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Sarah L. Pallas, *Georgia State University*
Peter Wenner, *Emory University*
Carlos Gonzalez Islas, *Emory University*
Michela Fagiolini, *RIKEN Brain Science Institute*
Khaleel A. Razak, *Georgia State University*
Gunsoo Kim, *University of Pittsburgh*
Dan Sanes, *New York University*
Birgit Roerig, *Sucampo Pharmaceuticals*

Journal Title: Journal of Neuroscience Nursing
Volume: Volume 26, Number 41
Publisher: Lippincott, Williams & Wilkins | 2006-10-11, Pages 10358-10361
Type of Work: Article | Final Publisher PDF
Publisher DOI: 10.1523/JNEUROSCI.3516-06.2006
Permanent URL: https://pid.emory.edu/ark:/25593/v433v

Final published version: http://dx.doi.org/10.1523/JNEUROSCI.3516-06.2006

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Mini-Symposium

Developmental Plasticity of Inhibitory Circuitry

Sarah L. Pallas,[1] Peter Wenner,[2] Carlos Gonzalez-Islas,[2] Michela Fagiolini,[3] Khaleel A. Razak,[1] Gunsoo Kim,[4] Dan Sanes,[5] and Birgit Roerig[6]

[1]Department of Biology, Georgia State University, Atlanta, Georgia 30303, [2]Department of Physiology, Emory University, Atlanta, Georgia 30322, [3]Laboratory for Neuronal Circuit Development, RIKEN Brain Science Institute, Wako, Saitama 351-0198, Japan, [4]Department of Neurobiology, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania 15213, [5]Center for Neural Science, New York University, New York, New York 10003, and [6]Sucampo Pharmaceuticals, Bethesda, Maryland 20814

In 1949, Donald Hebb proposed a mechanism for use-dependent synaptic plasticity, suggesting that input neurons that reliably activate their postsynaptic target will strengthen their connections (Hebb, 1949). Since then, studies of use-dependent plasticity during development have been almost entirely focused on excitatory synapses, particularly those incorporating NMDA receptors (NMDARs). Neural circuits depend heavily on inhibition, however. Although there have been several *in vitro* studies of possible synaptic mechanisms underlying inhibitory plasticity (Pitler and Alger, 1992, 1994; Komatsu, 1994; Kano, 1995; Zilberter, 2000; Kreitzer and Regehr, 2001; Wilson and Nicoll, 2001; Kilman et al., 2002; Maffei et al., 2006), little is known at the systems level about use-dependent plasticity of inhibitory synapses. The realization that "inhibitory" neurotransmitters often depolarize immature neurons (Ben-Ari, 2002) further complicates the picture. This issue is important because clinical treatments for epilepsy, sensory dysfunction, or brain damage need to be informed by an understanding of both excitatory and inhibitory components of the circuits they are aimed at influencing. This mini-symposium, presented at the 36th Annual Meeting of the Society for Neuroscience, will address the roles and mechanisms of inhibitory synaptic plasticity during development of the mammalian CNS, using primarily *in vivo* approaches to examine circuit-level plasticity in a wide array of model systems. The goal of the mini-symposium is to bring this important research area into the spotlight and to encourage other investigators to participate in developing a better understanding of this underappreciated issue.

Inhibitory plasticity in motor systems

The transient presence of episodic bursts of spontaneous network activity (SNA) is observed throughout the developing CNS. In the spinal cord, SNA is important for axon guidance, motoneuron survival, neurochemical expression, and joint and muscle development (O'Donovan et al., 1998). Despite its importance, the role of SNA in the maturation of spinal connectivity is poorly understood. In the laboratory of Peter Wenner, co-chair of the mini-symposium, postdoctoral fellow Carlos Gonzalez-Islas has been investigating the role of SNA in homeostatic plasticity within the embryonic chick spinal cord. Despite significant developmental challenges to the production of SNA, it is clear that the network is capable of maintaining its activity levels (Chub and O'Donovan, 1998). Wenner and Gonzalez-Islas hypothesized that SNA is maintained through compensatory changes in synaptic strength. To test this hypothesis, they reduced network activity with lidocaine for 2 d *in ovo*. This increased the strength of both glutamatergic synapses and immature, depolarizing GABAergic synapses (Gonzalez-Islas and Wenner, 2006) and accelerated the modulation of GABAergic synaptic strength normally observed between episodes of SNA. Together, these compensatory responses appeared to increase the excitability of the embryonic spinal cord in an attempt to maintain appropriate SNA levels. Homeostatic regulation of SNA via changes in synaptic strength may therefore drive a coordinated maturation of GABAergic and AMPAergic synaptic strength at a dynamic developmental stage when both transmitters are excitatory.

