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Tinnitus and hyperacusis: Contributions of paraflocculus, reticular formation and stress

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ABSTRACT

Tinnitus and hyperacusis are common and potentially serious hearing disorders associated with noise-, age- or drug-induced hearing loss. Accumulating evidence suggests that tinnitus and hyperacusis are linked to excessive neural activity in a distributed brain network that not only includes the central auditory pathway, but also brain regions involved in arousal, emotion, stress and motor control. Here we examine electrophysiological changes in two novel non-auditory areas implicated in tinnitus and hyperacusis: the caudal pontine reticular nucleus (PnC), involved in arousal, and the paraflocculus lobe of the cerebellum (PFL), implicated in head-eye coordination and gating tinnitus and we measure the changes in corticosterone stress hormone levels. Using the salicylate-induced model of tinnitus and hyperacusis, we found that long-latency (>10 ms) sound-evoked response components in both the brain regions were significantly enhanced after salicylate administration, while the short-latency responses were reduced, likely reflecting cochlear hearing loss. These results are consistent with the central gain model of tinnitus and hyperacusis, which proposes that these disorders arise from the amplification of neural activity in central auditory pathway plus other regions linked to arousal, emotion, tinnitus gating and motor control. Finally, we demonstrate that salicylate results in an increase in corticosterone level in a dose-dependent manner consistent with the notion that stress may interact with hearing loss in tinnitus and hyperacusis development. This increased stress response has the potential to have wide-ranging effects on the central nervous system and may therefore contribute to brain-wide changes in neural activity.

1. Introduction

Military personnel, mostly those in combat, often develop noise-induced hearing loss (NIHL) (Cave et al., 2007; Helfer et al., 2011), a condition exacerbated in some individuals by tinnitus (a phantom buzzing or ringing sensation) and hyperacusis (sounds perceived as intolerably loud or even painful) (Gilles et al., 2012; Henry et al., 2014; Sun et al., 2011). Recent evidence suggests that tinnitus and hyperacusis arise from maladaptive neuroplastic changes in a distributed neural network that involves portions of the central auditory pathway plus direct and indirect neural connections with other brain regions associated with arousal, stress, anxiety and attention (Auerbach et al., 2014; Baguley et al., 2013; Dornhoffer et al., 2006; Leaver et al., 2016; Lockwood et al., 1999; Moller, 2003). A common feature of intense noise or ototoxic drug exposure is that they reduce the neural output from the cochlea (hypoactivity). To adapt to this altered acoustic input homeostatic mechanisms in the central nervous system "kick in" and increase the gain at successively higher levels of the auditory pathway (Auerbach et al., 2014; Turrigiano, 1999). By the time the neural activity reaches the medial geniculate body (MGB) and auditory cortex (AC) sound-evoked responses are generally larger than normal, a phenomenon referred to as enhanced central gain (Brotherton et al., 2015; Chambers et al., 2016; Chen et al., 2016; Qiu et al., 2000; Salvi et al., 1990). In the case of salicylate-induced hearing loss where there is consistent evidence of tinnitus and hyperacusis, our functional magnetic resonance imaging (fMRI) studies revealed neural hyperactivity in an auditory network

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consisting of AC, MGB and inferior colliculus (IC) (Fig. 1A) plus an emotional center, the amygdala (AMY), that is linked to the AC (Antunes and Moita, 2010; Chen et al., 2015; Newton et al., 2004) (Fig. 1). Unexpectedly, salicylate-induced hyperactivity was also observed in the reticular formation (RF), an area of the brain involved in arousal and sleep, and the paraflocculus (PFL), a part of the cerebellum involved in head-eye motor control and which receives some auditory inputs (Azizi and Woodward, 1990; Horikawa and Suga, 1986). When a functional connectivity analysis was performed on our fMRI data, the AC was found to be strongly coupled to both the RF and PFL.

Paraflocculu and reticular formation: Although the PFL is best known for its role in coordinating eye and head movements (Nagao, 1992; Rambold et al., 2002), some neurons in this region respond to sound through direct and indirect connections with neurons in the cochlear nucleus (CN), IC and AC (Aitkin and Boyd, 1978; Azizi and Woodward, 1990; Azizi et al., 1985, 1981; Horikawa and Suga, 1986; Huang and Liu, 1990; Huang et al., 1982; Kawamura, 1975; Lockwood et al., 1999; Misrahy et al., 1961; Morest et al., 1997; Snider, 1950; Snider and Eldred, 1948). The cerebellum in turn can influence the auditory system (Rossi et al., 1967; Velluti and Crispino, 1979). Importantly, recent studies suggest that the PFL is involved in gating or regulating tinnitus and hyperacusis (Bauer et al., 2013; Chen et al., 2015). In the case of chronic noise-induced tinnitus, manganese enhanced magnetic resonance imaging (MEMRI) revealed enhanced spontaneous activity in the PFL. Moreover, behavioral evidence of chronic noise-induced tinnitus was abolished by lesioning or inactivating the PFL (Bauer et al., 2013; Brozoski et al., 2007, 2013). Collectively, the imaging and behavioral results suggest that the PFL is involved in gating or modulating tinnitus and hyperacusis. In the case of salicylate-induced tinnitus, fMRI revealed enhanced spontaneous activity in the PFL and stronger functional coupling between the PFL and the AC as well (Chen et al., 2015) (Fig. 1B).

