Topical Review

Activity-dependent regulation of synaptic strength and neuronal excitability in central auditory pathways

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Neural activity plays an important role in regulating synaptic strength and neuronal membrane properties. Attempts to establish guiding rules for activity-dependent neuronal changes have led to such concepts as *homeostasis* of cellular activity and Hebbian reinforcement of synaptic strength. However, it is clear that there are diverse effects resulting from activity changes, and that these changes depend on the experimental preparation, and the developmental stage of the neural circuits under study. In addition, most experimental evidence on activity-dependent regulation comes from reduced preparations such as neuronal cultures. This review highlights recent results from studies of the intact mammalian auditory system, where changes in activity have been shown to produce alterations in synaptic and membrane properties at the level of individual neurons, and changes in network properties, including the formation of tonotopic maps.

It is generally assumed that sensory input to the developing mammalian brain shapes the strength of synaptic connections and the membrane properties of neurons. However, although there is a wealth of experimental data showing that the gross aspects of neural pathways are dependent on sensory input, there is very little *in vivo* information on the effects of activity during development at the fundamental membrane and channel level, and much of our knowledge has come from neuronal culture systems. In addition to the familiar Hebbian plasticity, a prominent hypothesis to emerge from recent studies is the concept of *homeostasis* (Burrone & Murthy, 2003; Murphy, 2003; Turrigiano & Nelson, 2004; Thiagarajan *et al.* 2005). Homeostasis is commonly used to describe the attempt of a neuron to regulate its average firing rate to some 'desired' set point, in response to a change in the activity of the cell. The hypothetical homeostatic response may manifest itself as a change in the strength of synaptic inputs, and/or a change in the properties of the postsynaptic neuron. The basic premise of homeostasis is that, if the average firing rate of a neuron *decreases*, then the system will compensate by increasing the firing rate back to the 'desired' level by mechanisms that may include (1) increasing the strength of excitatory inputs, decreasing the strength of inhibitory inputs, or increasing the ratio of excitation to

inhibition, and/or by (2) increasing the excitability of the postsynaptic neuron. (The opposite changes are proposed to occur as a consequence of an *increase* in the firing rate of a neuron.) In support of this hypothesis, a variety of experimental studies have shown that reduction in the firing rate of a neuron leads to an enhancement in the strength of excitatory inputs and a decrease in the strength of inhibitory inputs to that neuron. A change in synaptic strength may occur through a change in the total number of synaptic contacts, a change in presynaptic release, and/or a change in the postsynaptic response to neurotransmitter release. Distinct from homeostasis, Hebbian plasticity involves the strengthening of synaptic transmission through co-ordinated pre- and post-synaptic activity, and there is ample evidence for this process. Experimental manipulation of neuronal activity has led to a variety of effects, including changes in quantal size, attributed to changes in postsynaptic receptors (O'Brien *et al.* 1998; Turrigiano *et al.* 1998; Watt *et al.* 2000; Leslie *et al.* 2001; Kilman *et al.* 2002; Wierenga *et al.* 2005) or presynaptic changes in the amount of neurotransmitter packaged into vesicles (de Gois *et al.* 2005; Wang *et al.* 2005; Wilson *et al.* 2005), changes in quantal content without a change in quantal size (Paradis *et al.* 2001; Bacci *et al.* 2001), changes in synaptic size (Murthy *et al.*

2001) and changes in postsynaptic membrane properties (Daoudal & Debanne, 2003; Saar & Barkai, 2003; Zhang & Linden, 2003). Changes in neuronal excitability may occur through a variety of means, including a change in passive membrane properties (capacitance and resistance) or changes in voltage-activated currents (Daoudal & Debanne, 2003; Saar & Barkai, 2003; Zhang & Linden, 2003). In addition, morphological changes may alter the electrotonic architecture of the neuron. Experimental evidence has shown that changes in activity may alter the magnitude of voltage-activated sodium, potassium and calcium currents, and hyperpolarization-activated (I_h) currents (Daoudal & Debanne, 2003; Saar & Barkai, 2003; Zhang & Linden, 2003). For example, Desai *et al.* (1999) have demonstrated that, in visual cortex cultures, silencing of activity with TTX leads to a down-regulation of potassium currents and an up-regulation of sodium currents, with a resultant increase in cell excitability.

