REVIEW ARTICLE

A POSSIBLE CENTRAL MECHANISM IN AUTISM SPECTRUM DISORDERS, PART 2: IMMUNOEXCITOTOXICITY

Russell L. Blaylock, MD

In this section, I explore the effects of mercury and inflammation on transsulfuration reactions, which can lead to elevations in androgens, and how this might relate to the male preponderance of autism spectrum disorders (ASD). It is known that mercury interferes with these biochemical reactions and that chronically elevated androgen levels also enhance the neurodevelopmental effects of excitotoxins. Both androgens and glutamate alter neuronal and glial calcium oscillations, which are known to regulate cell migration, maturation, and final brain cytoarchitectural structure. Studies have also shown high levels of DHEA and low levels of DHEA-S in ASD, which can result from both mercury toxicity and chronic inflammation.

Chronic microglial activation appears to be a hallmark of ASD. Peripheral immune stimulation, mercury, and elevated levels of androgens can all stimulate microglial activation. Linked to both transsulfuration problems and chronic mercury toxicity are elevations in homocysteine levels in ASD patients. Homocysteine and especially its metabolic products are powerful excitotoxins.

Intimately linked to elevations in DHEA, excitotoxicity and mercury toxicity are abnormalities in mitochondrial function. A number of studies have shown that reduced energy production by mitochondria greatly enhances excitotoxicity. Finally, I discuss the effects of chronic inflammation and elevated mercury levels on glutathione and metallothionein. (*Altern Ther Health Med.* 2009;15(1):60-67.)

Russell L. Blaylock, MD, is a retired neurosurgeon and professor of biology at Belhaven College, Jackson, Mississippi.

Editor's note: The following is part 2 of a 3-part series. Part 3 will appear in the Mar/Apr 2009 issue of Alternative Therapies in Health and Medicine.

EXCESSIVE ANDROGENS AND AUTISM

There is strong evidence that mercury exposure in humans increases androgen levels. For example, Barregård et al reported that there was a significant correlation between increasing concentration of mercury in chloralkali workers and testosterone levels.[1] Animal studies also show a link between sex steroid production and mercury dosing.[2] Studies have also shown a link between elevated prenatal testosterone,[3] postnatal serum testosterone,[4] and autism spectrum disorders.

As to the mechanism of testosterone elevation by mercury exposure, it has been suggested that Hg^{2+} directly causes a defect in adrenal steroid biosynthesis by inhibiting the activity of 21 alpha-hydroxylase,[5] while others have suggested inactivation of hydroxysteroid steroid sulfotransferase either directly[6] or by way of inflammation.[7] It has also been shown that DHEA-S, the proposed storage form of active DHEA, is also significantly lowered in autistic disorders.[8]

Kim et al have shown that even very small doses of LPS (1 nmoL) can dramatically decrease the levels of mRNA for SULT2A1 and PAPSS2, which are responsible for sulfonation of a number of endogenous hydroxysteroids, bile acid, and xenobiotics as well as sulfonation of DHEA to DHEA-S.[7] Normally, DHEA-S plasma levels are 300- to 500-fold higher than DHEA levels. Kim et al found that TNF-α and IL-1ß were responsible for the decrease. Unlike in autistic patients, DHEA levels were not increased in LPS-exposed animals, which can occur with mercury toxicity. Reductions in DHEA-S are common with other chronic inflammatory disorders, such as rheumatoid arthritis.[9]

In keeping with the finding of a defect in transsulfuration, one frequently sees associated elevations in androgens and elevations in homocysteine. For instance, several workers have found elevated levels of homocysteine in cases of polycystic ovary syndrome.[10,11] Normally, men have higher homocysteine levels than women, thought to be secondary to higher androgen levels.[12]

Androgen excess interferes with the conversion of homocysteine to cysthathionine, which by conversion to cysteine becomes a major source of glutathione.[13] Thus androgen excess can not only raise homocysteine levels, it can lower glutathione, a major antioxidant in brain. Other pathways in the methionine cycle are also affected, which may partially explain the significant reduction in methionine seen in autistic children, as well as s-adenosyl methionine levels.[4,14]

James et al found not only low total glutathione levels in autistic subjects but also oxidized glutathione levels that were 2-fold higher, which strongly indicate oxidative stress.[14] Several of