Mini-Symposium

Emerging Mechanisms Underlying Dynamics of GABAergic Synapses

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Inhibitory circuits are diverse, yet with a poorly understood cell biology. Functional characterization of distinct inhibitory neuron subtypes has not been sufficient to explain how GABAergic neurotransmission sculpts principal cell activity in a relevant fashion. Our Mini-Symposium brings together several emerging mechanisms that modulate GABAergic neurotransmission dynamically from either the presynaptic or the postsynaptic site. The first two talks discuss novel developmental and neuronal subtype-specific contributions to the excitatory/inhibitory balance and circuit maturation. The next three talks examine how interactions between cellular pathways, lateral diffusion of proteins between synapses, and chloride transporter function at excitatory and inhibitory synapses and facilitate inhibitory synapse adaptations. Finally, we address functional differences within GABAergic interneurons to highlight the importance of diverse, flexible, and versatile inputs that shape network function. Together, the selection of topics demonstrates how developmental and activity-dependent mechanisms coordinate inhibition in relation to the excitatory inputs and vice versa.

Key words: **CaMKIIa; gephyrn; homeostatic plasticity; interneurons; KCC2; postsynaptic density**

Introduction

The mechanisms underlying the control of the neuronal networks by inhibitory neurons have become a central topic of investigation in neuroscience. As studies advance, it is becoming clear that inhibitory neurotransmission is dynamic in nature and facilitates a diverse range of functions, including dendritic integration, control of neural excitability, circuit reorganization, and fine-scale refinement of network activity.

Diverse inhibitory neuron populations ensure morphological and functional specificity of GABA signaling on principal cells in a coordinated fashion (Klausberger and Somogyi, 2008; Lapray et al., 2012). Specific subcellular targeting (e.g., dendrites, soma, axon-initial segment) of postsynaptic cells by different GABAergic neurons contributes to input differences; similarly, heterogeneity within postsynaptic compartments is considered to couple inhibitory neuron-specific inputs to principal cell outputs. However, molecular events governing input coupling at different GABAergic postsynaptic sites are currently not fully understood. It is easy to conceive that many of the functional processes involving circuit maturation and fine-scale refinement of network activity depend on interactions between GABAergic and glutamatergic synapses. Hence, it is not surprising that several neurodevelopmental and neuropsychiatric disorders implicate both excitatory and inhibitory neurotransmission systems (Rubenstein and Merzenich, 2003; Nelson and Valakh, 2015; Mullins et al., 2016).

A major tenet of our Mini-Symposium is that synaptic and circuit adaptability relies on signaling cascades regulating in parallel, or even coregulating, the efficacy of GABAergic and glutamatergic transmission. Such convergence becomes apparent when concerted changes in synaptic function are produced by specific proteins, signaling molecules, as well as in the differential regulation of interacting protein complexes that are present at both excitatory and inhibitory postsynaptic compartments. This Mini-Symposium will provide evidence for six emerging concepts in the field of GABAergic inhibitory neurotransmission: (1) intrinsic molecular mechanisms coordinate excitatory and inhibitory synaptogenesis in the postsynaptic neuron; (2) developmental control of Gi/o coupled signaling shapes the function of a subset of parvalbumin (PV) interneurons in mouse PFC; (3) intracellular signaling cascades modulate synaptic protein scaffold for dynamic GABAergic neurotransmission; (4) local synaptic interactions and diffusion events coordinate glutamatergic and GABAergic synaptic plasticity; (5) protein moonlighting between glutamatergic and GABAergic synapses couple chloride homeostasis and synapse function; and (6) distinct inhibitory inputs refine and define cortical networks. The common

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thread for these apparently disparate topics is the discussion of "mechanisms regulating dynamics at GABAergic synapses."