Thus, a variety of model systems have been used to demonstrate that activity can alter synaptic strength (both pre- and post-synaptically) and postsynaptic cell excitability. Some of these results are consistent with a so-called 'homeostatic response', and some are consistent with opposing mechanisms, such as 'Hebbian' strengthening of active synapses (Burrone & Murthy, 2003; Murphy, 2003). Furthermore, there is evidence that the response of a neuron to a change in activity may be different during development than in maturity (Burrone *et al.* 2002; Murphy, 2003). Despite these complications, recent studies, primarily using neuronal cultures, emphasize that the predominant response to a reduction in neuronal activity is a postsynaptic increase in quantal size (Turrigiano & Nelson, 2004). This raises the issue of what happens in the intact nervous system (Desai *et al.* 2002). This review highlights recent results from studies of the mammalian auditory system, in particular using deafness as a model of reduced or abolished sensory input during development. The results reveal that altered activity during development has multiple effects, including changes in excitatory and/or inhibitory synaptic transmission, and postsynaptic membrane properties. Furthermore, these changes may be different in different neuronal types, as previously described for long-term plasticity in the dorsal cochlear nucleus by Tzounopoulos *et al.* (2004). In addition, the results show that spontaneous activity during development is necessary for the proper formation of neural circuits (tonotopic maps) in central auditory nuclei.

Auditory pathways in the mammalian brainstem

Figure 1 illustrates the pathways in the mammalian brainstem that contribute to the initial central processing of auditory input. Sound entering the ear stimulates hair cells in the cochlea. Hair cells make synaptic connection via special ribbon synapses with spiral ganglion cells, which in turn give rise to the primary auditory nerve fibres carrying auditory information to the brain. Under normal circumstances, the ribbon synapses continually release neurotransmitter, even in the absence of sound stimulation, and this results in the generation of spontaneous nerve impulses in the auditory nerves. The rate of spontaneous nerve impulses varies between auditory nerve fibres, but can reach high rates (100 Hz or more; Liberman, 1991). Spontaneous activity occurs before the opening of the ear canal and the onset of airborne sound-generated responses.

An important aspect of the auditory system is the existence of tonotopic maps. The cochlea is arranged with the basal hair cells responding to highest sound frequencies and apical hair cells responding best to low frequencies. This spatial arrangement is maintained centrally, and most of the brainstem auditory nuclei are organized topographically according to their best response to acoustic frequencies (i.e. tonotopically). For example, the medial nucleus of the trapezoid body (MNTB) is
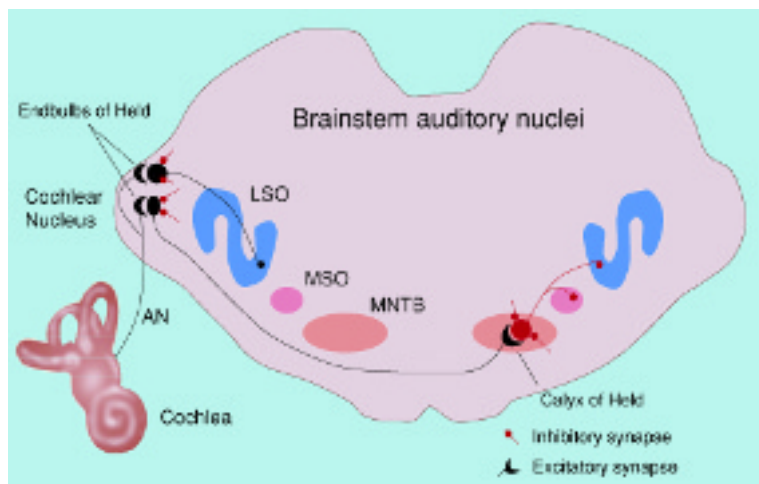

