Role for the Lateral Olivocochlear Neurons in Auditory Function. Focus on “Selective Removal of Lateral Olivocochlear Efferents Increases Vulnerability to Acute Acoustic Injury”

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In a paper published in this issue of *Journal of Neurophysiology* (p. 1775–1785), Darrow and colleagues report that lesions of the lateral superior olive, where the lateral olivocochlear (LOC) efferent originate, enhance auditory evoked potentials in mice. The report also shows that noise-traumatized mouse ears without LOC input are more susceptible to noise-induced trauma than contralateral ears with intact LOC innervation. The current results contrast with those of previous studies on guinea pigs, chinchillas, and cats that revealed lesion-induced depression of auditory nerve activity. Species differences in LOC transmitter co-localization and release provide likely mechanisms for species differences in inhibitory LOC transmitter production, localization, and/or release. Differences in the balance of excitatory/inhibitory LOC transmitter production, localization, and/or release provide likely mechanisms for species differences in LOC function.

The LOC efferent pathway originates in and around the lateral superior olive (LSO) and projects to the cochlea. There the LOC neurons terminate on the type I auditory nerve peripheral processes postsynaptic to the inner hair cell/auditory nerve synapse (for reviews, see Warr 1992; Warr et al. 1986). LOC efferent neurons are thus strategically placed to provide a powerful and dynamic regulation of auditory nerve activity, including the regulation of noise-induced hearing loss. Immunocytochemical labeling studies reveal the LOC neurons contain both excitatory and inhibitory neurotransmitters and neuromodulating peptides, including acetylcholine (ACh), dopamine (DA), dynorphin, enkephalin, γ-aminobutyric acid (GABA), and calcitonin-gene-related-peptide (CGRP) (for reviews, see Eybalin 1992; Le Prell et al. 2001a; Puel 1995). This chemical richness provides significant potential for either up- or downregulation of auditory nerve activity (for one model, see Le Prell et al. 2003a). Darrow and colleagues report that LSO lesions in mice enhance auditory evoked potential amplitude, a result that suggests the net effect of the intact LOC innervation is to downregulate auditory nerve activity (Darrow et al. 2007). In this same report, noise-traumatized mouse ears that lack LOC input are described as more susceptible to noise-induced trauma than contralateral ears with intact LOC innervation. The current results directly contrast with previous studies in other rodent species (reviewed in the following text) and suggest a diversity of roles for the LOC and thus multiple challenges for future investigations.

The earliest “lesions” of the LOC system were knife cuts of the olivocochlear bundle (OCB) in cats (Liberman 1990) and chinchillas (Zheng et al. 1999). Both studies suggested the possibility of an excitatory LOC influence on the AN, although neither provided definitive evidence as these cuts disrupted both lateral and medial OC (MOC) pathways, which travel together in the OCB. Spontaneous auditory nerve firing rates were reduced in both studies; driven responses were reduced in lesioned chinchillas but not lesioned cats. Differences in species, anesthesia, and postlesion survival duration all provided potential explanations for differences in the pattern of results. A more selective LSO lesion technique was developed to try and resolve the discrepancies between the early studies and confirm the extent to which LOC neurons modulate auditory nerve activity in the absence of MOC disruptions (Le Prell et al. 2003b).

In the guinea pig, LSO lesions produced depressed auditory-evoked potential amplitudes, indicating that the net effect of the intact LOC system was excitatory (Le Prell et al. 2003b). Liberman and colleagues observed the opposite effect in mice (Darrow et al. 2007). Clearly, species differences provide one potential explanation. Differences in the balance of excitatory/inhibitory LOC transmitter production, localization, and/or release provide likely mechanisms for species differences in LOC function.

LOC transmitter colocalization has been well described with many studies using guinea pigs as subjects. For example, double-labeling studies have shown that LSO cell bodies co-localize enkephalin and dynorphin (Abou-Madi et al. 1987; Altschuler et al. 1988), enkephalin and ACh (Altschuler et al. 1983), enkephalin and choline acetyltransferase (ChAT: the enzyme responsible for synthesizing ACh) (Altschuler et al. 1984), or dynorphin and ChAT (Abou-Madi et al. 1987). Other studies have shown colocalization of enkephalin and CGRP (Tohyama et al. 1990) or enkephalin, ACh, and CGRP (Safieddine and Eybalin 1992). Finally, extensive colocalization has been observed with double and triple immunolabeling for ChAT and glutamate decarboxylase (GAD), the enzyme that decarboxylates glutamate to make GABA), tyrosine hydroxylase (TH, the enzyme responsible for catalyzing the conversion of L-tyrosine to the DA precursor dihydroxyphenylalanine), enkephalin, or CGRP, resulting in the conclusion that >90% of the ChAT-positive LSO neurons are also GAD and TH positive, or GAD and enkephalin positive (Safieddine et al. 1997). These results contrast with an early characterization of rat LSO neurons as chemically distinct subpopulations that are either...
GAD-positive or ACh/CGRP-positive (Vetter et al. 1991). They also contrast with the recent reports that GABA and CGRP are extensively co-localized with ACh in the mouse LOC terminals (Maison et al. 2003a), whereas dopaminergic neurons are a separate subpopulation (Darrow et al. 2006). Taken together, species differences in LOC transmitter colocalization are clearly emerging.

