

# Autism: a mitochondrial disorder?

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**Abstract** — Autism is a developmental disorder characterized by disturbance in language, perception and socialization. A variety of biochemical, anatomical and neuroradiographical studies imply a disturbance of brain energy metabolism in autistic patients. The underlying etiology of a disturbed bioenergetic metabolism in autism is unknown. A likely etiological possibility may involve mitochondrial dysfunction with concomitant defects in neuronal oxidative phosphorylation within the central nervous system. This hypothesis is supported by a frequent association of lactic acidosis and carnitine deficiency in autistic patients.

Mitochondria are vulnerable to a wide array of endogenous and exogenous factors which appear to be linked by excessive nitric oxide production. Strategies to augment mitochondrial function, either by decreasing production of endogenous toxic metabolites, reducing nitric oxide production, or stimulating mitochondrial enzyme activity may be beneficial in the treatment of autism.

Autism is a developmental disorder characterized by disturbances in language, perception and socialization. A variety of biochemical, anatomical and neuroradiographical studies imply a disturbance of brain energy metabolism in autistic patients. These include findings of elevated serum lactate levels (1), regional disturbances of fluorodeoxyglucose uptake seen on PET scanning (2), and reduced high-energy phosphate compounds using P31 nuclear magnetic resonance spectroscopy (3). The underlying etiology of disturbed bioenergetic metabolism in autism is unknown. A likely etiological possibility may involve mitochondrial dysfunction with concomitant defects in neuronal oxidative phosphorylation within the central nervous system.

Mitochondria are the energy-producing units of the cell. This organelle is a source of production of adenosine triphosphate (ATP), the chemical energy in all living matter. ATP is derived from a process

known as oxidative phosphorylation, a biochemical process mediated by five intramitochondrial enzyme complexes (complex I to complex V) (4). These intramitochondrial enzyme complexes are collectively referred to as the electron transport chain.

Brain function is critically dependent on ATP production. Oxidative phosphorylation via the mitochondria provides over 95% of total brain ATP (5). Therefore, adequate mitochondrial metabolism is essential for normal brain function. The regions of the brain which are functionally more active (e.g. temporal cortex) are sites of enhanced mitochondrial activity (6). It follows that processes which inhibit oxidative phosphorylation will result in defects in brain bioenergetic metabolism and in impaired central nervous system functioning. It is those areas with greater functional demand that are also more vulnerable to the effects of impairments in mitochondrial function.

Central nervous system dysfunction is commonly associated with mitochondrial disorders. Developmental regression, learning disability and behavioral disturbances have been described in association with mitochondrial syndromes (7). Mitochondrial disturbances in these patients are clinically suggested by increased blood lactate levels, abnormal urinary organic acids and decreases in blood carnitine levels (8). P31 nuclear magnetic resonance spectroscopy has also demonstrated reduced high-energy phosphate compounds in patients with diagnostically confirmed mitochondrial encephalopathies (9).

Mitochondrial dysfunction may result from a variety of divergent factors. These include primary defects in respiratory chain enzyme, organic acidemias, and impairments of mitochondrial fatty acid oxidation (10). Immune-mediated mechanisms of mitochondrial damage are also now being recognized. This latter effect appears related to nitric oxide (11).

Nitric oxide is a free-radical gas elaborated by macrophages in response to infection or inflammation. Its immunocompetency is dependent upon its ability to uncouple all antigen's oxidative phosphorylative capacity. Nitric oxide also is believed to play an important role in neurotoxicity. Although speculative at present, the proposed mechanism of nitric-oxide-mediated neurotoxicity may involve its binding to mitochondrial respiratory chain enzymes, including NADH ubiquinone oxidoreductase, NADH succinate oxidoreductase and cis aconitase (12). The binding of nitric oxide to these respiratory chain enzymes results in an uncoupling effect on mitochondrial oxidative phosphorylation and subsequent depressed glycolysis. This effect has also been demonstrated in the central nervous system where induction of nitric oxide synthetase (the rate-limiting step of nitric oxide production) in cultured astrocytes has been shown to inhibit cytochrome C oxidase activity (13). Thus, nitric oxide may play a key role in immune-mediated neurotoxicity via mitochondrial inhibition.