Inhibitory plasticity in sensory systems

Visual cortical circuits are sculpted by sensory experience during critical periods (CPs) in early life. Even brief monocular occlusion results in a permanent loss of visual acuity through the deprived eye (amblyopia) (Daw, 1995; Prusky and Douglas, 2003). Michela Fagiolini will discuss her work in Takao Hensch's laboratory at the RIKEN Brain Science Institute on the role of inhibition in this ocular dominance plasticity. $GABA_A$ receptors incorporating the $\alpha 1$ subunit mediate the competition between the eyes (Fagiolini et al., 2004). Interestingly, the $\alpha 1$ subunits are enriched opposite parvalbumin (PV)-positive synaptic boutons innervating the soma-proximal dendrite (SPD) but not the axon initial segment of pyramidal cells (Klausberger et al., 2002), suggesting highly precise points of information transfer and regulation (Pouille and Scanziani, 2004). To determine whether the SPD exhibits maturational changes predictive of CP onset, Fagiolini and colleagues examined these two sites at high spatial resolution, using laser photo-uncaging. In addition, benzodiazepine sensitivity was investigated in animals lacking the ability to synthesize GABA. The GAD65 knock-out mouse fails to enter the CP but can be made plastic by treating with the GABA agonist diaz-

Received Aug. 14, 2006; revised Sept. 15, 2006; accepted Sept. 16, 2006.

This work was supported by National Institutes of Health Grants NS046510 (P.W.), EY12696 (S.L.P.), EY12702 (B.R.), DC006864 (D.S.), DC05202 (to Zoltan Fuzessery), and DC4199 (to Karl Kandler), and National Science Foundation Grants IBN-0078110 (S.L.P.) and IOB-0616097 (P.W.).

Correspondence should be addressed to Sarah L. Pallas, Graduate Program in Neurobiology and Behavior, Department of Biology, Georgia State University, 24 Peachtree Center Avenue, Atlanta, GA 30303. E-mail: spallas@gsu.edu.

K. A. Razak's present address: Department of Zoology and Physiology, Biological Sciences Building, University of Wyoming, Laramie, WY 82071.

G. Kim's present address: University of California, San Francisco, 513 Parnassus Avenue, Box 0444, San Francisco, CA 94118.

DOI:10.1523/JNEUROSCI.3516-06.2006

 0270-6474/06/2610358-04$15.00/0

epam (DZ) (Hensch et al., 1998; Iwai et al., 2003). Natural CP timing can similarly be accelerated with DZ in immature wild-type mice (Fagiolini and Hensch, 2000). Their results reveal a dynamic regulation of GABA receptor number, specifically at the SPD, that is predictive of CP onset. Moreover, complete sensory deprivation and repeated DZ treatment had strikingly similar effects, optimizing somatic GABA receptor number and the induction of CP plasticity. The findings have important implications for the understanding and potential treatment of amblyopia, which is the behavioral consequence of reduced ocular dominance (Daw, 1995; Prusky and Douglas, 2003).

In experiments done in the laboratory of the mini-symposium chair, Sarah Pallas, using dark-reared Syrian hamsters, a species born very early in brain development, it was shown that receptive fields in superior colliculus (SC) could refine normally without visual experience. Refinement was lost in adulthood, however, in the continued absence of light (Carrasco et al., 2005). Reexposure to light in adulthood could not reverse the effects of early dark rearing, but 30 d of exposure to light in juveniles protected against later deprivation (Carrasco and Pallas, 2006). The failure to maintain refinement occurred at least in part through a reduction in surround inhibition (Carrasco et al., 2005). Thus, early sensory experience is required to maintain a balance between inhibitory and excitatory inputs to SC circuits in adulthood.

