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Synaptic plasticity in inhibitory neurons of the auditory brainstem

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Abstract

There is a growing appreciation of synaptic plasticity in the early levels of auditory processing, and particularly of its role in inhibitory circuits. Synaptic strength in auditory brainstem and midbrain is sensitive to standard protocols for induction of long-term depression, potentiation, and spike-timing-dependent plasticity. Differential forms of plasticity are operative at synapses onto inhibitory versus excitatory neurons within a circuit, and together these could serve to tune circuits involved in sound localization or multisensory integration. Such activity-dependent control of synaptic function in inhibitory neurons may also be expressed after hearing loss and could underlie persistent neuronal activity in patients with tinnitus.

1. Introduction

The study of plasticity in the auditory system is relatively young, with the most prominent efforts focusing on cortical plasticity in response to altered sensory input ((Weinberger, 2004; Sanes and Constantine-Paton, 1983). Most subcortical work has been directed towards defining the anatomy and function of the highly complex ascending and descending pathways that encode sound location, intensity, and pitch, that are sensitive to behaviorally relevant sound patterns and combinations, and that can extract information from noisy or complex environments. However, in recent years, there has been an emerging interest in identifying and understanding plasticity at the cellular level in auditory brainstem and midbrain. These studies have pointed to refinements in synaptic inhibition as a major outcome of plasticity.

At a superficial level, one might be rather surprised that classical synaptic plasticity is a prominent property of the early levels of auditory processing, based on the assumption that synaptic properties must be invariant in order to support correct perception of acoustic features. Computations that require precise preservation of maps, whether in the brainstem or the cortex, might not be well served by time-dependent changes in synaptic function. For example, the sub-millisecond interaural time differences that underlie the detection of a sound's location in space could be compromised by weakening or strengthening of synapses in different environments. On the other hand, neural representation and discrimination of sound space and frequency may change with development in head size or in structural

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features of ear canals (Sanes and Walsh, 1997; Werner and Gray, 1997). Moreover, convergence of auditory maps with other sensory modalities requires a mechanism for tuning the precision of overlap, as has been shown in the midbrain of owls (Keuroghlian and Knudsen, 2007). The generality of hearing loss in humans has motivated a wealth of studies of its neural consequences in animal models, and the results offer clear evidence for plasticity at every level of the central auditory system (Takesian et al., 2009). Furthermore, studies of auditory deficits or alteration in multisensory representations highlight a key role for plasticity of inhibitory neurons that control the magnitude, distribution, and temporal features of acoustic responses in the brain.

Here, we review work on plasticity mechanisms and function in the auditory brainstem and midbrain, focusing on areas where plasticity of inhibitory signaling may contribute to developmental circuit refinement and multimodal integration.

2. Circuits and inhibitory neurons subserving auditory processing

The hallmarks of the auditory pathways are parallel streams of information, their convergence at multiple levels of the neuraxis, and prominent descending inputs at all levels (Smith and Spirou, 2001). Auditory nerve fibers, each containing limited information about sound frequency and intensity, branch in the cochlear nucleus to contact diverse cell types that establish particular processing pathways. Six primary way stations of processing are found, including the cochlear nuclei, the superior olivary nuclei, the lateral lemniscal nuclei, the inferior colliculus, thalamus and cortex (fig 1). Diverse subtypes of inhibitory neurons are found at every level. The roles of these cells are just beginning to be appreciated as newer methods for identification and recording from such cells are developed.