Developmental and neuron specific contributions to excitatory/inhibitory (E/I) ratios

Postsynaptic mechanisms coordinating excitatory and inhibitory synaptogenesis

The proportion of excitatory and inhibitory synapses (E/I ratio) is established early in life, before fine-scale experience-dependent refinement (Zhao et al., 2005; Soto et al., 2011; Froemke, 2015). Yet, the cell-autonomous, genetic mechanisms coordinating the development of both types of synapses are poorly understood. Recent reports on the role of a gene specifically duplicated in humans, *SRGAP2* (Slit-Robo Rho GTPAse-activating protein 2), have provided new insights into the balanced development of excitatory and inhibitory synapses.

The parental gene, SRGAP2A, is highly expressed during synaptogenesis (Guerrier et al., 2009). It accumulates at both excitatory and inhibitory synapses (Fossati et al., 2016), where it promotes their maturation and limits their density. Partial duplication of *SRGAP2A* generated a human-specific gene, *SRGAP2C*, at a time corresponding to the emergence of *Homo* (Charrier et al., 2012; Dennis et al., 2012). SRGAP2C is expressed in the human brain along with *SRGAP2A* and inhibits its function (Charrier et al., 2012; Dennis et al., 2012). Similarly, in mouse neurons, SRGA2C expression or SRGAP2A inactivation delays the maturation of excitatory and inhibitory synapses, also increasing both inhibitory and excitatory synapse density. Cortical pyramidal neurons expressing SRGAP2C exhibit dendritic spines with longer necks, along with a higher occurrence of inhibitory synapses formed directly on spines. These morphological changes reflect an increased compartmentalization of synapses, which are more frequently silent in juvenile mice (Charrier et al., 2012; Fossati et al., 2016). Protracted maturation, increased synaptic density, and increased morphological complexity characterize human cortical pyramidal neurons compared with rodents or nonhuman primates (Defelipe, 2011). This suggests that SRGAP2 genes support E/I coordination in mammalian species and may contribute to distinctive properties of human neurons.

Biochemical characterization and *in vivo* molecular dissection of SRGAP2A function demonstrated that the protein interacts, via distinct functional domains, with major excitatory and inhibitory postsynaptic scaffolding proteins, namely, homer and gephyrin (Okada et al., 2011; Fossati et al., 2016), through which it promotes excitatory and inhibitory synaptic maturation, respectively. Furthermore, SRGAP2A limits the density of both types of synapses through its Rac1-GAP activity. With regard to inhibitory synapses, this unravels the role of SRGAP2A in promoting the growth of gephyrin clusters and the accumulation of $GABA_A$ receptors. It also highlights the role of Rac1 signaling in regulating the density of inhibitory synapses within dendrites and their subcellular distribution. Together, it is emerging that proteins, such as SRGAP2, cannot be classified as excitatory or inhibitory synapse component, instead go on to create a novel class of shared molecular component, which plays a key role in E/I coordination.

Neuronal cell specific contribution to GABAergic inhibition

Single-cell RNA sequencing (RNA-seq), combined with classical single-cell morphological and electrophysiological analysis, represents a powerful tool to disclose the exquisite functional diversity of inhibitory neuron subtypes within specific brain regions (Cembrowski et al., 2016; Tasic et al., 2016). This graded change in neuronal identity is emerging as a general feature defining neuronal development, connectivity, and function.

One specific example of cell type specific gene expression that contributes to functional identity is the $G_{i/o}$ protein-coupled cannabinoid receptor (CB1r). Widely distributed in the brain, CB1r were originally thought to be localized predominantly at cholecystokinin (CCK^+) presynaptic terminals where they modulate synaptic transmission and activity-dependent synaptic plasticity. However, development of novel experimental tools in recent years has identified these receptor expression and function within diverse other cell types (including glutamatergic and serotoninergic neurons, among others) (for an extensive review, see Busquets-Garcia et al., 2017), unraveling an extraordinary complexity, whose functional implications are far from being fully deciphered.