In another series of studies in the Pallas laboratory, Khaleel Razak examined plasticity of stimulus tuning in the visual system. Velocity tuning is important for visual motion processing, a task that uses the SC of hamsters. In the hamster SC, most neurons depend on surround inhibition for velocity tuning (Razak and Pallas, 2005). Experimentally enlarging the excitatory receptive field (eRF) by chronically blocking NMDAR during development (Huang and Pallas, 2001) increases the relative amount of time that a moving stimulus spends in the eRF versus the inhibitory surround [(inhibitory receptive field (iRF)], predicting that NMDAR blockade should alter velocity tuning. However, this was not the case (Razak et al., 2003), suggesting that changes in the iRF compensate for increases in the eRF size. Razak and Pallas found that the chronic NMDAR blockade increased the strength and extent of the iRF and that the dependence of velocity selectivity on the iRF was greater in the NMDAR-blocked group than in controls. These results show that inhibitory plasticity can maintain homeostatic balance at the circuit level, compensating for developmentally induced changes in excitation.

Velocity tuning is also seen in the auditory system of bats. Khaleel Razak will report on his and Zoltan Fuzessery's work on plasticity of velocity tuning in pallid bats. Most echolocation-sensitive cortical neurons in pallid bats exhibit neural selectivity for the downward rate of the frequency-modulated (FM) sweeps of their echolocation calls, a property akin to velocity tuning in the visual system. These neurons depend on a delayed, high-frequency band of inhibition for their selectivity (Razak and Fuzessery, 2006). At postnatal day 14 (P14), when the bat first hears echolocation frequencies, adult-like FM rate tuning and the underlying inhibitory mechanism are already present, suggesting that the initial development of selectivity is essentially independent of experience. To determine whether maintenance of this tuning requires echolocation experience, bat pups were isolated before P14 and their calls were silenced. This led to a reduction in high-frequency inhibition and an alteration in its timing, resulting in abnormal selectivity. Like the work on dark-reared hamsters, these data suggest that activity driven by experience is necessary for the maintenance of refined tuning in sensory circuits and that plasticity of inhibition is a mechanism through which experience can affect neural selectivity for sensory stimuli.

In the mammalian auditory brainstem, the lateral superior olive (LSO) is a binaural nucleus that uses interaural sound intensity differences to report sound location. In adults, it receives tonotopically organized excitatory inputs from the ipsilateral cochlear nucleus and inhibitory inputs from the contralateral side via the medial nucleus of the trapezoid body (MNTB). The topography of the MNTB–LSO projection becomes refined during development (Sanes and Siverts, 1991; Sanes et al., 1992; Kim and Kandler, 2003) and thus serves as a model system for studying the development of inhibitory circuits. Gunsoo Kim will present his evidence from Karl Kandler's laboratory supporting the idea that cochlea-generated spontaneous activity is crucial for the topographic refinement of the MNTB–LSO pathway. Before hearing onset, cholinergic efferent neurons in the brainstem suppressed spontaneous firing of inner hair cells in the cochlea (Glowatzki and Fuchs, 2000) and contributed to burst-like activity (Walsh and McGee, 1997). Kim and Kandler investigated how disruption of this cholinergic inhibition influences the refinement of inhibitory sound localization circuits. Using electrophysiological mapping of MNTB–LSO connectivity, they found that the topographic refinement of developing GABA/glycinergic connections was significantly impaired in rats subjected to surgical lesion of the efferent pathway and in $\alpha 9$ nicotinic acetylcholine receptor knock-out mice in which inner hair cells lack cholinergic responses (Vetter et al., 1999). These results indicate that the early, transient cholinergic innervation of cochlear hair cells plays an important role in the establishment of the precise organization of this auditory inhibitory circuit, likely by modulating spontaneous activity.