The extent to which LOC transmitters are co-released into the cochlear perilymph, or differentially released, has not been established in any species. For species differences to explain apparent discrepancies across reports, differences in transmitter co-localization presumably must be accompanied by species differences in tonic and/or sound-driven release of the LOC transmitter substances. Thus in the guinea pig, tonic release of excitatory LOC transmitters may shift auditory nerve activity to a higher set-point (as evidenced by decreased spontaneous rates in the LOC-lesioned guinea pig, see Le Prell et al. 2006a) with sound-driven release of excitatory LOC transmitters maintaining greater auditory nerve firing (following Le Prell et al. 2003b, 2005). In contrast, in the mouse, a more likely prediction may be that tonic and/or sound-driven release of an inhibitory LOC transmitter acts to depress auditory nerve activity in the normal animal as LSO disruption had the net effect of enhancing sound-driven activity and suggesting a loss of net inhibitory activity. This result is seemingly contrary to Maison et al. (2003b), who demonstrated that the amplitude of auditory evoked potentials is depressed in αCGRP-null mice. However, these results can be reconciled by the fact that the LSO lesions performed by Darrow et al. (2007) disrupt all of the LOC transmitters, not just those that are potentially excitatory.

Taken together, the evidence suggests that the direction of LOC modulation of auditory nerve activity is in opposite directions in the guinea pig and the mouse. However, during periods of exposure to traumatizing sound, it appears that the LOC system may act to reduce noise-induced trauma in both mice and guinea pigs. Liberman and colleagues report a greater hearing loss 6 h after noise exposure in LSO-lesioned mice (Darrow et al. 2007). Although Le Prell et al. (2003a) observed no differences in threshold shifts measured immediately or 90 min postnoise, they described greater noise-induced depression of evoked potential amplitude in LSO-lesioned guinea pigs exposed to loud sound (10-kHz tone, 110-dB SPL, 20 min). This result is consistent with a greater loss of ANFs and increased excitotoxic trauma in the absence of LOC efferents, a result that is now suggested in mice (although, we note that electron microscopy was not used to measure neuronal swelling in either mice or guinea pigs). There are several recent reviews of the many mechanisms of noise-induced hearing loss and potential pathways for prevention of such deficits (Henderson et al. 2006; Le Prell et al. 2006b); the current report suggests an increasing rationale for including efferent mechanisms with other potential interventions.

The function of the LOC efferent neurons is a long-standing mystery and the findings described by Liberman and colleagues in this issue are an exciting step toward identifying a functional role for the LOC system. This study confirms that the LOC efferent neurons act to modulate auditory nerve firing. That the amplitude of auditory evoked potentials changes postlesion presumably has important perceptual consequences that can only be characterized using psychophysical tasks. One hypothesis is that excitatory effects of the LOC efferent neurons on the guinea pig auditory nerve increase the dynamic response range across the auditory nerve fiber population, which in turn could improve intensity discrimination. The range of individual auditory nerve fiber sensitivities and their different saturation properties has long been thought to underlie the broad dynamic range within which intensity variation is detected (Delgutte 1987; Viemeister 1983, 1988a,b; Winslow and Sachs 1988). In normal-hearing human subjects, the growth of the sensation of loudness and the ability to discriminate small changes in intensity in quiet and background noise extends across a large range (as great as 100–120 dB). The considerable dynamic range of human psychophysical performance suggests the existence of mechanisms for expanding the dynamic range of neural responses in quiet and for preserving dynamic range in the presence of background noise. If the LOC neurons do act to extend auditory nerve dynamic range in guinea pigs and in humans, they likely also contribute to the ability to discriminate more complex signals, such as vowel-like speech sounds, given that vowel discrimination is based on formant amplitude and frequency (Assmann and Nearey 1987; Le Prell et al. 2001b; Sinnott and Kreiter 1991; Sinnott et al. 1997; Sommers et al. 1992; Sommers and Kewley-Port 1996). That the net effect of disrupting the LOC innervation has the opposite effect in the mouse would suggest that LOC efferent neurons in the mouse do NOT have the primary action of increasing auditory nerve dynamic range. Indeed, dynamic ranges for mouse high spontaneous rate fibers are smaller than those measured in other mammals (Taberner and Liberman 2005).

Taken together, the LOC efferents are strategically positioned to provide a dynamic excitatory/inhibitory up- and downregulation of auditory nerve activity, and lesion-studies clearly reveal that they do so in multiple species. Other approaches that may be useful in defining the roles of specific LOC transmitters include tests of mice that have been genetically modified such that they lack the capability to produce specific proteins (and, thus specific transmitters or specific receptors). This approach has been useful in generating an initial description of the effects of CGRP on auditory nerve activity (Maison et al. 2003b) and defining sensory changes with loss of MOC-mediated cholinergic activity at α9 receptors (May et al. 2002; Prosen et al. 2000). Alternatively, the guinea pig cochlea can be readily accessed and the fluid contents of the scala tympani manipulated. This approach has been helpful in defining the effects of dopamine (d’Aldin et al. 1995; Ruel et al. 2001), dynorphin-like kappa-opioid receptor agonists and also antagonists (Le Prell et al. 2004), as well as CGRP receptor agonists and antagonists (Le Prell et al. 2007).

Although the functional role(s) of the LOC system and its multiple transmitters remains mysterious, a small number of key experiments may ultimately provide insight into functional changes at the systems level. The possibility that the LOC modulates auditory nerve activity in opposite directions in different species raises challenging questions as to the most appropriate experimental model and should ultimately drive in-depth consideration of the selection pressures that would drive the system to act in divergent directions across rodent (and other mammalian) species.
REFERENCES


