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Excitation/Inhibition Imbalance in Animal Models of Autism Spectrum Disorders

Eunee Lee, Jiseok Lee, and Eunjoon Kim

ABSTRACT

Imbalances between excitation and inhibition in synaptic transmission and neural circuits have been implicated in autism spectrum disorders. Excitation and inhibition imbalances are frequently observed in animal models of autism spectrum disorders, and their correction normalizes key autistic-like phenotypes in these animals. These results suggest that excitation and inhibition imbalances may contribute to the development and maintenance of autism spectrum disorders and represent an important therapeutic target.

Keywords: Autism spectrum disorders, Circuit, Excitation/inhibition balance, Mouse models, Psychiatric disorders, Synapse

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A tight balance between excitation and inhibition (E/I balance) in synaptic inputs to a neuron and in neural circuits is important for normal brain development and function. Accordingly, disturbed E/I balances have been implicated in various brain disorders, including autism spectrum disorders (ASDs) (1–6). An early, illuminating review by Rubenstein and Merzenich (1) suggested the hypothesis that an increased E/I ratio in sensory, mnemonic, social, and emotional systems can cause ASDs. Since that time, a large body of clinical and neurobiological data has accumulated to support and refine this hypothesis.

ASDs represent neurodevelopmental disorders characterized by social deficits and repetitive behaviors and accompanying comorbidities, including intellectual disability, epilepsy, hyperactivity, and anxiety. ASDs are associated with heterogeneous genetic variations, and the number of ASD-associated genes has risen to approximately 800 (7). ASDs are now the subject of intense worldwide investigations that seek to identify key underlying mechanisms capable of accounting for a large portion of ASD-related genetic variations and thus can serve as important therapeutic targets.

This review summarizes results from animal models of ASD showing altered E/I balances. E/I balance is established and tightly regulated by a large number of factors, making it difficult to differentiate primary changes from secondary alterations in model animals, as was recently noted (3). Therefore, the emphasis is on those models that demonstrate rescue of ASD phenotypes using pharmacologic or cell type–specific gene-rescue approaches, or those models that use conditional gene-ablation approaches. Though valuable, other studies, including some that do not strongly support a causal relationship between the observed E/I imbalances and autistic-like phenotypes, are unavoidably less highlighted.

E/I IMBALANCE AND AUTISTIC-LIKE BEHAVIORS

Abnormal connectivity and neural integration (or temporal binding), manifesting as abnormal brain rhythms, have been suggested to underlie ASDs (8). Recent optogenetic studies have demonstrated that gamma-aminobutyric acidergic (GABAergic) interneurons expressing the calcium-buffering protein parvalbumin (PV) drive gamma rhythms and promote cortical circuit performance and cognitive flexibility (9,10). Importantly, a recent study has demonstrated that optogenetic stimulation of pyramidal neurons in the medial prefrontal cortex in mice induces social deficits associated with enhanced gamma oscillations, whereas coactivation of PV and pyramidal neurons does not induce social deficits (11). These results collectively suggest that an increased neocortical E/I ratio caused by malfunctions of PV-expressing interneurons induces excessive gamma oscillations and autistic-like behaviors.

FACTORS CONTRIBUTING TO E/I IMBALANCE

Neuronal E/I balance involves regulation at synaptic or circuit levels. Specific factors that contribute to synaptic E/I balance would include excitatory/inhibitory synapse development, synaptic transmission and plasticity, downstream signaling pathways, homeostatic synaptic plasticity, and intrinsic neuronal excitability (Table 1). At the circuit level, E/I balance involves local circuits such as the interplay between GABAergic interneurons and target pyramidal neurons, which would modulate long-range connections.

EXCITATORY SYNAPSE DEVELOPMENT

Cell adhesion molecules organize synapse development through transsynaptic adhesion and synaptic protein recruitment. Neuroligins and neurexins are prototypical members (6),

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Table 1. Mechanisms Underlying E/I Imbalances in Animal Models of ASD