Beyond the level of description of cell types and activity dependence of synaptic function, understanding the function of plasticity at inhibitory neurons will be a major challenge. Three interesting aspects of inhibition in the auditory system add to this challenge. First, inhibitory neurons, at least in the brainstem, are both local interneurons and projection cells. For example, auditory nerve fibers synapse upon glycinergic D-stellate cells of the ventral cochlear nucleus, which in turn provide inhibition both to ipsi- and contralateral cochlear nuclei, and contact cells of quite diverse computational function. D-stellate cells mediate broadband inhibition within the dorsal cochlear nucleus (DCN), a nucleus involved in localizing sound elevation, and also mediate contralateral inhibition of ventral cochlear nuclear T-stellate cells, which are involved in pitch coding (Doucet et al., 2009; Needham and Paolini, 2007). As another example, glycinergic principal cells of the medial nucleus of the trapezoid body (MNTB) project to regions involved in binaural processing based on both interaural timing and intensity (Tollin, 2003). As a result, plasticity of neurons in these examples would have quite diverse consequences. Second, inhibition in the auditory system is mediated by glycine, GABA, and, not uncommonly, by co-release of both transmitters (Lu et al., 2008). Thus, receptor regulation associated with inhibitory plasticity in a single local circuit may in principle involve multiple receptor subtypes. Finally, even within a single subregion, the interneuronal connectivity can be staggering. An important example is the fusiform (pyramidal) cell of the DCN, whose activity is probably controlled by D-stellate, tuberculoventral, cartwheel, superficial stellate cells and (possibly) golgi cells (Oertel and Young, 2004). Plasticity at a single type of synapse would have to be interpreted in the context of such a rich circuitry.

3. Plasticity in the dorsal cochlear nucleus

Auditory nerve synapses in the ventral cochlear nucleus mark the start of processing pathways that utilize binaural cues to localize sound in the horizontal plane. The DCN, in contrast, relies on monaural cues to encode elevation of a sound source (Oertel and Young,

2004). The external ears impose a directionally sensitive filter on the spectrum of acoustic signals. The DCN, particularly its array of inhibitory connections, heightens the sensitivity of principal cells to key elements of these filtered spectra, and may thus serve in sound localization.

Beyond the task of localization based on monaural cues, the DCN's circuitry indicates that it also serves as a site of multisensory integration, in part to compare auditory input to information about the placement of the ears and head in space (Oertel and Young, 2004; Young and Davis, 2001). This is done within a laminated circuit resembling that found in the cerebellar cortex (fig 2A). Non-auditory inputs are relayed to DCN neurons via a series of excitatory parallel fibers arising from granule cells that receive mossy fiber input from multiple brain regions, including somatosensory dorsal column and trigeminal nuclei, vestibular nuclei and pontine nuclei (Shore et al., 2000; Weedman and Ryugo, 1996; Wright and Ryugo, 1996). Parallel fibers occupy the upper, molecular layer of the DCN, synapsing on the spiny apical dendrites of DCN principle cells, termed fusiform or pyramidal cells. Fusiform somata occupy the second, fusiform cell layer, and auditory nerve fibers, which synapse on the aspiny basal dendrites of fusiform cells, occupy the third, or deep layer.

In vivo studies in the 1990s indicated that Pavlovian conditioning stimuli could induce long-term plasticity in the DCN (Beroukha et al., 1998; Woody et al., 1992). Later, a brain slice study reported that, quite remarkably, parallel fiber inputs carrying multimodal signals to spiny apical fusiform dendrites support high- and low-frequency induced long-term potentiation (LTP) and depression (LTD), whereas auditory fiber inputs to aspiny basal dendrites do not (Fujino and Oertel, 2003). Thus, plasticity at principal cell synapses may vary with sensory modality. Plasticity could also be induced in molecular layer cartwheel cells, which are interneurons that also receive parallel fiber input and subsequently make glycinergic/GABAergic synapses on neighboring cartwheel cells and fusiform cells. While all forms of plasticity in both cell types required postsynaptic calcium, induction mechanisms were mixed: cartwheel cell LTD, but not LTP, was dependent on NMDA receptors, and in fusiform cells, LTP and LTD was blocked by NMDA receptor antagonists in only a fraction of experiments (Fujino and Oertel, 2003). Thus, these experiments established that plasticity does occur at parallel fiber synapses onto principal cells and interneurons in the DCN, but also hint that synapses in the DCN are shaped by forms of plasticity that may involve mechanisms more complex than classical postsynaptic NMDA receptor-dependent mechanisms.