Deprivation or abnormal experience often perturbs response properties of excitatory sensory neurons. Evidence from the Sanes laboratory demonstrates that inhibitory neurons react similarly. Sanes pioneered investigations into the plasticity of inhibitory synapses in the 1980s using the auditory brainstem of gerbils (Sanes and Rubel, 1988), a rodent species with an audiogram that primarily overlaps that of humans. He will report on two studies done in collaboration with Carmen Vale and Vibhakar Kotak showing how hearing loss alters inhibitory synaptic function. They found that, after bilateral hearing loss, inhibitory synaptic strength was profoundly reduced in inferior colliculus (IC) and auditory cortex (A1) neurons recorded in brain slice preparations. One cause of this change is the disruption of chloride homeostasis. In the IC of deafened animals, synaptically released GABA could not hyperpolarize the postsynaptic neurons (Vale et al., 2003). The synaptic release properties were also disrupted; paired-pulse facilitation was nearly eliminated after hearing loss (Vale and Sanes, 2000). In A1, intracortical inhibitory synaptic potentials were decreased in amplitude after hearing loss (Kotak et al., 2005). Receptor trafficking may account in part for this effect: $GABA_A$ receptor isoforms were membrane associated in hearing animals but intracellular in deafened animals. In both IC and A1, the loss of inhibitory drive was accompanied by enhanced excitatory responses (Vale and Sanes, 2002; Kotak et al., 2005). Thus, changes in synaptic properties after deafness may reflect an attempt by the central auditory system to maintain homeostasis of cortical excitability. Together, results from the Sanes and Kandler laboratories emphasize the dynamic nature of inhibitory gain and suggest that endogenous activity regulates inhibitory synaptic strength during development in the auditory system.

Inhibitory neuronal morphology can be regulated by dopamine

GABAergic and dopaminergic neurons interact closely in regulating prefrontal cortical function, and alterations in these transmitter systems underlie a number of neuropsychiatric disorders (Abi-Dargham et al., 2002). Despite the importance of inhibitory interneurons in shaping cortical response properties and network behavior, however, little is known about the factors regulating postnatal development of different interneuron types. Birgit Roerig, who unfortunately will be unable to attend the meeting, investigated the effect of a dopamine D_2 receptor (D_2R) null mutation on the development of a class of PV-containing GABAergic interneurons (Celio, 1986; Hendry et al., 1989; Soriano et al., 1992; del Rio et al., 1994; Kawaguchi and Kubota, 1997) in the mouse prefrontal cortex. She found a dramatic reduction in the number of PV-immunoreactive neurons and in the frequency and amplitude of IPSCs. Dendritic differentiation of D_2R-expressing layer 5 pyramidal cells was also impaired in the D_2R null animal, indicating that D_2 receptor signaling is involved in dendritic growth and refinement. In view of these results, the D_2 null mutant represents an interesting model system to study how the absence of a single neuromodulatory transmitter receptor affects the development of selective cell populations and the structure and function of synaptic circuits in the prefrontal area. In addition to its potential relevance for understanding the cellular mechanisms of mental diseases, it also provides information on the regulation of the development of different interneuron populations, an essentially unexplored area.

Summary

A growing body of evidence suggests that plasticity at GABAergic synapses is of critical importance during development and aging. A balance between excitation and inhibition maintains homeostasis at the neuronal and circuit levels, and inhibitory plasticity can function to drive a perturbed system toward homeostasis. Activity-dependent modification of inhibitory synaptic strength must be non-Hebbian, however, because the interaction between an inhibitory neuron and its target prevents them from firing together. Mechanisms that may underlie inhibitory plasticity will be discussed, including the possibility that it is limited to the early period when GABA/glycine release is excitatory (Ben-Ari, 2002) or that corelease of another substance alters synapses that produce inhibition (Gillespie et al., 2005). Alternatively, inhibitory synapses may decline in strength through long-term depression (Kotak et al., 2001; Chang et al., 2003), or an as-yet undiscovered mechanism may be responsible. Whatever the mechanism, it is clear that inhibitory plasticity plays an important role in activity-dependent modification of developing circuits.

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