Intriguingly, the expression of CB1r is highly developmentally regulated (Caiati et al., 2012; Long et al., 2012; Yoneda et al., 2013) and plays a central role in critical period plasticity in somatosensory (Liu et al., 2008), visual (Jiang et al., 2010; Garkun and Maffei, 2014), and PFC (Cass et al., 2014; Lee et al., 2016; Renard et al., 2016; Rubino and Parolaro, 2016). However, despite the wealth of studies linking age-dependent CB1r disruption to altered cortical maturation and function (Cass et al., 2014; Raver and Keller, 2014), the precise underlying cellular mechanisms remain poorly understood.

Recent work showed that CB1r are also localized at the somatodendritic compartment in a subset of pyramidal neurons in hippocampal CA1 and regulate hyperpolarization-activated cyclic nucleotide-gated (HCN)-mediated h-current (Ih) (Maroso et al., 2016). Intriguingly, HCN channel can be enriched in parvalbumin-expressing (PV^+) neurons (Omrani et al., 2015), which orchestrate cortical critical period plasticity (Hensch, 2005). New experimental evidence has revealed a surprising cell-autonomous and developmental modulation of Ih by CB1r in a subset of PV^+ neurons in mouse PFC and visual cortex, highlighting a novel functional identity for a subset of PV^+ cells and linking CB1r modulation of Ih currents to GABAergic inhibition.

Shared molecular pathways for plasticity at excitatory and inhibitory postsynaptic sites

Post-translational modification of protein scaffold regulates dynamic GABAergic neurotransmission

The generation and characterization of various knock-out mice lines for specific $GABA_A$ receptor ($GABA_AR$) subunits advanced the morphological and functional understanding of circuit-specific $GABA_AR$ in the rodent brain (Rudolph and Möhler, 2014). The protein identified to play a preeminent role in the formation and maintenance of the inhibitory postsynaptic density is gephyrin, a multifunctional scaffolding protein that interacts with numerous signaling molecules, and with $\alpha1$, $\alpha2$, and $\alpha3$ subunit-containing $GABA_AR$ (Tyagarajan and Fritschy, 2014).

Synaptic proteins are often heavily regulated by diverse post-translational modifications, including phosphorylation, acetylation, SUMOylation, ubiquitination, palmitoylation, nitrosylation, proteolytic cleavage, etc. (Tyagarajan and Fritschy, 2014). However, regulation of post-translational modifications for GABAergic synaptic function has received less attention so far compared with glutamatergic postsynapse. Several signal transduction pathways crosstalk to influence gephyrin post-translational modification, and, in turn, altering protein networks at synapses (Ghosh et al., 2016). Although these modifications are often reversible, they impact the biochemical properties of gephyrin, initiating long-lasting downstream signaling changes. Post-translational modifications of synaptic proteins are known to regulate intracellular

trafficking, synapse turnover, and protein conformation changes leading to the formation of new protein networks, etc. Therefore, signaling pathways offer a dynamic springboard for adapting synaptic strength over vastly different time scales, and responding to specific synaptic inputs to ensure stability of neuronal networks following changes in connectivity or activity.

Several studies demonstrated that variations in inhibitory synaptic strength closely match changes in synaptic accumulation of gephyrin (Charrier et al., 2010; Muir et al., 2010; Tyagarajan et al., 2013; Petrini et al., 2014; Flores et al., 2015). In addition, phosphorylation, nitrosylation, palmitoylation, acetylation, and SUMOylation pathways converge onto GABAergic postsynaptic density and influence inhibitory neurotransmission (Tyagarajan et al., 2011, 2013; Dejanovic et al., 2014; Ghosh et al., 2016). More importantly, these observations have given support to the notion that GABAergic synapses are highly dynamic structures. Identification and characterization of gephyrin at the resolution of single amino acid provide the necessary molecular tools to render GABAergic synapses insensitive to specific signal transduction pathways. For example, ERK1/2 and GSK3β pathways reduce GABAergic neurotransmission by phosphorylating gephyrin at S268 and S270, respectively, resulting in destabilization of inhibitory synapses. In addition, NMDAR activity causes gephyrin phosphorylation at S305 by the CaMKIIα pathway, leading to activity-dependent adaptation at the GABAergic postsynapse (Flores et al., 2015).