Figure 1. Major pathways in the mammalian auditory brainstem
This schematic shows the auditory nerve (AN) arising from the cochlea and making monosynaptic connections with neurons in the cochlea nucleus of the brainstem (AVCN – anteroventral cochlear nucleus). Also shown are some of the major brainstem auditory nuclei: the medial nucleus of the trapezoid body (MNTB), the medial superior olive (MSO) and the lateral superior olive (LSO). Auditory nerve fibres make large excitatory synaptic contacts, the endbulbs of Held, with bushy cells in the AVCN. Globular bushy cells in the AVCN, in turn, make large calyceal contacts, the calyces of Held, with principal cells in the contralateral MNTB. Spherical bushy cells make ipsilateral contacts with the dendrites of neurons in the MSO. Excitatory neurons and synapses are shown in black; inhibitory neurons and synapses are shown in red.

organized with medial cells responding better to higher frequencies than lateral cells.

Figure 1 illustrates the major brainstem auditory nuclei and connections, highlighting several large synaptic connections which have received much attention for study; the endbulb of Held connection between auditory nerve fibres and bushy cells in the anteroventral cochlear nucleus (AVCN), and the calyx of Held connection arising from bushy cells and contacting principal cells in the MNTB (Yin, 2002). At these connections, both pre- and post-synaptic properties can be assessed directly (e.g. Forsythe, 1994; Isaacson & Walmsley, 1995; Borst & Sakmann, 1996; Sakaba *et al.* 2002; Schneggenburger *et al.* 2002; Taschenburger *et al.* 2002). In addition to large excitatory terminals, AVCN and MNTB neurons also receive many small inhibitory boutons (Leao *et al.* 2004*b*).

MNTB principal neurons, in turn, send inhibitory inputs to the lateral superior olive (LSO) and medial superior olive (MSO). These pathways are involved primarily in sound localization, for which precise timing is required, involving both excitatory and inhibitory inputs (Friauf & Lohmann, 1999; FitzGerald *et al.* 2001; McAlpine *et al.* 2001; Paolini *et al.* 2001, 2004; Brand *et al.* 2002; Yin, 2002; Rubel & Fritzsch, 2002; Grothe, 2003; Kim & Kandler, 2003; McAlpine & Grothe, 2003; Mauk & Buonomano, 2004; Kandler & Gillespie, 2005).

Deafness-induced changes in central auditory pathways

Insight into the role of activity in regulating synaptic transmission and neuronal membrane properties has been
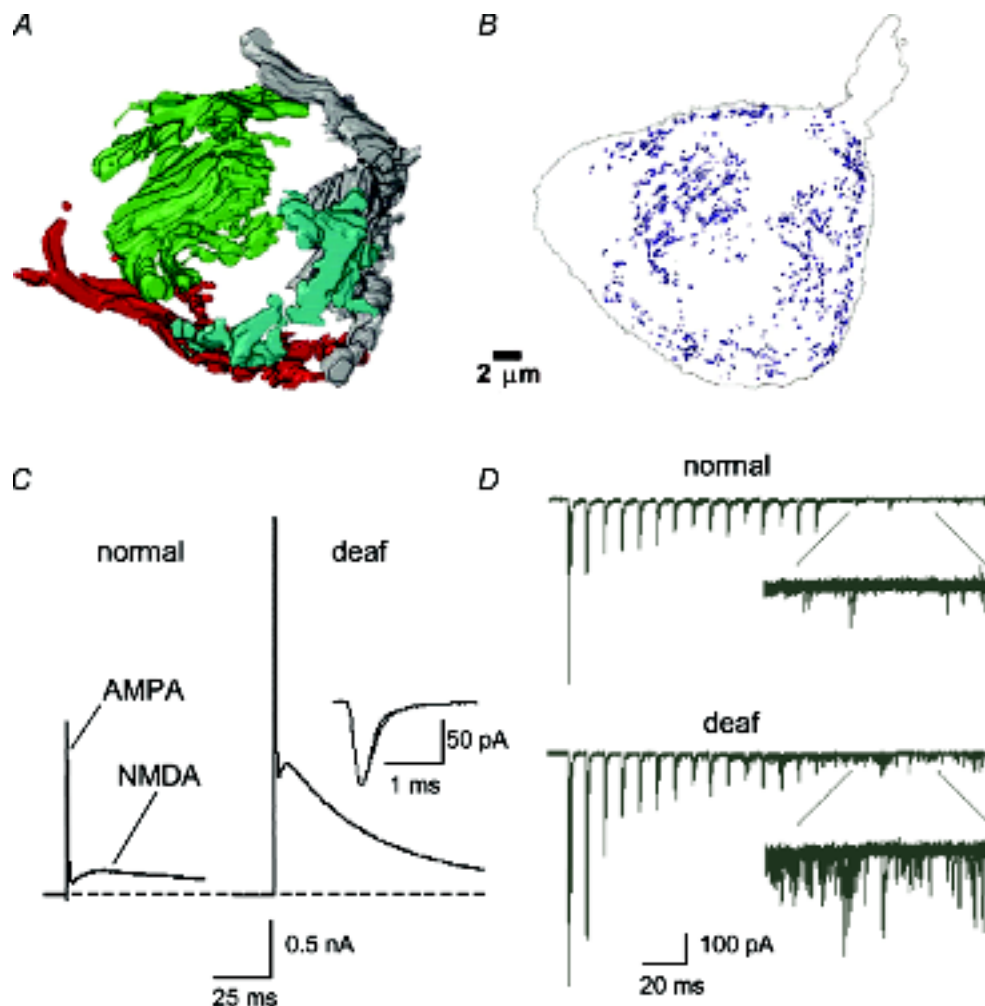