Salicylate also enhances spontaneous activity in the RF and increased the functional coupling between the RF and the AC (Fig. 1B). The RF plays an important role in generating the acoustic startle reflex, a strong reflex movement of the head, neck and eyes elicited by brief sound at intensities above ~75 dB SPL. Acoustic signals for eliciting the startle reflex are routed through the cochlear nerve root and the PnC to facial and spinal cord motor neurons that produce abrupt motor responses linked to the acoustic startle reflex (Davis et al., 1982; Lee et al., 1996). Interestingly, high doses of sodium salicylate (SS) greatly enhance the amplitude of the acoustic startle reflex (Lu et al., 2011). Recent research suggests that the preceding effects could be mediated locally or modulated by descending effects from the IC, AC or AMY (Bowen et al., 2003; Chen et al., 2012; Du et al., 2011; Yeomans et al., 2006).

Altogether, the composite results reviewed above suggest that the perceptual features or salience of SS-induced tinnitus may arise from enhanced spontaneous activity, decreased inhibition, increased excitation and/or increased functional connectivity in a distributed network involving the AC, AMY, RF and PFL. While both MEMRI and fMRI imaging techniques revealed enhanced activity in the PFL and RF in animals with noise-induced and salicylate-

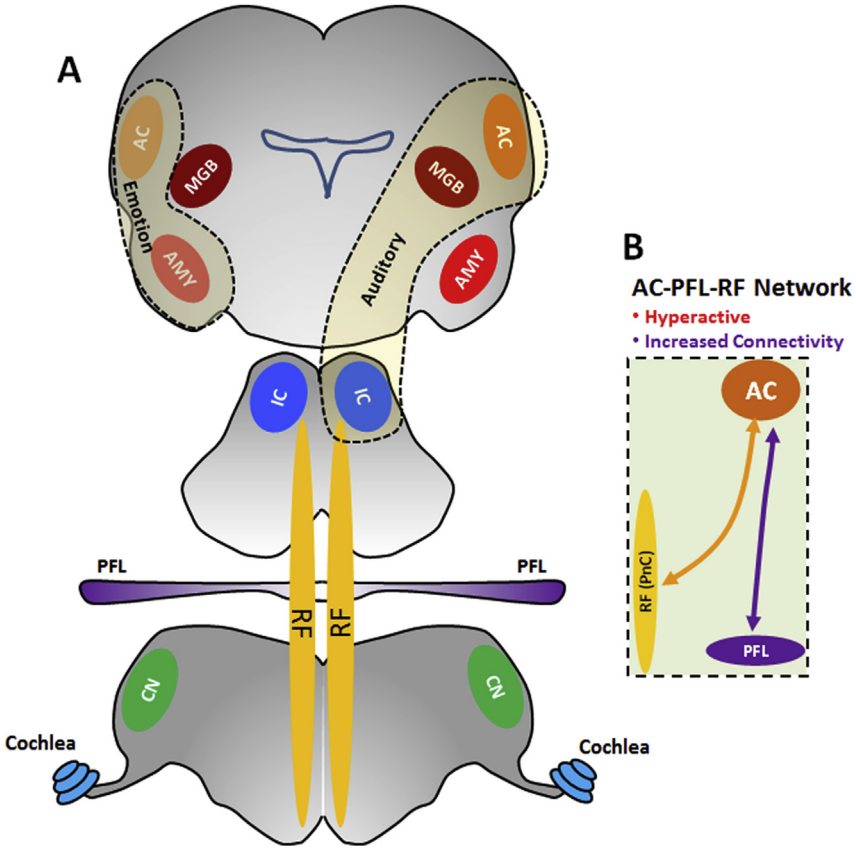

Fig. 1. Model of Tinnitus-Hyperacusis network: (A) High-dose SS induces hyperactivity and increases functional connectivity in an auditory network consisting of AC, MGB and IC (thin dashed line) and emotional network linking the amygdala (AMY) with the AC (thick dashed line). The hyperactivity and enhanced functional connectivity are also occurred in the PFL and RF, areas outside the classical auditory pathway but connected to the AC. (B) SS increases the functional coupling between the AC and the two regions outside the classical auditory pathway, the PFL and RF (PnC).