Review

Biological Psychiatry

Mitochondrial Etiology of Neuropsychiatric Disorders

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ABSTRACT

The brain has the highest mitochondrial energy demand of any organ. Therefore, subtle changes in mitochondrial energy production will preferentially affect the brain. Considerable biochemical evidence has accumulated revealing mitochondrial defects associated with neuropsychiatric diseases. Moreover, the mitochondrial genome encompasses over a thousand nuclear DNA genes plus hundreds to thousands of copies of the maternally inherited mitochondrial DNA (mtDNA). Therefore, partial defects in either the nuclear DNA or mtDNA genes or combinations of the two can be sufficient to cause neuropsychiatric disorders. Inherited and acquired mtDNA mutations have recently been associated with autism spectrum disorder, which parallels previous evidence of mtDNA variation in other neurological diseases. Therefore, mitochondrial dysfunction may be central to the etiology of a wide spectrum of neurological diseases. The mitochondria and the nucleus communicate to coordinate energy production and utilization, providing the potential for therapeutics by manipulating nuclear regulation of mitochondrial gene expression.

Keywords: Alzheimer's disease, Autism, Mitochondria, mtDNA, nuclear receptors, OXPHOS

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Prodigious efforts have been invested in understanding the genetics and pathophysiology of pediatric and adult neurological diseases, yet a definitive understanding of their etiology and the anticipated rationally designed therapies have yet to be realized. One possible reason for this impasse may be the assumptions on which these investigations have been based. In Western medicine it is assumed that clinical manifestations that primarily affect the brain are the product of brain-specific defects and that the important genes for neurological diseases are located on the nuclear DNA (nDNA). The alternative is that systemic mitochondrial bioenergetics defects are the cause of neuropsychiatric disorders, because the brain is the most energetic tissue in the body and the most important mitochondrial bioenergetics genes are not in the nDNA, but rather are located on the mitochondrial DNA (mtDNA).

A mitochondrial etiology of neuropsychiatric disorders is likely because the brain represents 2% to 3% of our body's mass yet consumes up to 20% of our oxygen and 25% of our glucose (1). Pyruvate generated from glucose via glycolysis is reacted with oxygen within our mitochondria to generate energy by oxidative phosphorylation (OXPHOS). Because of the brain's high reliance on mitochondrial energy, partial systemic mitochondrial defects can predispose to a wide range of neuropsychiatric disorders from autism to Alzheimer's disease.

MITOCHONDRIAL GENETICS AND BIOLOGY

The mitochondrial genome encompasses between 1000 and 2000 nDNA-encoded genes required for mitochondrial function plus hundreds to thousands of copies per cell of the maternally inherited mtDNA. The mtDNA codes for the 13 most important polypeptides for mitochondrial OXPHOS plus the 12S and 16S ribosomal RNAs and the 22 transfer RNAs for mitochondrial protein synthesis. While classical Mendelian clinical disorders involve homozygous loss of function mutations, partial mitochondrial defects resulting from heterozygous nDNA gene mutations or heteroplasmic (mixed mutant and normal) mtDNA mutations can reduce mitochondrial function sufficiently to fall below the minimum bioenergetics levels for normal brain function, the brain's bioenergetics threshold (2–4).

The tissues with the highest energy demand are in rough rank order the brain, heart and muscle, kidney, and endocrine system. Hence, the brain will be the first to be affected by the milder mitochondrial defects, while more severe mitochondrial defects will begin to affect other organ systems, as is commonly seen in neuropsychiatric disorders. Inefficient mitochondria will be less able to oxidize pyruvate and fatty acids, resulting in the accumulation of glucose and triglycerides in the blood as seen in diabetes, obesity, and cardiovascular disease (2–4).

mtDNA variation has a number of unique genetic features that may contribute to the unorthodox genetics of the psychiatric, metabolic, and cardiovascular diseases. The mtDNA codes for the core OXPHOS genes, which include seven (ND 1–4, 4L, 5, and 6) of the ~45 polypeptides of OXPHOS complex I, one (cytochrome b) of the 11 polypeptides of OXPHOS complex III, three (cytochrome c oxidase subunits I–III) of the

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13 polypeptides of complex IV, and two (adenosine triphosphate [ATP] synthase 6 and 8) of the 18 polypeptides of OXPHOS complex V. The remaining ~80 OXPHOS polypeptides are coded in the nDNA. The inner mitochondrial membrane complexes I to IV constitute the electron transport chain, with complex I (reduced nicotinamide adenine dinucleotide dehydrogenase) oxidizing reduced nicotinamide adenine dinucleotide to oxidized nicotinamide adenine dinucleotide and complex II (succinate dehydrogenase) oxidizing succinate to fumarate. Complexes I and II transfer the collected electrons to the inner membrane electron carrier, coenzyme Q, which ferries the electrons to complex III. Complex III transfers the electrons to cytochrome c, which further transfers the electrons to complex IV (cytochrome oxidase), which uses four electrons to reduce one molecule of O_2 to two molecules of H_2O. As the electrons traverse complexes I, III, and IV the energy released is used to transport protons out across the mitochondrial inner membrane from the mitochondrial matrix to the intermembrane space. The resulting proton electrochemical gradient across the mitochondrial inner membrane is utilized as a source of potential energy to drive complex V (ATP synthase) to condense adenosine diphosphate + Pi to ATP within the mitochondrion. The mitochondrial ATP is then exchanged for the cytosolic adenosine diphosphate across the inner membrane by the various adenine nucleotide translocator isoforms. Hence, the 13 mtDNA polypeptides are key electron and proton carriers of OXPHOS while nDNA encodes both mitochondrial OXPHOS and structural elements (2–4).