### **Evidence for mitochondrial dysfunction in autism**

Lactic acidosis has frequently been found in association with autism (14). However, the precise biochemical abnormality has not been identified to date. Lactic acidosis may be secondary to pyruvate dehydrogenase deficiency or mitochondrial respiratory chain defects including co-enzyme Q and cytochrome oxidase deficiency (15). Rett syndrome, a pervasive developmental disorder similar clinically to autism, affecting only girls, has been associated with lactic acidosis and respiratory chain abnormalities (16). Recently, marked increases in analogs of

Krebs cycle metabolites were found in the urine of autistic patients (17). These metabolites may be involved in disturbances of mitochondrial Krebs cycle function, resulting in defects in brain bioenergetic metabolism.

Carnitine deficiency is commonly found associated with autistic patients (18). Carnitine is essential for the utilization of fatty acids by the mitochondria, and a deficient state results in impaired ATP production and decreased availability of high-energy phosphate compounds.

Mitochondrial dysfunction in autism is also suggested by neuroimaging procedures, including positron emission tomography (PET) scanning and nuclear magnetic resonance (NMR) spectroscopy. PET scans of autistic patients have demonstrated areas of diminished fluorodeoxyglucose uptake in certain brain regions (19). Reduced fluorodeoxyglucose uptake reflects reduced glucose utilization and brain metabolism. The areas most adversely affected in autistic patients are the cortical association processes (20). Magnetic resonance spectroscopy provides another means of measuring brain energy metabolism by analyzing levels of cerebral ATP. Autistic patients have diminished levels of ATP in cortical association areas, adding support to the concept of defective bioenergetic metabolism in the central nervous system (21).

In the absence of an identifiable metabolic disturbance in autism, how may the mitochondria become damaged and result in defects in brain bioenergetic metabolism? A possible source of mitochondrial toxicity may involve the production of the free-radical nitric oxide via immune-mediated mechanisms.

Immunological defects have been found in association with autism. These have included decreased number of T-lymphocytes (22), with altered ratios of helper to suppressor T-cells, and decreased natural killer cell activity (23). As a consequence, frequent opportunistic infections appear to affect autistic patients in greater proportion. These opportunistic infections may lead to increased production of cytokines and result in an increase in nitric oxide synthesis. It is known that viruses, bacteria and fungi are susceptible to the cytotoxic effects of nitric oxide. Nitric oxide facilitates microbial death by interfering with intracellular energy production at the level of the mitochondrion (24). Increased nitric oxide production secondary to recurrent endotoxemia may adversely affect the host's own mitochondrial activity. Areas of increased metabolic activity, specifically in the developing brain, are likely more susceptible to mitochondrial dysfunction. An intriguing hypothesis relates the developmental of autism to a cascade involving initial immune deficiency, opportunistic

infections associated with excessive nitric oxide production and, finally, central nervous system mitochondrial inhibition.

### Therapeutic implications

Bioenergetic defects secondary to mitochondrial dysfunction in autism may require two types of approaches for therapeutic intervention. The first approach is identification of biochemical factors which may inhibit mitochondrial function. Organic acidemias and other disorders of metabolism need to be routinely screened for and identified. The next step would entail removal of toxins or reduction of levels of endogenous toxic metabolites which are impeding mitochondrial function. As mentioned earlier, a common link between immune and neurological toxicity involves the excess production of nitric oxide in response to infection or inflammation.

Nitric oxide is enzymatically-formed from L-arginine by nitric oxide synthetase (25). This enzyme is induced by endotoxemia and macrophage activation (26). Identification and then removal of these toxins will attenuate nitric oxide synthetase activity and reduce the production of nitric oxide. Nicotinamide, a B vitamin, has been reported to prevent activation of nitric oxide synthetase in macrophages in a dose-dependent fashion (27).

A second approach to treat autism entails the administration of mitochondrial respiratory chain co-factors to enhance mitochondrial function. This strategy employs stimulation of enzyme activity by supplying precursors or co-enzyme and alternative substrates. This would include thiamine, riboflavin, pyridoxine, co-enzyme Q and carnitine.

### Conclusion

Autism is a disorder of brain bioenergetic metabolism whose cause is unknown, but may be secondary to mitochondrial dysfunction. Mitochondria are vulnerable to a wide array of endogenous and exogenous factors which appear to be linked by excessive nitric oxide production. Strategies to augment mitochondrial function, either by decreasing production of endogenous toxic metabolites, reducing nitric oxide production, or stimulating mitochondrial enzyme activity, may be beneficial in the treatment of autism.

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