Figure 2. Excitatory synaptic transmission is greater in deaf mice
A, reconstructions from electron micrographs of 4 different endbulbs of Held contacting a bushy cell in the AVCN. *B* shows the individual synaptic specializations contained within the boutons shown in *A*. *C* shows that both AMPA and NMDA components of the synaptic current arising from individual auditory nerve fibres are larger in deaf (*dn/dn*) mice. *D* illustrates that delayed asynchronous spontaneous release is much larger in deaf mice (insets). (*A* adapted from Nicol & Walmsley, 2002, with permission from Blackwell Publishing Ltd, *B–D* adapted from Oleskevich & Walmsley, 2002, with permission from Blackwell Publishing Ltd.)

gained by studying the effects of eliminating or reducing auditory nerve activity i.e. deafness. These studies have revealed a variety of changes in central auditory neurons following experimentally induced or naturally occurring deafness.

Cochlear ablation studies

Cochlear ablation, which destroys the hair cells and spiral ganglion cells (and hence the auditory nerve), has been reported to increase the excitability of brainstem auditory neurons (McAlpine *et al.* 1997; Kotak *et al.* 2005), reduce (Suneja *et al.* 1998; Mossop *et al.* 2000; Vale & Sanes, 2002; Vale *et al.* 2003) or increase inhibitory transmission (Suneja *et al.* 1998), increase (Vale & Sanes, 2002) or decrease (Kotak & Sanes, 1997) excitatory synaptic transmission, transiently reduce NMDA receptor expression (Nakagawa *et al.* 2000), reduce potassium-dependent chloride transport (Vale *et al.* 2003), depolarize neurons (Francis & Manis, 2000; Vale & Sanes, 2002), increase input resistance (Francis & Manis, 2000), elevate tyrosine kinase B levels (Suneja & Potashner, 2002), alter synaptic morphology (Russell & Moore, 2002), cause cell death (Hashisaki & Rubel, 1989; Mostafapour *et al.* 2000), alter GAP-43 expression (Illing *et al.* 1997),

reduce protein synthesis (Sie & Rubel, 1992) and reduce calretinin expression (Zettel *et al.* 2003). These studies emphasize the wide range of possible effects resulting from the complete removal of the auditory nerve, as is the case for the recent *in vitro* models of altered activity. However, cochlear ablation is a severe method of silencing auditory nerve input, and recently, investigations have been extended to the study of deaf mutant animals. The results of these studies are the focus of the remainder of this review.