More recent experiments have made important advances in our understanding of parallel fiber plasticity in the DCN. In these experiments, plasticity was induced by pairing precisely timed parallel fiber synaptic stimulation with postsynaptic action potentials evoked via somatic current injection. This type of plasticity induction, termed spike-timing-dependent plasticity (STDP), is a physiologically relevant form of plasticity that can instantiate Hebbian learning rules at synapses. In its Hebbian form, synaptic activity that precedes and evokes postsynaptic spiking will be potentiated whereas activity that does not correlate with postsynaptic spiking will be depressed. Tzounopoulos and colleagues found that STDP onto fusiform apical dendrites follows these Hebbian rules, but that STDP onto cartwheel cell dendrites did not (Tzounopoulos et al., 2004). In cartwheel cells, "anti-Hebbian" LTD, which was induced postsynaptically via NMDA receptor signaling but expressed presynaptically via an endocannabinoid-dependent reduction in transmitter release probability (Tzounopoulos et al., 2007), was observed when presynaptic spikes preceded postsynaptic spikes by 5 ms. Remarkably, no plasticity was observed at other pairing intervals, creating an STDP timing window with no LTP. As observed previously (Fujino and Oertel, 2003), higher frequency stimulation was sufficient to potentiate these synapses (Tzounopoulos et al., 2004). LTP was independent of spike timing, suggesting that

cartwheel cells exhibit spike-timing dependent depression under sparse spiking conditions, but can reverse this LTD and even potentiate parallel fiber synapses during periods of heightened synaptic activity.

Though anti-Hebbian STDP is rare, cases exist in various brain regions, especially at excitatory synapses onto interneurons (Bell et al., 1997; Fino et al., 2010; Lu et al., 2007). What function does this plasticity serve in the DCN? The DCN has strong anatomical similarities to both the mammalian cerebellum and the mormyrid electric fish electrosensory lobe (Oertel and Young, 2004; Sawtell and Bell, 2008). Notably, these structures also feature plasticity at parallel fiber synapses and are thought to serve as feature detectors for motor activity and fish electric fields (Bell et al., 2008). In electric fish, anti-Hebbian STDP is thought to weaken responses to an animal's own electric field, thus allowing for better detection of the electric fields of neighbors (Sawtell et al., 2005). Since fish often vary their own electric discharge frequency to accommodate for neighbor's frequencies, circuits in the electrosensory lobe are modified continuously. Parallels may exist between electrosensory processing and sound localization in the DCN. One hypothesis is that, much like in electric fish, self-generated or background noise can be cancelled out by cartwheel cell burst firing, increasing the salience of external sounds (Portfors and Roberts, 2007; Shore, 2005). Thus, anti-Hebbian LTD may serve to refine circuits that suppress background noise as environmental conditions change.

Several open questions must be answered to establish fully the role of STDP at DCN parallel fiber synapses. First, the auditory and non-auditory stimuli that evoke activity in cartwheel and fusiform cells must be defined. While basic information about fusiform cell responses to auditory input is known, a majority of experiments were done in anesthetized decerebrate preparations, which affects normal parallel fiber processing (Davis et al., 1996). More recently, recordings have been made from cartwheel cells in awake behaving mice, revealing that cartwheel cells respond to a wide range of stimuli, including auditory stimuli (perhaps through descending auditory input) (Portfors and Roberts, 2007). These response properties would then provide the framework necessary to test how STDP learning rules defined *in vitro* shape cartwheel and fusiform cell responses *in vivo*. While this question has been addressed in cortex and electrosensory lobe (Jacob et al., 2007; Meliza and Dan, 2006; Sawtell, 2010), practical limitations in obtaining whole-cell recordings from DCN neurons in awake behaving animals makes this a daunting task.

From there, a major remaining question is how plasticity across many DCN neurons affects overall circuit function. Though single cartwheel cells powerfully inhibit neighboring synaptically coupled neurons (Mancilla and Manis, 2009; Roberts et al., 2008), it is quite rare for these same neurons to receive common parallel fiber input (Roberts and Trussell, 2010). This suggests that plasticity onto any given neuron occurs independent of its local connectivity. Future models of overall DCN function must not only integrate STDP learning rules, but also take into account the unique features of both parallel fiber and local interneuron connectivity.

Lastly, neuromodulators may play a role in regulating plasticity in the DCN, not only by modulating intracellular molecular pathways that underlie plasticity (Seol et al., 2007), but also by altering overall spike output within the DCN. Indeed, the DCN is rich with monoaminergic fibers, (Klepper and Herbert, 1991), and it has recently been shown that dopaminergic signaling can alter the probability, timing, and pattern of cartwheel cell activity by modulating calcium channels involved in spike initiation (Bender et al., 2010; Bender and Trussell, 2009). Dopamine may alter the timing between when synaptic inputs evoke action potentials, and therefore affect the timing of the backpropagating action potential that provides instructive cues for plasticity at dendritic spines.

