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Developmental plasticity of auditory cortical inhibitory synapses

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ABSTRACT

Functional inhibitory synapses form in auditory cortex well before the onset of normal hearing. However, their properties change dramatically during normal development, and many of these maturational events are delayed by hearing loss. Here, we review recent findings on the developmental plasticity of inhibitory synapse strength, kinetics, and GABAA receptor localization in auditory cortex. Although hearing loss generally leads to a reduction of inhibitory strength, this depends on the type of presynaptic interneuron. Furthermore, plasticity of inhibitory synapses also depends on the postsynaptic target. Hearing loss leads reduced GABAA receptor localization to the membrane of excitatory, but not inhibitory neurons. A reduction in normal activity in development can also affect the use-dependent plasticity of inhibitory synapses. Even moderate hearing loss can disrupt inhibitory short- and long-term synaptic plasticity. Thus, the cortex did not compensate for the loss of inhibition in the brainstem, but rather exacerbated the response to hearing loss by further reducing inhibitory drive. Together, these results demonstrate that inhibitory synapses are exceptionally dynamic during development, and deafness-induced perturbation of inhibitory properties may have a profound impact on auditory processing.

1. Introduction

The regulation of synapse strength is a life-long process that permits neural circuits to adapt to an ever changing environment. This principle was initially established for excitatory connections, but inhibitory synapses are just as malleable, and many of the best examples emerge from studies on the central auditory system. During development, the strength of inhibitory synapses can decline or increase, as these connections become refined anatomically (for reviews, see Kandler et al., 2009; Sanes et al., 2009). At the other chronological extreme, during senescence, a decline in synaptic inhibition is associated with a diminished computational capacity of brainstem and cortical single neurons (Caspary et al., 2008). Perhaps, the most profound changes to inhibitory synapse function come about as a result of developmental hearing loss. This has been demonstrated at almost every level of the auditory neuraxis, and often includes a reduction in synaptic strength (for review, see Takesian et al., 2009).

In this review, we describe the maturational changes to inhibitory synapse function in auditory cortex (ACx), and present evidence that chronic deprivation elicits unique effects at inhibitory synapses that depend on the specific pre- and postsynaptic neurons. One clear reason for the focus on ACx is that it inherits and filters subcortical inputs and serves as the primary sensory representation to decoding centers (Budinger et al., 2000, 2006; Kaas and Hackett, 2000). Furthermore, changes to ACx processing that occur during normal development or following to environmental manipulations - including hearing loss - are thought to involve the modification of intrinsic inhibitory networks (Calford et al., 1993; Rajan, 1998, 2001; Kimura and Eggermont, 1999; Raggio and Schreiner, 1999; Kral et al., 2000; Qiu et al., 2000; Noreña et al., 2003; Seki and Eggermont, 2003; Noreña et al., 2003; Chang et al., 2005; Razak and Fuzessery, 2007; Razak et al., 2008; Scholl and Wehr, 2008).

Despite being outnumbered by excitatory neurons by almost 4:1, inhibitory connections exert a profound influence on the pattern and magnitude of cortical network activity. This may reflect both the expansive architecture of inhibitory axonal arbors as well as the unique functional properties of interneurons (Chagnac-Amitai and Connors, 1989; Shuz and Palm, 1989; DeFelipe and Farinas, 1992; Bacci et al., 2003; Markram et al., 2004; Silberberg, 2008). Most neurons in auditory cortex receive synaptic input

Abbreviations: ACx, auditory cortex; BDNF, brain-derived neurotrophic factor; CHL, conductive hearing loss; FS, fast-spiking; GABA, gamma-aminobutyric acid; GAD, glutamic acid decarboxylase; IC, inferior colliculus; IPSC, inhibitory post-synaptic current; IPSP, inhibitory postsynaptic potential; LTP, long-term potentiation; LTS, low-threshold spiking; P, pyramidal neuron; SIG, silver-intensified colloidal gold; sIPSC, spontaneous inhibitory synaptic currents; SNHL, sensorineural hearing loss; STD, short-term depression.

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from a broad range of the audible spectrum (Wehr and Zador, 2003; Kaur et al., 2004; Liu et al., 2007; Wu et al., 2008). Furthermore, inhibitory interneurons may have even broader suprathreshold frequency tuning curves than excitatory cells (Atencio and Schreiner, 2008). A basic implication of this convergence is that activation of inhibitory circuits is often associated with the sharpening of excitatory receptive fields, while inactivation broadens receptive fields (Müller and Scheich, 1988; Chen and Jen, 2000; Wang et al., 2000, 2002; Foeller et al., 2001; Kaur et al., 2004). The overall goal of this review is to demonstrate that even moderate developmental hearing loss leads to a pervasive failure of ACx inhibitory synapses to mature properly, an outcome that is expected to compromise rate or temporal codes, thereby reducing stimulus selectivity.

1.1. Experimental approaches

The amount of synaptic integration that occurs in auditory centers beneath the cortex is staggering. Therefore, to measure the function of cortical inhibitory synapses independent of the brain stem, one must stimulate inhibitory inputs selectively. This can be accomplished with a brain slice preparation of the auditory cortex that includes the projection from thalamus (Cruikshank et al., 2002). With this approach, it is possible to deliver electrical stimuli to a small region of tissue, pharmacologically isolate inhibitory synaptic currents under voltage-clamp conditions, and record from inhibitory interneuron-pyramidal cell pairs (Fig. 1). These methods were used to record from gerbil ACx neurons, and are covered in detail elsewhere (Kotak et al., 2005; Xu et al., 2007; Kotak et al., 2008; Takesian et al., 2010). Neurons were recorded at postnatal (P) 8–11 (pre-hearing), or P17–22 (post-hearing, and age-matched hearing loss).