Naturally occurring deafness

There are a variety of naturally occurring animal models of deafness, some of which exhibit deficits from birth, and others which show age-related hearing loss (Keats & Berlin, 1999). DBA mice exhibit age-related hearing loss, beginning with a loss of high-frequency responses in spiral ganglion cells in the cochlea. Wang & Manis (2005) found that, in the AVCN of old DBA mice, synaptic transmission at the endbulb of Held–bushy cell connection is impaired; spontaneous mEPSC frequency is reduced, mEPSCs are slower and smaller, and release probability is lower in old DBA mice compared with young DBA mice. Wang & Manis (2005) suggested that auditory nerve activity regulates presynaptic release probability *and* postsynaptic
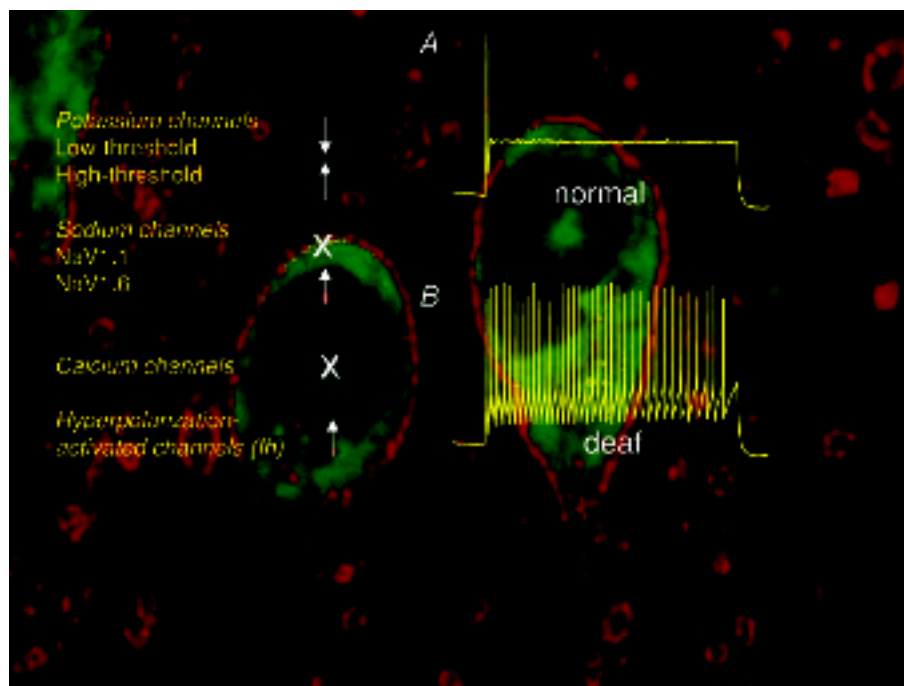

Figure 3. MNTB neurons are more excitable in MNTB neurons
A illustrates that MNTB neurons usually respond to depolarizing currents with a single or a few, action potentials, whereas MNTB neurons in deaf (*dn/dn*) mice respond with multiple action potentials. Panels on the left indicate the up- (arrows up), down- (arrows down) or no change (X) in the magnitude of voltage-activated currents in MNTB neurons from deaf cf. normal mice. Background immunolabelling shows HCN1 immunoreactivity (red) on LSO neurons (green).

receptor composition and kinetics at the endbulb of Held synapse. These results are opposite to those expected from a 'homeostatic' mechanism as commonly defined, and are more consistent with a 'Hebbian' reduction in synaptic strength due to a lack of correlated firing of pre- and post-synaptic cells.