4. Plasticity in other brainstem nuclei and midbrain

Sound localization based on interaural intensity differences requires the convergence of ipsilateral excitatory and contralateral inhibitory signals in the lateral superior olive (LSO, see fig 2B). The inhibitory pathway is formed at the MNTB, which is a sign-inverting relay nucleus. Glycinergic neurons of the MNTB map tonotopically onto LSO principal cells, which also receive excitation from ipsilateral bushy cells. As sounds move from the ipsilateral ear to the contralateral ear, LSO neurons go from excitation to inhibition, and the level of excitation therefore provides an index of the location of a sound source (Tollin, 2003). Clearly both the specificity of the projection, the number of inputs, and the strength of the inputs must be precisely specified. Moreover, these will be dependent on long-term changes to the animal, such as growth of the head, or short-term changes, such as the propensity for echos in the acoustic environment (a room vs. a meadow) or in levels of background noise.

Intense efforts have gone into understanding how the MNTB-to-LSO circuit forms developmentally, from the standpoints of anatomy and physiology. In rodents just after birth, it is known that MNTB fibers map broadly onto LSO neurons, i.e., the precision of the tonotopic map is poor (Sanes and Siverls, 1991). Individual LSO neurons receive weak inputs from many MNTB neurons (Kim and Kandler, 2003). After the first postnatal week, this map is refined, such that each cell receives stronger and fewer inputs. It has been proposed that the weakening of supernumerary inputs might require an LTD-like mechanism. Indeed, Sanes and colleagues have shown in P3-5 gerbils that low-frequency stimuli to MNTB results in LTD of their synaptic inputs (Chang et al., 2003). Young, but not mature, MNTB neurons release GABA as well as glycine (Kotak et al., 1998; Nabekura et al., 2004). Interestingly, LTD at these synapses was blocked by antagonists of GABA_B receptors, indicating that GABA_B receptors are required to trigger depression (Kotak et al., 2001). Accordingly, this depression was mimicked by application of exogenous GABA but not glycine. Postsynaptic application of kinase inhibitors or Ca²⁺ chelators inhibited LTD. This and the reduction in mIPSC amplitude following LTD induction indicate postsynaptic mediation and expression of plasticity (Chang et al., 2003).

It remains unclear however if LTD occurs in the LSO *in vivo*, or if it has a role to play in tonotopic map refinement. Other players in this process are the depolarizing nature of GABA/glycine transmission during the early postnatal period, which leads to Ca²⁺ elevation in LSO neurons dependent on MNTB activity (Kullmann and Kandler, 2008), and the nature of the transmitters that are released. Gillespie and colleagues, found that glutamate is co-released with GABA and glycine in young rat MNTB terminals and this glutamate may activate NMDA receptors (Gillespie et al., 2005), thus introducing the possibility of a novel form of Hebbian plasticity. Is glutamate from MNTB terminals required for map refinement? VGLUT3 is the vesicular glutamate transporter expressed at these synapses, and knockout of this transporter leads to reduction or delay in the elimination of excess inputs and strengthening of the remaining inputs (Noh et al., 2010). It is not known how glutamate might trigger synaptic refinement at inhibitory synapses, for example, whether it works to weaken inputs (perhaps playing a role in LTD) or to help strengthen the influence of other inputs.

Another aspect of plasticity is how activity might control the matching of excitation and inhibition in LSO to encode a particular sound source. Although this might seem to be the perfect domain for long-term plasticity mechanisms, Magnusson et al., (2008) found that in fact short-term plasticity by inhibitory neurons could refine the tuning of LSO neurons. They found that application of baclofen, a GABA_B receptor agonist, to LSO *in vivo* shifted the effectiveness of contralateral ear inputs (those inhibitory to LSO) relative to the

ipsilateral (excitatory) ear. Baclofen induced a reversible reduction in EPSCs in LSO neurons. Surprisingly, LSO neurons themselves provided an endogenous source of GABA via spike-dependent dendritic release. The authors proposed that retrograde transmission from dendrite to axon could help neurons adapt localization sensitivity in a changing acoustic environment.

