Upsetting the Excitatory-Inhibitory Balance Hypothesis of Autism

Editor's Choice Summary

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Overline: Autism Spectrum Disorder

Title: Upsetting the Excitatory-Inhibitory Balance Hypothesis of Autism

One-sentence summary: Increased excitatory-inhibitory ratio of neuronal activity may be protective rather than pathological in mouse model of autism.

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Text of summary

One of the conceptual frameworks used to explain pathological changes in the autistic brain is an increase in the ratio of excitatory to inhibitory (E-I) neuron activity. This hypothesis is based largely on the symptoms associated with Autism Spectrum Disorders (ASD), including seizures and hypersensitivity to sensory information. As more information is gathered regarding the interplay of excitation and inhibition in the nervous system, the E-I balance hypothesis of autism has been investigated in several studies with mixed results.

Antoine *et al.* tested the E-I hypothesis in a systematic fashion using four genetically defined mouse models of ASD. Their investigation centered on the layer (L) 4 to L2/3 circuit in the barrel cortex, critical for integrating sensory information from the whiskers. In an elegant series of experiments, E-I ratio was measured using electrophysiological recordings of excitatory and inhibitory currents in L4 neurons, and compared to the neuronal firing activity evoked in L2/3.

In keeping with several previous studies, the authors found changes in both excitatory and inhibitory currents that resulted in an increase in the E-I ratio in all four mutant models. However, to their surprise, the increase in E-I ratio did not result in the predicted increase in neuronal firing that would be suggestive of hyperexcitability. Computer modeling suggested the increase in E-I ratio served to stabilize output that would otherwise become unbalanced by changes in excitation or inhibition alone. The intriguing suggestion is that an increase in E-I balance does not contribute to hyperexcitability in autism and may in fact be an adaptive compensation.

The results of this study call into question the causal contribution of E-I imbalance to ASD pathology, and have important implications for researchers and clinicians pursuing therapies that dampen excitation in the autistic brain. However, the experiments were performed on only one of the multitude of brain circuits, using a subset of genetically defined ASD models. Future investigations of excitatory and inhibitory activity in additional ASD brain circuits and models will ultimately determine whether changes in E-I balance are helpful or harmful, and whether the E-I balance hypothesis of autism should be revisited.

Highlighted Article

M.W. Antoine, T. Langberg, P. Schnepel, D.E. Feldman. Increased Excitation-Inhibition Ratio Stabilizes Synapse and Circuit Excitability in Four Autism Mouse Models. *Neuron*. **101**(4):648-661.e4. 10.1016/j.neuron.2018.12.026 (2019).

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