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Research report

Attenuation of noise-induced hyperactivity in the dorsal cochlear nucleus by pre-treatment with MK-801

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ABSTRACT

It has previously been hypothesized that hyperactivity of central auditory neurons following exposure to intense noise is a consequence of synaptic alterations. Recent studies suggest the involvement of NMDA receptors in the induction of this hyperactive state. NMDA receptors can mediate long term changes in the excitability of neurons through their involvement in excitotoxic injury and long term potentiation and depression. In this study, we examined the effect of administering an NMDA receptor blocker on the induction of hyperactivity in the dorsal cochlear nucleus (DCN) following intense sound exposure. Our prediction was that if hyperactivity induced by intense sound exposure is dependent on NMDA receptors, then blocking these receptors by administering an NMDA receptor antagonist just before animals are exposed to intense sound should reduce the degree of hyperactivity that subsequently emerges. We compared the levels of hyperactivity that develop in the DCN after intense sound exposure to activity recorded in control animals that were not sound exposed. One group of animals to be sound exposed received intraperitoneal injection of MK-801 twenty minutes preceding the sound exposure, while the other group received injection of saline. Recordings performed in the DCN 26–28 days post-exposure revealed increased response thresholds and widespread increases in spontaneous activity in the saline-treated animals that had been sound exposed, consistent with earlier studies. The animals treated with MK-801 preceding sound exposure showed similarly elevated thresholds but an attenuation of hyperactivity in the DCN; the attenuation was most robust in the high frequency half of the DCN, but lower levels of hyperactivity were also found in the low frequency half. These findings suggest that NMDA receptors are an important component of the hyperactivity-inducing mechanism following intense sound exposure. They further suggest that blockade of NMDA receptors may offer a useful therapeutic approach to preventing induction of noise-induced hyperactivity-related hearing disorders, such as tinnitus and hyperacusis.

1. Introduction

Exposure to intense sound causes neurons in the central auditory system to become hyperactive, whereby their levels of spontaneous neural activity are elevated. There is an abundance of evidence that increased spontaneous activity is an important neural correlate of tinnitus (Roberts et al., 2010; Kaltenbach, 2011; Kalappa et al., 2014; Eggermont and Roberts, 2015; Shore et al., 2016). Thus, an understanding of the mechanism underlying the induction of hyperactivity has considerable clinical relevance. Two general categories of mechanisms are under investigation to understand the emergence of hyperactivity following intense sound exposure. One category involves a shift in the balance of the relative strengths of excitatory and inhibitory synapses, such that the balance swings toward the side of increasing excitation (Willott and Lu, 1982; Salvi et al., 1990; Kaltenbach and McCaslin, 1996; Morest et al., 1997; Shore et al., 2008; Wang et al., 2009; Middleton et al., 2011). This category of changes could occur either pre- or post-synaptically and manifest as perturbations in the relative numbers and/or functional properties of excitatory and inhibitory synapses. The second category of mechanism that could underlie the hyperactive state includes alterations in ion conductance channels, the so-called intrinsic membrane properties of neurons (Holt et al., 2006; Finlayson and Kaltenbach, 2009; Li et al., 2013, 2015). This category could involve alterations in the

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relative strengths of channels that increase (Ca^{++} and Na^{+} conductances) or decrease (K^{+} and Cl^{-} conductances) excitability.

Some receptors, most notably the ionotropic receptors, have both receptive and ion conductance functions. Among these, the N-methyl-D-aspartate receptors (NMDARs) figure prominently in the control of neural activity levels in the dorsal cochlear nucleus (DCN) by their role in the induction of spike-timing-dependent plasticity (Stefanescu and Shore, 2015; Shore et al., 2016). Long term potentiation (LTP) and long term depression (LTD) are two manifestations of spike-timing-dependent plasticity in which the synaptic connections between neurons are strengthened or weakened, respectively, by certain patterns of presynaptic stimulation, such as high frequency pulses, especially when combined with depolarization of the postsynaptic membrane. In the case of LTP, the result is a long lasting increase in the strength of synaptic transmission, which is observed as a sustained increase in postsynaptic excitatory currents. This can manifest as an enhanced level of resting activity and/or stimulus-evoked responsiveness. The mechanism of LTP has been reviewed and summarized recently (Henley and Wilkinson, 2016). It is initiated when NMDA receptors are activated by excess release of glutamate from presynaptic terminals. Unlike LTP, LTD is usually induced following low frequency pulses in the presence of postsynaptic membrane depolarization (Sweatt, 2016).