The inferior colliculus is the midbrain site of convergence of all cochlear nuclear, olivary and lemniscal inputs, and plays a role in encoding spatial, temporal and spectral components of sound. *In vivo* studies have shown that direct tetanic stimulation (Hosomi et al., 1995) or intense sound exposure (Salvi et al., 1990) can enhance postsynaptic responses in the IC, suggesting LTP induction. In an *in vitro* study, high-frequency lemniscal stimuli resulted in LTP of field potential responses. Curiously, this effect was blocked by GABA_B receptor antagonists, and moreover this blockade required active GABA_A receptors, as it could not be observed in the presence of bicuculline. These results were suggested to reflect inhibition of GABA release by GABA_B receptors, which could minimize a depolarization necessary for NMDA receptor-dependent LTP. Further evidence of GABAergic control of plasticity was seen *in vivo*, where LTP could be triggered only when GABA_A receptors were blocked (Hosomi et al., 1995). Whole-cell recordings demonstrated Hebbian plasticity in IC neurons (Wu et al., 2002), at least some of which are probably GABAergic neurons projecting to the thalamus (Ito et al., 2009). Thus, plasticity might serve to alter the relative strength or timing among parallel ascending channels of excitation and inhibition.

5.1 Inhibitory plasticity after hearing loss

Sensorineural and conductive hearing losses are major medical concerns in children, where they can impact learning (Moore, 2007), and in adults, where they affect work and quality of life (Sprinzl and Riechelmann, 2010). Such changes affect not only ongoing perception of the environment and ability to communicate, but also long-term development and functioning of neural circuits. Inhibitory neurons are believed to take center stage in such activity dependent alterations in circuit function (Takesian et al., 2009).

Disruption of normal hearing, either through cochlear ablation, degeneration, plugging the ear canals, or noise exposure, are all associated with changes in one or more aspects of synaptic function. The pattern of changes that occur, although generally in the direction of decreased inhibition, are complex and variable, and may reflect the distinct roles of inhibitory neurons on different aspects of sound processing. Glycine receptors in the cochlear nuclei are downregulated with unilateral and bilateral cochlear ablation (Asako et al., 2005; Sato et al., 2000) or earplugging (Whiting et al., 2009). The latter effect was partially reversible, indicating that an activity-dependent plasticity, rather than pathology, is at work. In keeping with the trend of reduced receptor expression, the amplitude of miniature glycinergic IPSCs (mIPSCs) in the MNTB is reduced in a line of mice with congenital deafness (Leao et al., 2004). Moreover, evoked IPSPs/Cs are reportedly reduced in auditory brainstem, midbrain and cortex in these mice (Kotak et al., 2005; Kotak and Sanes, 1996; Vale and Sanes, 2000, 2002). Interestingly, reduced receptor expression in the deafferented inferior colliculus was temporarily reversed by stimulating the auditory nerve with a cochlear implant (Argence et al., 2008).

However, the broader patterns of changes in inhibitory function are complex, varying in physiological mechanisms, differing in brain region, and possibly varying with the type of deafferentation. In congenitally deaf mice, glycine single channel conductance increased in the MNTB, and synaptic decay times slowed (Leao et al., 2004). By contrast, cochlear ablation in the midbrain led to faster GABAergic PSCs, but with a higher release probability (assessed with paired-pulse facilitation) and a depolarized reversal potential (Vale and

Sanes, 2000). A similarly complex assortment of changes was observed in auditory cortex following deafness (Kotak et al., 2005; Kotak et al., 2008). Together, these changes indicate that inhibitory circuitry is dependent on sensory input for its development and possibly its maintenance, but that the mechanisms and consequences of sensory deprivation may be circuit-specific. Moreover, the meaning of *in vivo* plasticity of inhibitory function must be viewed in the context of the many other cellular responses that occur upon hearing loss, such as alteration in excitatory synapses, voltage-gated channels, or intrinsic excitability (Francis and Manis, 2000; Walmsley et al., 2006).