E/I Imbalance Mechanisms	Examples of Animal Models of ASD
Excitatory Synapse Development	*Eif4ebp2* (12)
AMPARs	BTBR (14), *Emx1-Cre;Syngap1*$^{+/fl}$ (35), *Emx1-Cre;Syngap1*$^{+/lox\text{-}stop}$ (35), *Mecp2* (28,29), *Mecp2*^{Tg1} (31), *Shank3* duplication (27), *Shank3* (various exon deletions) (19–24), *Tau-Mecp2* (30), *Syngap1*$^{+/-}$ (34), *Ube3a* (15)
NMDARs	*Baiap2* (IRSp53) (53), BALB/c (46,47), BTBR (45), *Grid1* (GluD1) (44), *Grin1* (GluN1) (37), *Nlgn1* (38), Rats with low prosocial USVs (48), *Shank2* (exons 6–7) (39,40), *Shank2* (exon 7) (41), *Shank3* (exons 4–9) (18), *Shank3* (exon 21G) (23), *Shank3*$^{+/\Delta C}$ (43), *Tbr1*$^{+/-}$ (40,42), VPA rats and mice (49–52)
mGluRs	*Baiap2* (IRSp53) (53), BTBR (61–63), *Fmr1* (57–60,64,65), *Nlgn3* (88), *Shank2* (exons 6–7) (39)
Signaling Pathways	BTBR (82), *Cntnap2* (79), *Emx1-Cre;Tsc1* (71), *Fmr1* (76,78,81), *Nf1*$^{+/-}$ (77), *Nse-Cre;Pten* (69), *Pcp2/L7-Cre;Tsc1* (70), *Tsc2*$^{+/-}$ (72–74), *Ube3a* (15,75), *Shank3*$^{+/\Delta C}$ (43)
Inhibitory Synapse Development and Function	*D1-Cre;Nlgn3* (89), *Fmr1* (92–94,96–98), *Gabrb3* (90,91), *Nlgn2* (84,85), *Nlgn3* (86,87,89), *Nlgn3* R451C (86,87,89), *Ube3a* (101,102)
Interneurons	BTBR (95,106,119), *Cntnap2* (79,113), *Cntnap4* (80), *Dlx1/2;Scn1a*$^{+/fl}$ (118), *Dlx5/6-Cre;Tsc1* (110), *Fmr1* (108), *Gad2* (GAD65) (106), *Mecp2* (106,120), *Nkx2.1-Cre;Pten* (109), *Nlgn3* R451C (2), *Oxtr* (127), *Pvalb* (112), *PV-Cre;ErbB4* (123), *Pv-Cre;Mecp2* (107), *PV-RFP;Shank1* (111), *Scn1a*$^{+/-}$ (118), *Scn1a*$^{+/R1407X}$ (117), *Shank3* (exons 13–16) (106), *SST-Cre;Mecp2* (107), *SynI* (121,122), *Ube3a* (126), *Viaat-Cre;Mecp2* (120), VPA mice (2)
Glial Cells	*Gfap-Cre;ERT2;Mecp2*$^{lox\text{-}stop/y}$ (130), *Gfap-Cre;Pten* (129), *Glast-CreERT2;Glt1* (128), *Lysm-Cre;Mecp2*$^{lox\text{-}stop/y}$ (131)
Intrinsic Neuronal Excitability	*Nestin-Cre;Foxp1* (133), *Fmr1* (134), *Pv-Cre;ErbB4* (124,125), *Shank3* (exons 13–16) (135)
Homeostatic Synaptic Plasticity	*Fmr1* (140,141), *Mecp2* (137–139)
Temporal E/I Regulation	*CreERT2;MECP2* and *TG;Mecp2*$^{lox/y}$ (148), *CreERT2;Syngap1*$^{+/lox\text{-}stop}$ (146), *CreEsr1*;Mecp2*$^{lox\text{-}stop/y}$ (147), *CreEsr1*;Ube3a*$^{Stop/p}$ (149), *Fmr1* (144,145), *Nlgn3*$^{stop\text{-}tetO}$*;Pcp2*^{tTA} (88), VPA rats (144,145)