Such dynamic interactions between signaling pathways may be at play in processes that have the potential to destabilize networks, such as synapse strengthening as a consequence of learning and memory consolidation. The evidence supporting common signaling pathways between GABAergic and glutamatergic synapse in baseline transmission and plasticity further demonstrates the need to explore the full extent of their molecular overlap and determine possible pathways of interactions.

Local synaptic interactions and diffusion events coordinate glutamatergic and GABAergic synaptic plasticity

The use of single-particle tracking techniques to study the lateral mobility of surface neurotransmitter receptors has offered a unique opportunity to investigate the implications of $GABA_AR$ recruitment at synapses to adjust synaptic strength (Choquet and Triller, 2013; Petrini and Barberis, 2014). Sustained network activity reduces inhibitory synaptic strength through the dispersal of $GABA_AR$ from synapses due to calcineurin-dependent increased lateral mobility of synaptic $GABA_ARs$ (Bannai et al., 2009; Muir et al., 2010). Rapid dispersal of $GABA_AR$ leading to reduced inhibition is paralleled by the decreased clustering of gephyrin clustering (Bannai et al., 2009). In a reverse paradigm, Petrini et al. (2014) studied the mechanisms potentiating inhibitory neurotransmission and reported induction of chemical inhibitory LTP, where $GABA_ARs$ are confined and immobilized at synapses while extrasynaptic gephyrin is actively recruited to synaptic compartments, leading to larger scaffolding. Such increase of both $GABA_AR$ and gephyrin at synapses during inhibitory LTP requires the phosphorylation of the $GABA_AR$-β3 subunit by CaMKIIα. Likewise, the CaMKIIα phosphorylation of β3: (1) increases the surface expression of $GABA_ARs$ (Houston and Smart, 2006); (2) modulates the amplitude and the kinetics of synaptic currents (Houston et al., 2008); and (3) promotes the exocytosis of the α5-containing $GABA_AR$ mediating inhibitory tonic currents (Saliba et al., 2012). In line with these findings, CaMKIIα activity has been implicated in postsynaptic mIPSC potentiation both at cerebellar (Kano et al., 1996) and hippocampal inhibitory synapses (Marsden et al., 2007). Taking into account the well-established roles for CaMKIIα in glutamatergic synaptic plasticity (Herring and Nicoll, 2016), it is emerging that CaMKIIα signaling contributes to both excitatory and inhibitory synaptic plasticity. Most kinases may phosphorylate many proteins at both excitatory and inhibitory synapses. However, selective control of phosphorylation (or other post-translational modification) at excitatory or inhibitory synapses, in contrast, may be crucial for the coordination of plasticity and synapse crosstalk.

The notion that neuronal activity may concomitantly elicit inhibitory and excitatory synaptic plasticity poses the obvious question about the spatial rules of such plasticity interplay. Glutamatergic LTP can be restricted to single-spine level (Matsuzaki et al., 2004), and dendritic calcium signaling can be shaped at single inhibitory and excitatory inputs (Chiu et al., 2013). Thus, interactions between plasticity at glutamatergic and GABAergic synapses are likely to occur in microdomains generated by diffusion of calcium, CaMKIIα, or other signaling molecules. Recently, it was revealed that desensitized $GABA_ARs$ may laterally diffuse from a "donor" GABAergic synapse to an adjacent "acceptor" GABAergic synapse (spaced by 2–4 μm), where inclusion of desensitized receptors decreases the amplitude of synaptic inhibitory signals (de Luca et al., 2017). Interestingly, intracellular calcium rise due to activation of intercalated glutamatergic synapses limits the receptor diffusion-dependent functional interplay among neighboring GABAergic synapses. This short-term synaptic plasticity paradigm reveals the general concept that "local synaptic interactions" and "diffusion events" significantly shape synaptic signaling, implying that the relative distance/distribution of glutamatergic and GABAergic synapses along dendrites is an important player in activity-dependent modifications of synaptic strength.