5.2 Tinnitus

Changes in inhibitory synaptic function in brainstem circuits may be etiological to tinnitus, which is a subjective sound, often characterized by phantom, persistent ringing in one or both ears. Noise-induced tinnitus in rodent models correlates with increased activity in many auditory regions, including cortex (Norena and Eggermont, 2003), colliculus (Bauer et al., 2008), and DCN (Brozoski et al., 2002; Finlayson and Kaltenbach, 2009; Kaltenbach, 2007; Shore et al., 2008). In humans, tinnitus can often be induced or modulated by tactile stimulation, implying that the DCN, where somatosensory and auditory processing converge, may be the site of origin in some cases (Levine, 1999; but see Brozoski and Bauer, 2005; Eggermont and Roberts, 2004). Here, noise exposure results in increased activity from DCN fusiform cells. This increase may reflect some degree of disinhibition following noise exposure (Finlayson and Kaltenbach, 2009). Indeed, message and protein levels for GlyR change dramatically following noise exposure, with a net reduction in GlyR synaptic transmission (Wang et al., 2009). Alternatively, disinhibition may also arise from plasticity at parallel fiber synapses. Hyperactive somatosensory inputs to DCN parallel fibers could elicit Hebbian LTP at fusiform synapses and anti-Hebbian LTD at cartwheel synapses, simultaneously strengthening excitatory synaptic drive onto fusiform cells while removing inhibition from cartwheel cells (Tzounopoulos, 2008). Thus, tinnitus may co-opt synaptic learning mechanisms, possibly driving the circuit to a state of maximal fusiform LTP and cartwheel LTD. This idea reflects a long-standing issue in the plasticity field: e.g., LTP naturally begets more LTP, eventually driving synapses, and cellular excitability, to saturation (Abbott and Nelson, 2000). In many brain regions, runaway synaptic plasticity is tempered by homeostatic mechanisms, which allows for changes in synaptic strength relative to other inputs while maintaining a set overall level of neuronal excitability (Turrigiano, 1999). Homeostatic mechanisms exist in the DCN (Whiting et al., 2009), therefore it may be important to explore whether excessive synaptic plasticity combined with dysfunctional homeostatic regulation result in hyperactive DCN circuits.

6. Summary and Conclusions

Synaptic plasticity is an important feature at subsets of synapses made onto and by inhibitory neurons of the lower auditory pathways. Some circuits—those that function primarily as relays—probably do not exhibit prominent plasticity. However there are settings in which plasticity enhances the capacity of the brain to take advantage of complex sensory signals, including refinement of space or frequency maps and multisensory integration. Further analysis of signaling pathways involved in plasticity may suggest pharmacological or genetic tools that could be used to determine the role of plasticity *in vivo*. Moreover, such manipulations could also contribute to a more refined understanding of the physiological functions of brain regions whose roles were previously studied solely by lesioning or by applying local anesthetics. Auditory deficits result in changes in the balance of excitation and inhibition throughout the central auditory pathways, and drugs or noise that trigger tinnitus could lead to persistent activity in these same circuits. Knowledge of the

cellular mechanisms of such changes could diminish the central consequences of auditory trauma and possibly aid in the restoration of hearing.

[NP_4091] Bulleted points

- Overviews general layout of auditory pathways and where and why synaptic plasticity is found in different brain regions.
- Examines in detail forms of plasticity related to synaptic inhibition in two regions, the dorsal cochlear nucleus and the superior olivary complex.
- Also covers how plasticity of inhibition may be related to central neurological disorders such as tinnitus.

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Fig. 1.

Outline of the 5 major parts of the central auditory pathway. Adapted with permission from an image by S Blatrix, from "Promenade around the cochlea" <http://www.cochlea.org> EDU website by R Pujol et al., INSERM and University Montpellier.

Fig. 2.

Primary circuits and synapses discussed in this review. A) Cells of the DCN and their interconnections. Long-term plasticity is observed in connections between granule cells (GC) and both cartwheel cells (CC) and fusiform cells (FC). B) Basic circuit used in azimuthal localization of high-frequency sound. Excitatory input derives from spherical bushy cells (SBC) and probably also stellate neurons (Stel). Inhibitory input derives from the contralateral globular bushy cell (GBC) by way of the sign-inverting MNTB. Refinement in axon branches, synapse number, synaptic strength, and transmitter phenotype is seen in the MNTB projection to LSO.