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Abnormal Metal Homeostasis as a Key Regulator of Autism Spectrum Disorder Pathologies New Vistas for Treatment and Prevention Strategies

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Abstract

Since hundreds of years ago, metals have been recognized as impacting our body's physiology. However, the link between aberrant perinatal metal levels and neurodevelopmental disorders like Autism Spectrum Disorders (ASDs) is a relatively new finding. Toxic heavy metals are linked to ASD-relevant pathologies such as chronic inflammation/immune activation, mitochondrial malfunction, and increased oxidative stress. In particular, they compete with essential metals such as zinc, which may explain why both the presence of certain toxic metals and prenatal zinc deficiency have emerged as risk factors for ASD. Although often investigated separately, through the antagonistic effects, a common metal imbalance results that may be the underlying cause for gastrointestinal (GI) problems and brain abnormalities frequently reported in ASD. Ultimately, different genetic and environmental factors, such as metal imbalances, seem to converge on a neurobiological process that determines the characteristic ASD-linked behaviours. Our studies reveal that a critical convergence point is synaptic vesicle release and recycling. We could show that compromised GI barrier tightness (leaky gut) is zinc status-dependent, as are the key central nervous system processes such as synaptic vesicle recycling. Therefore, altering zinc signalling by removing competition with heavy metals and elevating zinc levels could be a preventive and treatment strategy for a large share of ASD cases caused by various genetic and non-genetic risk factors.