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Dysregulated redox balance associated with glutamate excitotoxicity in autism spectrum disorders

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Background: Autistic spectrum disorders (ASD) are characterized by three core behavioral domains: social deficits, impaired language and communication, and repetitive behaviors. Glutamate excitotoxicity has been found in various preclinical models of Autism Spectrum Disorders (ASD). On the other hand, inefficient detoxification system leads to oxidative stress, gut dysbiosis, and immune dysfunction has been also accepted as etiological mechanism of autism. In a trial to understand the relationship between glutamate excitotoxicity and impaired detoxification mechanisms, selected parameters representing both pathways will be measured in autistic patients compared to age and sex matching control participants.

Methods: 20 male autistic children aged 3-15 years and 20 age and gender matching healthy children as control group were included in this study. Levels of reduced glutathione (GSH), glutathione status (GSH/GSSG), glutathione reductase (GR), glutathione-s-transferase (GST), thioredoxin (Trx), thioredoxin reductase (TrxR) and peroxidoxins (Prxs I and III), glutamate, glutamine, glutamate/glutamine ratio glutamate dehydrogenase (GDH) in plasma and mercury in red blood cells were determined in both groups.

Results: Glutamate excitotoxicity was ascertained in autistic patients. While glutamate was significantly elevated, glutamine was remarkably lower, resulting in a much lower glutamate/glutamine ratio in autistic patients compared to control. Reduced glutathione, GSH/GSSG and activity levels of GST were significantly lower, GR shows non-significant differences, while, Trx, TrxR and both Prx I and III recorded a remarkably higher values in autistics compared to control subjects.

Conclusion: Multiple regression analysis show an association between glutamate excitotoxicity and GSH/GSSG, thioredoxin1, peroxidoxin1, thioredoxin reductase as oxidative stress related parameters. As the consensus among physicians who treat autism with a biomedical approach is that those on the spectrum are burdened with oxidative stress and excitotoxicity thus the glutamate system could be an excellent target for therapeutics.

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