LTP and LTD have been observed in the DCN at the parallel fiber-fusiform cell synapse and the parallel fiber-cartwheel cell synapse when high frequency or low frequency stimuli are paired with depolarization of the postsynaptic membrane (Fujino and Oertel, 2003; Tzounopoulos, 2008). NMDA receptors are present on DCN fusiform and cartwheel cells (Petralia et al., 1994; Watanabe et al., 1994; Sato et al., 1998; Rubio et al., 2014) and are important for the induction of LTP in fusiform cells and LTD in cartwheel cells of the DCN (Manis and Molitor, 1996; Fujino and Oertel, 2003), as both processes can be blocked by NMDA receptor antagonists (Tzounopoulos et al., 2004, 2007; Fujino and Oertel, 2003). LTP has been hypothesized as a possible mechanism underlying induction of hyperactivity associated with tinnitus (Tzounopoulos, 2008; Mazurek et al., 2010), and recent evidence supports this hypothesis (Gao et al., 2012; Çakır et al., 2015). As mediators of LTP in fusiform cells and LTD in cartwheel cells, which are inhibitory to fusiform cells, NMDARs could serve as potential substrates for induction of tinnitus-related hyperactivity following excessive sound exposure, and thus NMDARs could make good therapeutic targets for its prevention (Brozoski et al., 2002; Shore et al., 2008; Finlayson and Kaltenbach, 2009; Manzoor et al., 2012).

Here, we compared the levels of hyperactivity that develop in intense sound exposed animals pretreated with either the NMDAR antagonist MK-801 or with saline. Our hypothesis was that if NMDARs are involved in the induction of hyperactivity through LTP or LTD type mechanisms, then pretreatment with MK-801 should reduce the induction of hyperactivity.

2. Results

Our results were obtained from the surface of the DCN of 24 animals (10 exposed-MK-801-treated, 10 exposed-saline-treated, and 4 control (unexposed)-saline-treated animals. Complete sets of spontaneous activity recordings were obtained from 150 sites in 10 exposed MK-801-treated animals, 150 sites in 10 exposed saline-treated animals, and 60 sites in 4 control saline treated animals. Frequency response areas were obtained from 9 of the exposed MK-801-treated animals, 9 of the exposed saline-treated animals, and all 4 of the control animals. Both sets of recordings were performed only at one time point at the end of the 26–28 day post-exposure recovery period (see Methods).

Fig. 2 compares neural response thresholds of the exposed-MK-801treated, exposed-saline-treated, and control groups. The data show that neural response thresholds were similarly elevated well above control levels in the two groups of exposed animals as a function of CF. Both exposed groups showed threshold elevations of between 25 and 45 dB above control levels. However, despite the finding that the difference between thresholds in control (unexposed) animals and both groups of exposed animals varied with CF, the thresholds in both groups of exposed animals were almost identical, indicating that MK-801 did not have any protective effect against the decrease in auditory sensitivity following the intense sound exposure.

Fig. 3A shows the spontaneous activity profiles for the three animal groups. Control animals (i.e., those not exposed to intense sound but treated with saline) showed activity of less than 20 events/s at all sites in the lateral 0.6 mm of the DCN. There was a

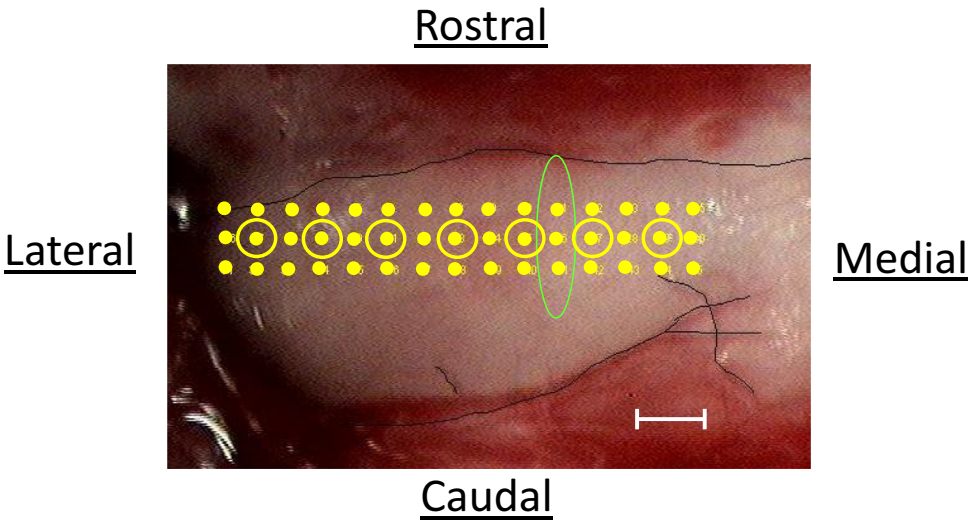

Fig. 1. Image of the left DCN of one of the animals in the control group, viewed from a dorsal perspective, showing the locations of the different recording sites used to map spontaneous activity. Points are spaced 100 μm apart both horizontally and vertically. Locations at which recordings of spontaneous activity were preceded by recordings of frequency tuning are shown by points surrounded by circles. The outline of the DCN is demarcated by the dark lines. The oval highlights 3 points that were averaged to contribute to the point in Fig. 3A for the mean activity at 1.1 mm. Scale bar = 200 μm.