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CORRESPONDENCE

Autism treatments proposed by clinical studies and human genetics are complementary

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The article by Wittkowski *et al.*[1] reports results of human genetic studies that suggest that a nonsteroidal anti-inflammatory drug (NSAID) given for a few months from the time of the first symptoms might help some children who are at risk of developing more severe forms of atrial septal defect. While the authors mention the recent article by Lemonnier *et al.*,[2] which reported that a clinical study of the diuretic Bumetanide was partially effective in children with milder forms of autism, they seem to have overlooked that these two treatments may well be complementary, leading to sequential interventions, each targeting specific risks related to well-defined stages in the development of brain and social interactions.

Since abnormal brain development in autistic disorder goes through different stages from infancy to childhood, targeting different developmental stages with different treatment interventions may well be necessary to foster continued normalization of brain growth.

Bumetanide is known to block inward chloride transporters, yet the relation of this mechanism to the etiology of autism is unknown. Wittkowski *et al.* identified mutations in calcium-activated (outward) chloride channels as associated with autistic disorder, suggesting loss-of-function mutations in anoctamins as one of the risk factors for autism. This provides a testable hypothesis for the mechanism by which Bumetanide alleviates symptoms of autism. For example, mouse models could test whether Bumetanide ameliorates a stress-induced phenotype caused by a knockout/down in ANO2 and/or ANO4.

A second cluster of genes identified receptor protein tyrosine phosphatases, which downregulate growth factors. These findings support the notion that successful treatment should start as early as possible,[3] while neuronal development still takes place.

The rationale for combining these two treatments rests on the fact that Bumetanide is contraindicated in infancy because it is known to interfere with neuronal development when used long term. In contrast, the NSAID proposed in the second study has been given for decades to children with juvenile idiopathic arthritis from 6 months of age on, with no adverse effects on brain development. It is known to modulate chloride channels (see above) as well as potassium channels.[4]

In conclusion, I wish to extend their hypothesis based on the synergy of the two treatment approaches: (1) early treatment with NSAID can reduce early maladaptive behaviors that cause abnormal pruning of neurons in the cortical areas; (2) these children could subsequently benefit from Bumetanide, which would compensate for the primary ion channel defect, but could not reverse the secondary effect of abnormal pruning.

This hypothesis allows for a novel two-way interaction between behavior and molecular events. Traditionally, one assumes that molecular events determine behavior. The new hypothesis, based on human genetics, also allows for symptoms (such as the absence of social interactions, delayed speech onset and language development) during certain sensitive periods to change molecular events (pruning of neurons in areas required for normal development).

CONFLICT OF INTEREST

The author declares no conflict of interest.

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