Candidate mechanisms involved in causing E/I imbalances in some animal models of ASD. In some cases, more than one mechanism appears to apply to the same mouse model, possibly due to multiple effects of a single mutation or homeostatic interplay among different mechanisms. Additional studies may be needed to determine whether certain mechanisms listed here represent primary changes and, hence, fundamental pathogenic mechanisms. Heterozygosity and conditional gene deletion or re-expression are indicated; all other gene names without additional identifiers represent homozygosity (–/– or fl/fl) or X chromosomal/maternal deletion (*Mecp2*$^{-/y}$;*Ube3a*$^{m-/p+}$). Full names of the genes and their known functions are as follows: *Baiap2* (brain-specific angiogenesis inhibitor 1-associated protein 2; also known as IRSp53; excitatory postsynaptic adaptor and scaffolding protein); *Cntnap2/4* (contactin-associated protein-like 2/4; a member of the neurexin family of cell protein 2); *Eif4ebp2* (a member of the eukaryotic translation initiation factor 4E binding protein family; bind eIF4E and inhibit translation initiation); *ErbB4* (erb-b2 receptor tyrosine kinase 4; a receptor for neuregulins with tyrosine kinase activity); *Fmr1* (fragile X mental retardation 1; an RNA-binding protein that regulates messenger RNA trafficking); *Foxp1* (forkhead box P1; a transcription factor); *Gabrb3* (gamma-aminobutyric acid A receptor subunit beta 3; a GABA receptor subunit); *Gad2* (glutamic acid decarboxylase 2; also known as GAD65; a GABA-synthesizing enzyme); *Glt1* (solute carrier family 1 [glial high affinity glutamate transporter], member 2; also known as Sla1a2 or EAAT2, a glutamate transporter); *Grid1* (glutamate receptor, ionotropic, delta 1; also known as GluD1; a subunit of glutamate receptors); *Grin1* (glutamate ionotropic receptor NMDA type subunit 1; also known as GluN1; an NMDA receptor subunit); *Mecp2* (methyl CpG binding protein 2; a transcription factor that binds to methylated DNA); *Nf1* (neurofibromin 1; a negative regulator of ras signaling); *Nlgn1/2/3* (neuroligin 1/2/3; a synaptic cell adhesion molecule); *Oxtr* (oxytocin receptor); *Pten* (phosphatase and tensin homolog; a phosphatase for phosphoinositides); *Pvalb* (parvalbumin; a calcium ion-binding protein); *Scn1a* (sodium voltage-gated channel alpha subunit 1; a subunit of voltage-dependent sodium channels); *Shank1/2/3* (excitatory postsynaptic scaffolding proteins); *Syngap1* (synaptic Ras GTPase activating protein 1, excitatory postsynaptic scaffolding protein with GTPase-activating protein activity); *SynI* (synapsin I; a protein that associates with synaptic vesicles); *Tbr1* (T-box, brain 1; a transcription factor); *Tsc1/2* (tuberous sclerosis 1; a growth inhibitory protein); *Ube3a* (ubiquitin protein ligase E3A; an E3 ubiquitin-protein ligase).

AMPAR, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; E/I, excitation/inhibition; GABA, gamma-aminobutyric acid; GTPase, guanosine triphosphatase; mGluR, metabotropic glutamate receptor; NMDAR, *N*-methyl-D-aspartate receptor; USV, ultrasonic vocalization; VPA, valproic acid.

and many additional molecules have recently been identified. Given their critical roles in synapse and circuit development, it is no wonder that neuroligin and neurexin genes have been among the first ASD-related genes identified in early autism studies (6). Contrary to initial expectations, however, neuroligin/neurexin knockout in mice did not induce significant changes in synapse number, except in a few specific brain regions; instead, it substantially modified synaptic functions (6), which may also contribute to impaired synaptic development in ASDs.

A recent study has shown that neuroligin expression can be altered indirectly. Knockout of 4E-BP2, known to inhibit eIF4E in the mechanistic target of rapamycin (mTOR) pathway in mice (*Eif4ebp2*, a member of the eukaryotic translation initiation factor 4E binding protein family), upregulates neuroligins (all four known isoforms), increases hippocampal synaptic E/I ratio, and induces autistic-like behaviors (12). Pharmacologic inhibition of eIF4E, or knockdown of neuroligin-1 (*Nlgn1*) but not neuroligin-2 (*Nlgn2*), which are excitatory and inhibitory synapse specific, respectively (6), normalizes the E/I ratio and rescues autistic-like behaviors.

AMPA RECEPTORS

Glutamatergic dysfunction involving alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), *N*-methyl-D-aspartate (NMDA), and metabotropic glutamate (mGluR) receptors (AMPARs, NMDARs, and mGluRs) alters E/I balance. Supporting the role of AMPARs, social deficits in BTBR mice, an inbred mouse strain modeling ASD (13), are rescued by the AMPAR-activator ampakine (14). Ampakine also rescues impaired long-term potentiation (LTP) and long-term memory in Ube3a-deficient mice (*Ube3a*$^{m-/p+}$) that lack the maternal copy of an E3 ubiquitin ligase gene (15), a model of Angelman syndrome, characterized by intellectual disability,

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