Proteins moonlighting between GABAergic and glutamatergic synapses couple chloride homeostasis with synapse function

The strength of GABAergic transmission not only depends on synaptic conductance mediated by Cl^--permeable $GABA_ARs$ but is also dependent on the gradient for Cl^- across the neuronal membrane. The neuronal Cl^- gradient is dynamically regulated by the cation-chloride cotransporters NKCC1 and KCC2 (Kaila et al., 2014). During embryonic development, NKCC1 expression is relatively high compared with KCC2, resulting in elevated neuronal Cl^-, which renders GABAergic transmission excitatory (Pfeffer et al., 2009). Early in postnatal development, upregulation of KCC2, which transports Cl^- out of the neuron, lowers intracellular Cl^-, resulting in hyperpolarizing inhibitory GABAergic transmission in the mature CNS (Rivera et al., 1999; Acton et al., 2012). Thus, KCC2 is primarily responsible for what is commonly termed the GABA "switch" from excitation to inhibition (Ben-Ari et al., 2012).

Despite the importance of KCC2 for inhibition, multiple independent lines of evidence indicate that KCC2 is highly localized at excitatory postsynaptic sites: (1) immunogold electron microscopy and single-particle tracking data reveal that KCC2 is highly expressed in the vicinity of excitatory synapses (Gulyás et al., 2001; Chamma et al., 2013); (2) KCC2 plays a critical role in spine formation, excitatory synaptogenesis, and synaptic plasticity (Li et al., 2007; Gauvain et al., 2011; Chamma et al., 2012; Fiumelli et al., 2013; Chevy et al., 2015; Llano et al., 2015); and (3) KCC2 interacts with proteins associated with neuronal excitation (Banke and Gegelashvili, 2008; Ivakine et al., 2013; Mahadevan et al., 2014; Mahadevan and Woodin, 2016; Pressey et al., 2017).

More recent quantum-dot-based single-particle tracking of KCC2 in cultured hippocampal neurons reported that KCC2 laterally diffuses in the surface membrane; however, this diffusion is constrained in the vicinity of synapses (Chamma et al., 2013). Although KCC2 dwells relatively longer at excitatory synapses, it also resides at inhibitory synapses, albeit for significantly shorter periods of time (Chamma et al., 2013). The mechanism underlying the relatively tight confinement of KCC2 to excitatory synapses involves a KCC2-actin interaction, whereas the mechanism for confinement at inhibitory synapses is unknown. Thus, KCC2 appears to be a "moonlighting" protein, where individual transporter molecules can shuttle between inhibitory and excitatory synapses.

Activity regulates the confinement of KCC2 at excitatory synapses via an NMDAR-mediated Ca^{2+} influx, which dephosphorylates the S940 residue and activates calpain protease cleavage of the transporter, resulting in reduced KCC2 clustering and transport (Chamma et al., 2013). Not only does excitatory synaptic transmission affect KCC2 expression and function, but KCC2 also regulates excitatory synapses. Specifically, KCC2 influences postsynaptic AMPAR content (Gauvain et al., 2011) and gates activity-driven AMPAR traffic (Chevy et al., 2015). Thus, the moonlighting of KCC2 between excitatory and inhibitory synapses could play an essential role in dynamically regulating synapse equilibrium.

Detailed analysis of KCC2 interactome has revealed 181 protein interaction partners in the mouse brain (Mahadevan et al., 2017). Of these interacting proteins, 60% are localized at either excitatory or inhibitory synapses, ~43% are exclusively expressed at excitatory synapses, whereas only ~2% are exclusive to inhibitory synapses. Ingenuity pathway analysis identified excitatory synapse-enriched regulators of receptor recycling as top candidates for determining KCC2 expression at excitatory synapses. Furthermore, pathway analysis also identified many regulators of dendritic cytoskeleton, suggesting that these are likely candidates for constraining KCC2 at excitatory synapse loci. In addition, ~15% of proteins in the interactome are found at both inhibitory and excitatory synapses, suggesting that KCC2 moonlighting between synapses might subserve previously unrecognized biological functions (Mahadevan et al., 2017).

