Suppressed GABAergic inhibition as a common factor in suspected etiologies of autism

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The primary inhibitory and excitatory amino acid neurotransmitters are gamma-aminobutyric acid (GABA) and glutamate, respectively. Despite their pervasiveness in brain function and sensory processes, the amino acid neurotransmitters have received limited attention in the study of autism and related developmental disabilities. While the ubiquity of GABA and glutamate pathways in the CNS suggests that nearly every pathology will affect amino acid neurotransmission, the verification of specific impairments common to autism might help to intensify and narrow the focus of research.

Although it is possible that the breadth of impairments in autism are caused by multiple defects in relatively independent systems, autism may instead reflect dysfunction in a single factor shared in common by many systems. Specifically, the severe disruptions observed in autism may be linked to suppression of GABAergic inhibition, resulting in excessive stimulation of glutamate-specialized neurons and loss of sensory gating. This view recognizes the possibility of multiple etiologies in autism. That is, there may exist a spectrum of genetic and environmental factors which impair inhibitory tone in a manner that expresses itself as autistic pathology.

GABAergic inhibition may be suppressed both by direct impairment of GABA receptors, and by antagonism of GABAergic neurons bearing receptors sensitive to the glutamate analogue N-methyl-D-aspartate (NMDA). Loss of inhibitory control from GABAergic neurons may result in hyperexcitation of vulnerable target neurons, with preferential damage to large- to medium-sized pyramidal and multipolar neurons (Farber, Newcomer, & Olney, 1998).

The hypothesis of suppressed GABAergic inhibition in autism is based on two observations. First, pathology relating to GABA receptors emerges as a common factor in several suspected etiologies of autism. Second, both disinhibition of GABAergic influence (for example, via

ketamine antagonism of NMDA receptor-bearing inhibitory neurons), and excessive stimulation of non-NMDA glutamate receptors, generate pathology which mirrors that observed in autism.

Among the first 100 cases in the South Carolina Autism Project, the most prevalent genetic or environmental factor is abnormality of chromosome 15q. Specific candidate genes affected by duplication and deletion include genes for three GABA receptor subunits. Recent evidence associates at least one form of autism with a genetic marker in this region (Martin *et al.*, 2000). Autism also displays comorbidity with fragile-X syndrome. Possible GABAergic involvement is suggested by the Xq28 site, which codes for the alpha-3 subunit of the GABA-A receptor.

Among environmental factors, perinatal exposure to viral infection such as rubella and meningitis is associated with increased incidence of autism. Again, suppressed inhibitory tone emerges as a possible candidate mechanism. Animal studies indicate that rats infected with lymphocytic choriomeningitis virus during development demonstrate a loss of GABAergic inhibition as adults, long after the virus has been cleared. In turn, this disinhibition results in excessive glutamatergic stimulation of dentate granule cells.

Neuroanatomically, autistic individuals have been found to demonstrate loss of pyramidal neurons in the frontal cortex, limbic system abnormalities, and significant loss of Purkinje cells in the cerebellar hemispheres. These brain areas have specialized responses to glutamate, or are selectively vulnerable to stress from high glutamate levels. For example, in vitro evidence suggests that excessive glutamate activation of non-NMDA receptors reduces the number of synapses and the extent of dendrite growth in the pyramidal neurons of the hippocampus. Significantly, this finding is mirrored in neuroanatomic evidence which demonstrates decreased complexity and dentritic arborization in the pyramidal cells of autistic individuals.

While it is not easy to correlate pathology in any given brain region with a high density of glutamate terminals, a number of these regions exhibit an overlap of functional and anatomical

pathology in autism and related developmental disorders. For example, autistic subjects demonstrate severe deficits in neuropsychological tests of frontal cortex function. Compromised GABAergic inhibition would be consistent with these findings. Ketamine administration results in impaired test performance in frontal lobe tasks, as well as neuropsychological symptoms characteristic of autism and schizophrenia. Evidently, the primary mechanism is suppression of NMDA receptor-bearing GABAergic neurons, as ketamine appears to increase glutamatergic neurotransmission in the prefrontal cortex at non-NMDA glutamate receptors. Excessive glutamatergic stimulation is also associated with epileptiform activity, which is common in autistic subjects.

Wallenstein & Hasselmo (1997) describe a detailed biophysical model of hippocampal region CA3. Learning in the network of neurons was measured postsynaptically through NMDA-receptor mediated conductances. When GABA-receptor mediated inhibition at intrinsic fibers was removed from the model, the learning and recall performance of the network declined markedly. This occurred because sensory information was obscured by competing activity from intrinsic and afferent fibers. Such a model may provide a reasonable characterization of autism. That is, loss of inhibitory control may cause a deterioration in the quality of sensory information due to the failure to suppress competing "noise". The ability to process sensory information and learning tasks would then be overwhelmed. Indeed, many autistic behaviors appear to be mechanisms for restricting sensory input to a narrow, repetitive or controllable scope.

Finally, Minshew (1994) presents clinical evidence from MR spectroscopy of autistic subjects revealing a metabolic pattern consistent with excessive activation and membrane degradation of nerve cells, compared to normal controls. In the same study, autistic subjects demonstrated a robust inverse relationship between verbal IQ measures and abnormal metabolite levels.

In summary, the hypothesis of impaired amino acid neurotransmission in autism is consistent with a broad range of findings from neuroanatomic and neurobiological research. Moreover, several functional deficits in autism are consistent with dysfunction in brain regions dependent on GABAergic inhibitory tone, or having specialized responses or selective vulnerability to glutamate. The limbic structures, frontal cortex, and cerebellum appear particularly important due to their probable role in the integration of sensory input. Among several suspected etiologies of autism, the possibility of impaired inhibitory tone emerges as a common factor. Clearly, the hypothesis of suppressed GABAergic inhibition in autism must be considered both preliminary and speculative until further evidence is accumulated. Accordingly, the study of amino acid neurotransmission in autism, and related pharmacological interventions, may be promising areas for research.

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