Related structural analyses have examined synaptic features that may correlate with synaptic strength. Shaker-2 mice have dysfunctional cochlear hair cells from birth, and electron microscopy shows that the endbulbs of Held in adult deaf mice exhibit fewer vesicles and larger postsynaptic densities (Lee *et al.* 2003). This is similar to deaf white cats (Ryugo *et al.* 1997), which have endbulbs with a reduced synaptic vesicle density, structural abnormalities in endulb mitochondria, thickening of the pre- and post-synaptic densities, and enlargement of synaptic size. Ryugo *et al.* (1998) further demonstrated in the deaf white cats that there is a correlation between the amount of auditory nerve activity and the degree of abnormality in endbulb morphology. This is consistent with observations in normal cats in which endbulbs arising from auditory nerve fibres with a high spontaneous discharge rate are larger, with more synaptic specializations (Ryugo *et al.* 1996). These results support the proposal that activity during development induces the endbulbs to grow and generate more release sites, perhaps through the splitting of large specializations into multiple smaller specializations. Again, the functional consequences associated with these changes in synaptic structure appear to be opposite to the result expected from a homeostatic mechanism. Ryugo's group also studied small bouton terminals in the AVCN of deaf white cats (Redd *et al.* 2002). Compared with normal-hearing cats, bouton endings of congenitally deaf cats were smaller, but there was no difference in synaptic vesicle density or size of synaptic specializations. These anatomical observations indicate that, while synaptic structure may be different in congenitally deaf animals, the differences depend on the type of synaptic connection and/or the type of postsynaptic neuron.

Physiological aspects of synaptic transmission have been examined in the AVCN and MNTB of congenitally deaf (*dn/dn*) mice, which lack spontaneous and acoustically driven input due to cochlea hair cell dysfunction (Bock *et al.* 1982). The large excitatory calyceal synapse, the endbulb of Held, formed with AVCN bushy cells, has been studied by Oleskevich & Walmsley (2002) who found that, in congenitally deaf mice, the amplitude of evoked EPSCs is larger, due to an increased presynaptic release probability; a result that is consistent with homeostasis. There is also a much greater occurrence of delayed asynchronous mEPSCs following a train of stimuli (Fig. 2). These differences may be explained by impaired calcium buffering in the presynaptic terminal. In contrast to the results on the effects of reduced activity in

neuronal culture systems, there appears to be no postsynaptic difference in quantal size, since the amplitude and time course of mEPSCs are the same in *dn/dn* and normal mice. Interestingly, no difference was found in synaptic transmission at the calyx of Held connection with MNTB principal cells, between normal and deaf mice (Oleskevich *et al.* 2004; Youssoufian *et al.* 2005). This is surprising as globular bushy cells give rise to the calyces of Held, and these cells have lost their major excitatory drive (the endbulbs of Held).

In contrast to the lack of difference at the calyx of Held–MNTB cell connection, there are differences in the glycinergic inhibitory synaptic input to MNTB neurons between normal and deaf mice (Leao *et al.* 2004*b*). The amplitude of mIPSCs is smaller and the time course is slower in MNTB neurons from deaf mice, but their frequency is much higher than normal. The altered kinetics suggests a delay in the normal developmental glycine receptor subunit switch from alpha2 to alpha1, since
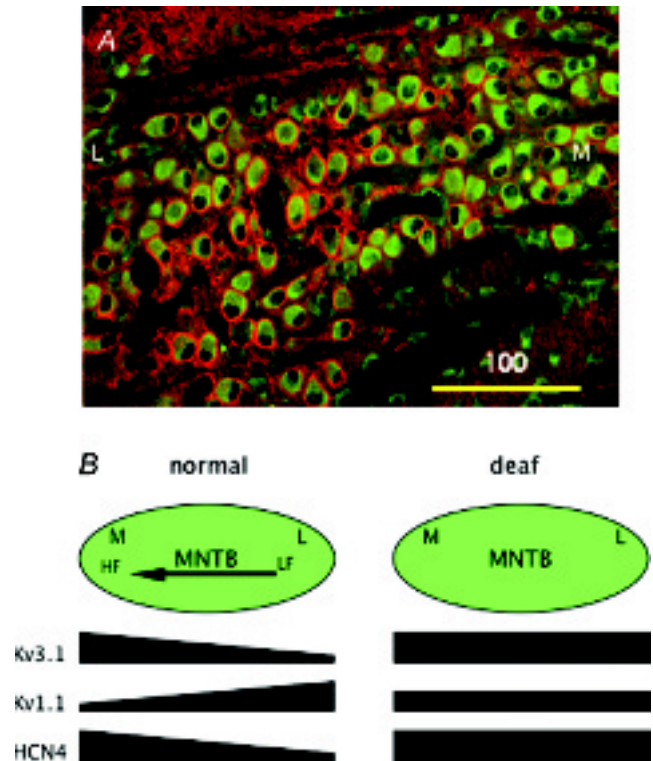