What does the emerging moonlighting of KCC2 between inhibitory and excitatory synapses reveal about KCC2 function and the dynamic nature of inhibition? Ionotropic and/or metabotropic glutamate receptor could regulate KCC2 function and, thus, the strength of inhibition in the immediate vicinity of excitatory synapses. Such a notion is supported by evidence showing that inhibitory synapses can be in very close proximity to excitatory synapses (Wang et al., 2004; Chen et al., 2012; Chiu et al., 2013; Higley, 2014). Furthermore, independent studies reported activity-dependent regulation of KCC2 for inhibitory synaptic plasticity (Woodin et al., 2003; Fiumelli et al., 2005; Ormond and Woodin, 2009; Lamsa et al., 2010; Lee et al., 2011; Ormond and Woodin, 2011; Woodin and Maffei, 2011; Huang et al., 2013; Vogels et al., 2013; Mahadevan and Woodin, 2016; Nakamura et al., 2016).

But how local are these Cl^- gradients or does the Cl^- diffuse to neighboring synapses, altering the strength of multiple inhibitory synapses? To answer such questions precisely, further advances in Cl^- imaging are required, in particular, the development of pH-insensitive Cl^- indicators with suitable dynamic ranges for low Cl^- concentrations. We can however make some informed estimates: it is clear that Cl^- gradients can be confined to neuronal compartments (Duebel et al., 2006; Szabadics et al., 2006), but how locally those gradients are confined within a dendrite is unclear. Cl^- can diffuse between synapses located in close proximity on the same dendritic branch (Ormond and Woodin, 2011), but computational studies predict that this diffusion is limited to ~50 μm in spiny dendrites (Mohapatra et al., 2016). Determining the kinetics of Cl^- diffusion within neuronal compartments is a critical avenue for future investigation that will be essential to our understanding of E/I balance.

Multiple roles for GABAergic inhibition in cortical circuits

A full understanding of the role of GABAergic inhibition in neural circuit depends not only on signaling mechanisms, but also on how inhibitory circuits are recruited. Many GABAergic neuron subgroups project locally, acting as interneurons (Fino et al., 2013; Pfeffer et al., 2013), and are thought to modulate gain (Cardin et al., 2009; Isaacson and Scanziani, 2011) and timing (Wehr and Zador, 2003) of incoming signals.

Independent reports demonstrated that diverse projection neurons can regulate GABAergic interneuron function within cortical circuits. Thalamic afferents, for example, directly regulate GABAergic neurons activity in sensory cortex (Porter et al., 2001; Hull et al., 2009; Kloc and Maffei, 2014; Delevich et al., 2015). While fast spiking, parvalbumin expressing (PV^+) inhibitory neurons receive direct thalamocortical inputs in many cortical regions; the contribution of other groups of inhibitory neurons to thalamocortical circuits varies by region (Porter et al., 2001; Beierlein et al., 2003; Verbny et al., 2006; Cruikshank et al., 2010; Kloc and Maffei, 2014), suggesting differential contribution to sensory processing. Cortical GABAergic neurons are also activated by axonal projections from higher-order thalamic nuclei (Lee et al., 2010; Delevich et al., 2015; Audette et al., 2017), contributing to the cortico-thalamo-cortical loop. Afferents from higher-order nuclei often exhibit connectivity preference to groups of GABAergic neurons that inhibit other inhibitory neurons (Dávid et al., 2007; Lee et al., 2010; Audette et al., 2017). Cortical GABAergic neurons can also be directly recruited by amygdalar afferents (Dilgen et al., 2013; Haley et al., 2016), carrying information about expectation (Samuelsen et al., 2012) and about the hedonic value of sensory stimuli (Piette et al., 2012). Thus, different behavioral states can recruit different GABAergic cells, influencing functional connectivity within cortical circuits.

