Autism as a NO/ONOO- Cycle disease

Martin L. Pall
Washington State University, USA

The NO/ONOO- cycle is a primarily local biochemical vicious cycle, such that depending where it is localized in the body, may be able to generate a variety of chronic inflammatory diseases. The elements of the cycle are: Elevated levels of oxidative stress, peroxynitrite (ONOO-), nitric oxide (NO), superoxide, intracellular Ca\(^{2+}\), inflammatory cytokines and other inflammatory markers, NF-kappaB, excitotoxicity glutamatergic activity and NMDA activity and some of the TRP group of receptors, as well as mitochondrial dysfunction and lowered tetrahydrobiopterin (BH4) activity. With two exceptions, each of these have been found to occur in autism patients and most have been shown to play a causal role in the disease. One exception, the TRP group of receptors, there are few data on their possible role in autism. There may be a second possible partial exception: although excitotoxicity and elevated glutamatergic activity are well documented, there is some evidence that the NMDA activity may be low, rather than high - this will be discussed in the presentation. In general, then, there is an excellent agreement between the predictions of the NO/ONOO- cycle and the biochemical properties of autism patients. There is similarly a good agreement between the cycle and the properties of stressors reported to cause autism, when exposures occur in the perinatal period; some of the unique properties of autism may be due to the impact of this biochemistry/physiology on the developing brain, as has been the conventional wisdom about autism. The properties of such initiating stressors, including infections, toxic metals and organic toxicant exposures and how they may act to initiate the cycle will be discussed. The local nature of the cycle may be expressed in part, by the common impact of autism on certain parts of the brain: corpus callosum, anterior cingulate cortex, fronto-temporal structures and possibly Broca's area. It may also be expressed through variations in regions and severity of impact, which may explain the varied symptoms in cases of autism spectrum disorders.

One of the areas of autism research that has been interpreted in other ways is the role of 5-methyltetrahydrofolate (5-MTHF) and other reduced folates and also vitamin B12 in autism. 5-MTHF is thought to have a protective role based on evidence that there is lowered methylation activity in patients, 5-MTHF appears to be useful in treatment and a genetic polymorphism which influences 5-MTHF levels helps control susceptibility. These various data have been interpreted in terms of a central role of methylation in autism. However, 5-MTHF is known to be a potent ONOO- scavenger and thus may act to protect by lowering ONOO- levels, with ONOO- being the most central element in the cycle. This will be discussed in detail. Vitamin B12 in the form of hydroxocobalamin is a potent NO scavenger at high concentrations and may act in other ways to lower both NO and ONOO-. The important point here is that while lowered methylation may well have a role in autism, it should be viewed as being a consequence of the cycle, rather than a primary cause of the disease.

There are multiple ways in which the cycle can influence brain function: Initiating apoptosis, causing excitotoxicity, having profound effects on brain function because of mitochondrial dysfunction, changed levels of catecholamines and serotonin (due to roles of BH4) and elevated NO. Neural circuitry may be influenced by roles of several cycle elements on long-term potentiation. The effects of these factors on brain development in autism, makes it particularly difficult to predict changes in brain function.

martin_pall@wsu.edu