Pharmacotherapy in autism: where to start?

Autism is a complex neurobiological syndrome that has a remarkable breadth in terms of etiologic heterogeneity and severity. The detection of abnormalities in neurotransmitters such as serotonin, glutamate and γ–aminobutyric acid (GABA) in patients with autism suggest that it could be worthwhile to concentrate research in these areas.

Several findings suggest that GABA pathways, which have been extensively studied in patients with epilepsy with some success, offer a good starting point to look for results that will translate into the improved evaluation and treatment of autism. First, changes in GABA levels in platelets, plasma and urine have been reported in autistic patients. Using a technique based on gas chromatography–mass spectrometry, Dhossche *et al.* [1] found an increase in GABA levels in the plasma of patients with autism. Second, a cluster of genes encoding for $GABA_A$-receptor subunits has been identified on chromosome 15 (15q11–13) and abnormalities in the long arm of this chromosome have been detected in a small proportion of autistic patients [2]. In addition, the $GABA_A$-receptor β3-subunit gene has been associated with autism. Third, abnormalities in the *RELN* gene coding for the extracellular protein reelin and reductions in reelin levels in the cerebellar cortex of patients with autism have been reported. Reelin plays a crucial role in defining architectonic patterns through the control of neuronal migration, axon growth and synaptic connectivity [3]. Fourth, Casanova *et al.* [4] have suggested that autism might result from important changes in the cortical organization of minicolumns. Minicolumns are anatomical units that are repeated throughout the neocortex and their function simultaneously reflects the holistic properties of the brain. Casanova and co-workers identified that minicolumns were more frequent and narrower in autistic patients. It has been proposed that deficits in GABAergic interneurons are associated with the narrowing of the minicolumns. This deficit in inhibition would provide a pathological relationship with some autistic symptoms. Furthermore, reelin appears to be involved in the development of these vertical columnar structures [3]. Fifth, a paradoxical effect of benzodiazepines on autistic patients has been described. Benzodiazepines, which are positive modulators of GABA metabolism, produced excitation, explosive aggression and anxiogenic effects, instead of anxiolitic effects, in autistic patients [5]. Finally, clinical observations also indicate a role for GABA in autistic disorder. By puberty, a third of autistic individuals will suffer from at least two unprovoked seizures [6]. In addition, several clinical manifestations in autism could potentially be explained as an altered processing of sensory input. Therefore, it is reasonable to propose that a disruption in the normal balance between excitation and inhibition could explain some of the most prominent features of the autistic condition, including hypersensitivity to different sensory stimulus, highly focused savant skills and eccentric behaviors [4].

Given all these seemingly unrelated findings, there is the potential to establish a coherent explanation that relates GABA, which is the most important inhibitory neurotransmitter in the cerebral cortex, with autism. Pharmacological treatment that targets the GABAergic pathway will perhaps improve the clinical manifestations of autism and will help to provide evidence for the role that alterations in GABAergic pathways play in the physiopathology of autism.

References

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