Figure 4. Tonotopic gradients of channel expression are disrupted in deaf mice
A illustrates an obvious medial (M) to lateral (L) gradient in pre- and post-synaptic immunolabelling of Kv3.4 channels (red) in MNTB neurons from a normal mouse. *B* illustrates a summary schematic (adapted from Leao *et al.* 2005*a*, with permission from Blackwell Publishing Ltd) of the MNTB (green shading) in normal and deaf (*dn/dn*) mice. Left panel shows the tonotopic (HF, high frequency; LF, low frequency) gradient of high-threshold potassium currents (Kv3.1), low-threshold potassium currents (Kv1.1) and hyperpolarization-activated currents (HCN4). Right panel shows that these gradients are not present in deaf (*dn/dn*) mice.

heteromers with alpha1 subunits exhibit faster kinetics. However, anatomical data shows that there is also a much greater number of glycinergic synapses on MNTB neurons in deaf mice, which argues against a simple developmental delay due to a lack of activity (Leao *et al.* 2004*b*). A greater frequency of mIPSCs and a larger number of inhibitory synapses seems to be opposite to the result expected from a homeostatic response to a decreased excitatory drive to these cells.

Membrane properties of auditory brainstem neurons in deaf mice

The postsynaptic membrane properties have also been examined in the AVCN and MNTB of normal and deaf (*dn/dn*) mice. In the AVCN, there appears to be no significant difference in the passive or active membrane properties of bushy cells, despite the loss of powerful excitatory auditory nerve input. However, MNTB principal cells in *dn/dn* mice exhibit a substantial increase in excitability, which is primarily due to smaller low-threshold potassium currents (Fig. 3; Dodson *et al.* 2002; Leao *et al.* 2004*a*). In addition, there is an increase in the high-threshold potassium currents and hyperpolarization-activated currents in the MNTB of *dn/dn* mice (Leao *et al.* 2004*a*, 2005*b*; see also Wang *et al.* 1998; Li *et al.* 2001; Lu *et al.* 2004). No differences were found between normal and deaf mice in voltage-activated calcium currents in the AVCN or MNTB (Leao *et al.* 2004*a*). These results show that a reduction in excitatory drive to auditory neurons can lead to no change (AVCN) or an increase (MNTB) in postsynaptic membrane excitability.

Tonotopic maps are disrupted in congenital deafness

As indicated above, neurons in brainstem auditory nuclei such as the AVCN and MNTB are tonotopically organized. The membrane properties of neurons within a particular nucleus are systematically different, an arrangement which has previously been demonstrated in cochlea hair cells (Pantelias *et al.* 2001). von Hehn *et al.* (2004) used immunolabelling to show that the normal gradient of high-threshold potassium channel expression in MNTB neurons is disrupted in age-related hearing loss. Recently, Brew & Forsythe (2005) described a tonotopic gradient of low-threshold potassium currents in MNTB neurons (see also Barnes-Davies *et al.* 2004). Leao *et al.* (2005*a*) have recently reported that there are gradients of low- and high-threshold potassium currents, and hyperpolarization-activated currents in the MNTB of normal mice. These gradients do not all increase in the same direction. Importantly, all gradients appear to be absent in *dn/dn* mice (see Fig. 4). This demonstrates that spontaneous activity during development plays a critical role in the expression of gradients of voltage-activated currents and the formation of tonotopic maps.

Conclusion

It is clear that neurons and circuits in the intact nervous system do not respond in a universal, stereotypical manner in response to a change in activity. Although the relevance of *homeostasis* and Hebbian processes to these responses both during development and in the mature nervous system is uncertain, the auditory system offers a valuable opportunity to investigate the mechanisms underlying activity-dependent changes in synaptic strength and membrane excitability. In this context, it is interesting to note that a recent study has demonstrated the restoration of synapses in congenitally deaf cats by stimulation of the auditory nerve by cochlear implants (Ryugo *et al.* 2005).

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