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Review

How environmental and genetic factors combine to cause autism: A redox/methylation hypothesis

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Abstract

Recently higher rates of autism diagnosis suggest involvement of environmental factors in causing this developmental disorder, in concert with genetic risk factors. Autistic children exhibit evidence of oxidative stress and impaired methylation, which may reflect effects of toxic exposure on sulfur metabolism. We review the metabolic relationship between oxidative stress and methylation, with particular emphasis on adaptive responses that limit activity of cobalamin and folate-dependent methionine synthase. Methionine synthase activity is required for dopamine-stimulated phospholipid methylation, a unique membrane-delimited signaling process mediated by the D4 dopamine receptor that promotes neuronal synchronization and attention, and synchrony is impaired in autism. Genetic polymorphisms adversely affecting sulfur metabolism, methylation, detoxification, dopamine signaling and the formation of neuronal networks occur more frequently in autistic subjects. On the basis of these observations, a ''redox/methylation hypothesis of autism'' is described, in which oxidative stress, initiated by environment factors in genetically vulnerable individuals, leads to impaired methylation and neurological deficits secondary to reductions in the capacity for synchronizing neural networks.
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Contents

During the past several decades the prevalence of autism and related pervasive developmental disorders in the U.S. has dramatically escalated to epidemic levels, affecting 3 in 10,000 children in 1970, but 66 in 10,000 in 2002 (Rice et al., 2007). The possible origins of this increase have been the subject of considerable public debate (Blaxill, 2004), and advances in detection and broadening of the diagnostic criteria for autism have been suggested to play a role (Fombonne et al., 2006), while genetic factors are clearly important, as indicated by high concordance rates among twins and siblings (Smalley et al., 1988). However, genetic factors alone cannot account for an epidemic that developed in the relatively short period of 10–20

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