Somatostatin-expressing inhibitory neurons are active in awake states (Kvitsiani et al., 2013); PV-expressing neurons act as gain modulators (Cardin et al., 2008); and vasointestinal peptide-positive neurons can be activated by locomotion (Fu et al., 2014). These patterns of activation also change with context (Pakan et al., 2016), highlighting the flexibility of inhibitory neuron recruitment. Within the cortex, GABAergic neurons can be connected by electrical coupling facilitating network synchronization (Cardin et al., 2009; Veit et al., 2017). Most work aimed at understanding the role of GABAergic neurons in cortical circuit function focused on locally projecting interneurons; however, there is now well-supported evidence that inhibitory neurons can also project to subcortical regions (Melzer et al., 2017), likely contributing to modulating activity across brain areas.

In addition to fast synaptic inhibition, extrasynaptic $GABA_A$Rs contribute to tonic inhibition (Kullmann et al., 2005). Volume transmission can influence circuit activity when GABAergic inhibitory neurons fire action potentials at high frequency, leading to tonic increases of GABA and following activation of a population of inhibitory neurons, neurogliaform cells (Oláh et al., 2009).

Finally, GABAergic synapses made by different groups of inhibitory neurons can locally alter their efficacy in response to patterned activity (Komatsu, 1996; Woodin et al., 2003; Maffei et al., 2006; Woodin and Maffei, 2011). GABAergic synaptic plasticity is altered during development (Lefort et al., 2013), by experience (Maffei et al., 2006; Wang and Maffei, 2014), and during learning (Letzkus et al., 2011). Such diversity within GABAergic neuron function and capacity for plasticity suggests that inhibitory neurons can play a diverse array of functions, including preserving circuit excitability (Maffei et al., 2004), as well as activity-dependent fine-scale circuit refinement.

In conclusion, in this Mini-Symposium, we discuss the emerging complexity regarding the role of GABAergic transmission in neural circuits. We report results demonstrating that specific signaling pathways are shared between excitatory and inhibitory synapses, and these pathways often share functional interactions. Identification of moonlighting proteins, such as SRGAP2, which is operational already during early brain development, and KCC2 and CaMKIIα, highlights complex aspects of synaptic transmission and plasticity. To add to this complexity, we also report the influence of CB1r on HCN channel, expressed by PV-expressing GABAergic neurons during postnatal development. These results are particularly relevant as smoking marijuana during adolescence is widely associated with impaired cognition, increased risk for psychiatric diseases, such as schizophrenia and depression, as well as increased propensity for substance abuse (Dow-Edwards and Silva, 2017). Such pathological conditions are associated with alterations in the E/I balance, highlighting the importance of investigating the mechanisms promoting coordinated regulation of E/I ratios to further our understanding of processes involved contributing to healthy circuit maturation and function.

In addition to regulating receptors, channels, and transporters, we highlighted a diverse range of cellular signaling pathways impinging upon GABAergic inhibition via the main protein scaffold gephyrin. Protein scaffolds are also fundamentally involved in regulating E/I ratios, although their effect is primarily exerted by contributing to plastic changes in synaptic strength. Emergence of protein scaffolds as signaling hubs offers yet another perspective into synaptic plasticity mechanisms connecting different neurotransmitter systems. Our data identify a central role for CaMKIIα not only in facilitating signal transduction downstream of GABAergic synapse, but also in assimilating information from other neurotransmission systems.

Finally, inhibitory neurons can be activated by a variety of inputs carrying information about different aspects of neural circuit function, including the perception of sensory stimuli and their affective dimensions, indicating that GABAergic inhibitory circuits are centrally positioned to participate in all aspects of brain function throughout life. Although much work is still needed to fully understand the role of inhibition in brain function, the scope of this Mini-Symposium was to bring to light the dynamics of interaction between inhibition and other neurotransmitter systems for healthy brain function and disease.

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