In addition to generating ATP, the mitochondria produce reactive oxygen species, which act as signaling molecules at lower levels but can become toxic at high levels, regulate cellular redox status; control intracellular Ca^{2+} levels, initiate the intrinsic pathway of apoptosis through activation of the mitochondrial permeability transition pore, and regulate the levels of the essential intermediates that activate cellular signal transduction pathways and epigenome (ATP, acetyl coenzyme A, S-adenosylmethionine, α-ketoglutarate, succinate, glutamate, etc.). The mitochondrion needs to control nuclear-cytosolic signaling pathways because all cellular functions require energy (5,6).

In addition to intermitochondrial and internuclear signaling, a variety of transcription factors and epigenomic regulators previously assumed to function exclusively in the nucleus have now been found to also be located in the mitochondrion. Examples include Foxg1 (7), p53 (8,9), DNA (cytosine-5)-methyltransferase 1 (10), DNA (cytosine-5)-methyltransferase 3 (11,12), estrogen receptor (ER) beta (13,14), and numerous others. Hence, there is a complex and intimate interaction between the mtDNA and the nDNA (15,16).

Clinically relevant mtDNA variants fall into three classes: ancient adaptive polymorphisms, recent deleterious mutations, and developmental-somatic mutations. Because the mtDNA is exclusively maternally inherited, male and female mtDNAs do not mix and thus cannot recombine. Therefore, the mtDNA sequence can only change by the sequential accumulation of mutations along radiating maternal lineages.

The sequence of a single mtDNA is called its haplotype, and a cluster of related mtDNA haplotypes is designated a haplogroup. The human mtDNA tree has its origin in Africa, where it radiated for approximately 200,000 years, giving rise to a plethora of African-specific mtDNA haplogroup lineages, designated African macrohaplogroup L. About 65,000 years ago, only two mtDNA lineages, which founded macrohaplogroups M and N, successfully left Africa and gave rise to all Eurasian and Native American mtDNA lineages. Macrohaplogroup N radiated into both Europe and Asia, while macrohaplogroup M was confined to Asia. In Europe macrohaplogroup N gave rise to the haplogroups H, I, J, K(Uk), T, U, V, W, and X, while in Asia N gave rise to haplogroups that include A, B, F, and O. Macrohaplogroup M generated a plethora of Asian mtDNA lineages (M1–M80), which include haplogroups C, D, G, and Z. Only five mtDNA lineages left Eurasia to give rise to all Native American mtDNAs: A, B, and X from N and C and D from M (Figure 1) (3,17).

mtDNA haplogroup lineages are highly geographically delineated and correlate with indigenous populations. This is because the founder haplotypes acquired functional mtDNA variants that changed mitochondrial energy metabolism. The resulting altered energetic states permitted our ancestors to adapt to new environmental factors such as alternative food sources, activity demands, high altitude, warm versus cold regions, and diverse infectious agents. Regional selection of a founder functional variant resulted in the regional expansion of the mtDNAs baring that variant leading to the haplogroups. As a result, each mtDNA haplogroup has distinctive mitochondrial physiological properties that strongly influence individuals' physiologies (17–19).

The mtDNA has a much higher mutation rate than the nDNA. As a result, new deleterious mtDNA mutations are continuously arising along the human female germline, resulting in maternally inherited diseases. Deleterious mtDNA mutations can range from mild to severe. Severe mtDNA mutations can affect individual phenotypes when heteroplasmic. while milder mutations may only cause disease when purely mutant (homoplasmic). In either case, the effect of the mtDNA mutation can be highly variable, with heteroplasmic mtDNA mutations varying in percentage of heteroplasmy between siblings and among an individual's tissues, resulting in variable energetic defects that may be slightly above or below the bioenergetic threshold. Similarly, mild homoplasmic mtDNA defects that are above the brain's bioenergetic threshold can by chance become associated with a mild nDNA genetic variant or exposed to a mitochondrial environmental toxin that impairs bioenergetics sufficiently to fall below bioenergetics thresholds and cause pathology (20).

mtDNA mutations not only arise in the female germline, but also during development and in tissues with age. These somatic mtDNA mutations are generally heteroplasmic and can augment the bioenergetic deficiencies of inherited mitochondrial defects. The accumulation of such somatic mtDNA mutations is thought to be an important factor in organ decline with aging and to also explain the delayed onset and progressive course of common diseases. There is a strong correlation with age and increasing risk of neuropsychiatric disorders. This follows directly from a mitochondrial etiology of these diseases, as the mtDNA accumulates mutations in tissues during development and aging. That these somatic mtDNA mutations relate to age-related phenotypic manifestations has been demonstrated by observing premature aging phenotypes in mice harboring error-prone mtDNA DNA