the chromatin structure histone modification. No change in the DNA sequence occurs. Although twin studies have demonstrated that there is a genetic influence when it comes to psychotic disorders, no genetic vulnerability can ensure the development of any mental illness, especially schizophrenia. The gene-environment interaction has to be considered (van Os et al., 2008) and there is a long list of environmental factors including complications during pregnancy and childbirth, what season the person was born in, viral exposure, and head trauma, that have shown to contribute to the emergence of the disorder (Tsuang et al., 2004). The influence of viral infections during critical periods of development has been examined, particularly during prenatal growth when rapid division and differentiation of cellular tissues is occurring with the influence of epigenetic mechanisms (Pidsley and Mill, 2011). Cytomegalovirus, influenza virus, and *Chlamydia* among other viral strains, have been implicated in the emergence of schizophrenia in animal models. This indicates that no particular infectious agent increase the risk of the disorder, however, it would be the immune response and its effects on normal function that can influence the emergence of symptoms. In fact, it has been demonstrated that the blunted type-1 immune response could cause the accumulation of kynureic acid, which has antagonistic affects at the NMDA receptors. NMDA receptors are crucial to proper function of interneurons that have been shown to regulate both the mesocortical and mesolimbic pathways (Müller and Dursun, 2010). Lead exposure is also another prenatal exposure noted in neurotoxic effects on GABA neurotransmission as well as the differentiation and development of the central nervous system. After the prenatal period, another major critical period of development is during the adolescent stage. Usage of cannabis, socioeconomic status, childhood trauma and infections during this period has been implicated in influencing the emergence of schizophrenic like symptoms (Brown, 2011). Understanding the influence of the environment in terms of proteomics and genomic could help explain early onset cases in schizophrenia. A new wave of gene-interaction studies is starting to enter into literature. Molecular investigation and new insights on the influence of the environment and medication on specific pathways within the brain can be studied with emerging technology such as new imaging techniques such as functional magnetic resonance imaging (fMRI), positron emission tomography (PET), and flurodeoxy-glucose (FDG) to examine changes in metabolic rates.

The most important thing when considering schizophrenia and other psychiatric disorders is that the exact biological cause is unknown. The medical field sometimes assumes that mood disorders are like somatic disorders. However, the difference between the two begins with the diagnosis. It is impossible to take culture from those who are affected with schizophrenia and diagnose them with the disorder. The implications of the environment influencing gene expression (nuclear or mitochondrial) and neurological pathways associated with the different categories of symptoms (positive and negative) cannot be ignored and should be examined thoroughly. With the development of “miracle drugs” and new imaging technology, it is important that the influence of the environment, the individual’s perception of the world is not forgotten. It is too often that psychiatric disorders are placed in a “biological box” implicating that fixing the biology solves the problem. Researchers and doctors cannot forget that although medication can clear the ‘haze’, individuals are still broken inside and that is something that should be attended to in order to prevent relapse and the prolonging of suffering (Rosenhan, 1973; Montgomery, 2006; Groopman, 2007).

CONCLUSION

Mitochondria play a crucial role in neuronal function. The brain is in constant activity and the demand for ATP is high. A high density of mitochondrial in the brain allows OXHPHOS through the ETC in the inner membrane of the mitochondria to produce large amounts of energy. Dysfunction in the mitochondria and especially mtDNA is detrimental for the higher-level functions of the brain and other systems that have a large energy demand (Orth and Schapira, 2001; Boekema and Braun, 2007). It is clear that mutations in the mtDNA that especially cause a change in the protein complexes that are associated with the ETC are particularly destructive. Conformational changes can inhibit the proteins efficiency in terms of transferring electrons and creating a proton gradient for ATP production for complex V. Due to the fact that complex I has the most electronegative reduction potential, inhibition of this proteins activities could completely shut down the ETC. Additionally, if complex V is altered, no ATP would be produced through OXPHOS, regardless of whether or not the protein gradient was created.

Through the emergence of psychotic symptoms seen in patients with mitochondrial disorders such as MELAS (Spellberg et al., 2000; Udea et al., 2004; Kaufmann et al., 2009), it became apparent that mitochondrial dysfunction could play a crucial role in the emergence of psychotic disorders. Schizophrenia is on the extreme end of the spectrum in terms of degree of severity for mental disorders. The inability for patients to distinguish between what is real and what is not, is extremely debilitating and it is further evidence that psychosis is a complex phenomenon. As medical science advances, further understanding of mitochondrial dysfunction in the mesocortical and mesolimbic pathways and the neurotransmitters involved (Stahl, 2008) may bring more clarity to the etiology of this disorder. It could be that those areas are either particularly vulnerable to changes dealing with oxidative stress and the risk of neuronal death is higher or that the GABA receptors and glutamate pathways have a greater effect of regulation in these particular areas. Understanding of these mechanisms could aid in the development of new therapeutic approaches in treating the variety of symptoms presented in schizophrenia. Additionally, it is clear that environmental factors have an influence on the expression of genes. Future research should aim to understand the effects of the environment like viral infections and the complications on the expression of crucial genes such as DISC-1 and Bcl-2 in terms of mitochondrial function during critical periods and especially in the pathways emphasized in the emergence of psychological symptoms.

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