To measure the sub-cellular anatomical characteristics of single cortical inhibitory synapses, it is necessary to quantify images obtained from tissue processed for electron microscopic immunocytochemistry. Here, proteins localized to the presynaptic terminal (glutamic acid decarboxylase, GAD) or postsynaptic membrane (GABAA receptor β2/3 subunit) are bound with a specific antibody, visualized with a silver-intensified gold technique, and quantified at the ultrastructural level from photomicrographs. These methods were used in P17 gerbil ACx, and are covered in detail elsewhere (Sarro et al., 2008).

Developmental hearing loss was induced surgically in gerbils aged P10. This is just prior to ear canal opening, an age when anteroventral cochlear nucleus cell number is unaffected by cochlear ablation (Tierney and Moore, 1997). Sensorineural hearing loss (SNHL) was induced by removal of both cochleae, and conductive hearing loss (CHL) was induced by malleus extirpation on both sides, using procedures identical to those described previously (Vale and Sanes, 2002; Xu et al., 2007). All protocols were reviewed and approved by New York University Institutional Animal Care and Use Committee.

2. Results and discussion

2.1. Unique pattern of inhibitory developmental plasticity in ACx

While studying the effect of hearing loss on synapse function in the auditory brainstem, we observed a significant loss of inhibition (Kotak and Sanes, 1996; Vale and Sanes, 2000). Therefore, we first sought to determine whether there was a similar outcome in thalamorecipient ACx. There were two broad possibilities: either the cortex compensated for the loss of inhibition in the brainstem, or it exacerbated the response to hearing loss by further reducing inhibitory drive. Our initial studies used 3 different approaches to assess inhibitory function. First, spontaneous inhibitory synaptic currents (sIPSC) were recorded from gerbil layers 2/3 pyramidal cells in the presence of ionotropic glutamate receptor antagonists. Although sIPSC amplitude is quite variable in each recorded pyramidal neuron, there is consistent 30% reduction following hearing loss (Kotak et al., 2008). Second, minimum-evoked IPSCs were obtained by delivering a minimally effective stimulus to a nearby region of cortex to elicit putative monosynaptic IPSCs from nearby GABAergic interneurons; the criterion for a minimum response is that half of the stimuli result in failures. This technique also reveals a >30% decline in the amplitude of putative unitary IPSCs following hearing loss (Kotak et al., 2008). Finally, inhibitory postsynaptic potentials (IPSP) were recorded in response to a maxiumum intracortical stimulus, once again ionotropic glutamate receptor antagonists. These maxiumum-evoked monosynaptic IPSPs were declined by >50% following hearing loss (Kotak et al., 2005). Each of these results were obtained with the more extreme form of hearing loss (SNHL), but similar reduction in inhibition can be observed with CHL (Takesian, Kotak, and Sanes, in submission).

Spontaneous and minimum-evoked inhibitory synaptic currents offer a global estimate of inhibitory function, and this sort of data also provides an efficient way to compare multiple age or treatment groups. However, it is important to bear in mind that there are many types of inhibitory neurons in cortex, and they display distinct patterns of connectivity and function (Markram et al., 2004). One must ultimately record the responses of individual interneurons to determine whether they are consistent with

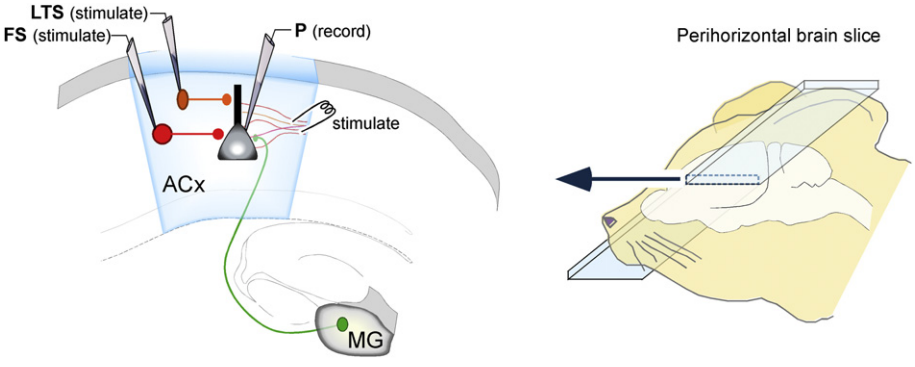

Fig. 1. Experimental preparation. A perihorizontal brain slice (right), contains the medial geniculate (MG) projection to auditory cortex (ACx). Whole cell voltage-clamp recordings are obtained from supragranular pyramidal (P) neurons, and spontaneous inhibitory postsynaptic currents, or evoked currents (stimulating electrode) are acquired. In other experiments, supragranular interneurons are recorded spike-elicited IPSCs are recorded in the pyramidal neuron. Fast-spiking (FS) and low-threshold spiking (LTS) interneurons are identified based on soma shape visualized under IR-DIC, and by their discharge pattern in response to direct current injection into the cell body via the recording eletrode.