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Research paper

Psychophysical and neural correlates of noised-induced tinnitus in animals: Intra- and inter-auditory and non-auditory brain structure studies

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ABSTRACT

Tinnitus, a ringing in the ear or head without an external sound source, is a prevalent health problem. It is often associated with a number of limbic-associated disorders such as anxiety, sleep disturbance, and emotional distress. Thus, to investigate tinnitus, it is important to consider both auditory and non-auditory brain structures. This paper summarizes the psychophysical, immunocytochemical and electrophysiological evidence found in rats or hamsters with behavioral evidence of tinnitus. Behaviorally, we tested for tinnitus using a conditioned suppression/avoidance paradigm, gap detection acoustic reflex behavioral paradigm, and our newly developed conditioned licking suppression paradigm. Our new tinnitus behavioral paradigm requires relatively short baseline training, examines frequency specification of tinnitus perception, and achieves sensitive tinnitus testing at an individual level. To test for tinnitus-related anxiety and cognitive impairment, we used the elevated plus maze and Morris water maze. Our results showed that not all animals with tinnitus demonstrate anxiety and cognitive impairment. Immunocytochemically, we found that animals with tinnitus manifested increased Fos-like immunoreactivity (FLI) in both auditory and non-auditory structures. The manner in which FLI appeared suggests that lower brainstem structures may be involved in acute tinnitus whereas the midbrain and cortex are involved in more chronic tinnitus. Meanwhile, animals with tinnitus also manifested increased FLI in non-auditory brain structures that are involved in autonomic reactions, stress, arousal and attention. Electrophysiologically, we found that rats with tinnitus developed increased spontaneous firing in the auditory cortex (AC) and amygdala (AMG), as well as intra- and inter-AC and AMG neurosynchrony, which demonstrate that tinnitus may be actively produced and maintained by the interactions between the AC and AMG.

1. Introduction

Tinnitus is a prevalent health condition that affects 10–15% of the adult population (Axelsson and Ringdahl, 1989) and 33% of the elderly population (Nondahl et al., 2002, 2007). In addition, 3–4 million veterans suffer from tinnitus, with up to 1 million in the US seeking clinical services (Cave et al., 2007; Elder and Cristian, 2009). If left untreated, tinnitus may have debilitating consequences and can impact daily life by causing anxiety, irritability, disturbed sleep patterns, and depression (Crocetti et al., 2009; Hasson et al., 2011; Hebert and Lupien, 2007; Hesser et al., 2009; Rossiter et al., 2006; Stevens et al., 2007). Economically, tinnitus has become a top service-connected disability that affects military personnel and veterans, leading to approximately $2 billion in annual disability compensation in the US (VBA, 2013). Therefore, there is an urgent need to find reliable therapies to treat and cure this condition. However, due to limited understanding of the underlying mechanisms of tinnitus, the development of effective treatment strategies have been hindered. Over the last 15 years, numerous animal and clinical studies have yielded a wealth of

Abbreviations: AC, auditory cortex; AMG, amygdala; FLI, Fos-like immunoreactivity

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information towards the understanding of tinnitus.

Mechanistically, there is a consensus that tinnitus can be of peripheral or central origin. This view is largely based on clinical studies where the auditory nerve has been resected or a microvascular decompression has been performed at the auditory nerve. These studies demonstrated that roughly 50% of tinnitus patients who undergo these resections continue to experience tinnitus, with some patients experiencing tinnitus exacerbation (House and Brackman, 1981; Moller et al., 1993). For tinnitus of central origin, many lines of evidence indicate that tinnitus arises from central maladaptive plasticity. This plasticity is triggered by peripheral damage, such as through noise exposures (including high-pressure blast shockwaves), salicylate, quinine and cisplatin, which can result in deafferentation and lead to compensatory enhancement of neural activity in the central auditory system (Kaltenbach, 2011; Mao et al., 2012; Roberts et al., 2010). Since noise exposure is the most common inducer of tinnitus, predominant efforts have been directed at investigating noise trauma-induced tinnitus and elucidating the underlying mechanisms. Based on published information, noise trauma may cause hyperactivity (increased spontaneous firing), increased bursting events, hypersynchrony (increased neural synchrony), and tonotopic map reorganization along the auditory pathways. The studied auditory brain structures include the dorsal cochlear nucleus, ventral cochlear nucleus (Kraus et al., 2011; Vogler et al., 2011), inferior colliculus and auditory cortex (AC) (Bauer et al., 2008; Eggermont and Roberts, 2004; Kaltenbach, 2011; Mulders and Robertson, 2011; Zhang et al., 2006).

As described above, tinnitus is frequently accompanied by anxiety, irritability, disturbed sleep patterns, and depression, illustrating the involvement of limbic-associated dysfunctions in the etiology of tinnitus. Thus, in addition to the contribution of neural activity changes in auditory structures, neural activity changes in limbic structures may play an important role in tinnitus. This is not surprising given the direct and indirect connections between the central auditory system and limbic structures (Kraus and Canlon, 2012), as well as the fact that limbic-associated functioning, including cognition and emotion, are frequently compromised in tinnitus sufferers (Hallam et al., 2004; Hebert et al., 2012a; Lewis, 2002; Oishi et al., 2010). Some regard the limbic system as obligatory machinery necessary for tinnitus perception, whereas others consider it an auxiliary neural substrate that is involved in the cognitive and emotional impairments in tinnitus (Hallam et al., 2004; Hallberg and Erlandsson, 1993; Lewis, 2002; Oishi et al., 2010). For example, Jastreboff's model proposes that tinnitus originates in the auditory pathway and involves the limbic system where memories of the phantom sound encoded by the amygdala (AMG) are linked to fear and negative emotions stored in the hippocampus. Nevertheless, it is unclear how the AMG directly contributes to the etiology of tinnitus, how its interactions with auditory structures contribute to the development of tinnitus, and whether other non-auditory brain structures are involved in the etiology of tinnitus.

This paper reviews recent findings from the projects supported by the Tinnitus Research Consortium by focusing on psychophysical correlates of tinnitus, auditory and non-auditory neural correlates of tinnitus, as well as the neurophysiological interactions between auditory and non-auditory centers. Psychophysically, we have, over the years, adopted conditioned suppression/avoidance (Heffner and Harrington, 2002) and unconditioned (gap detection acoustic startle reflex paradigm, Turner et al., 2006) paradigms. Our lab has recently developed a conditioned-licking suppression paradigm that requires relatively short baseline training, possesses tinnitus frequency-specific and loudness-sensitive testing at the individual level, as well as versatility for testing tinnitus that results from different inducers (Pace et al., 2015). In addition to testing for tinnitus, we also tested animals' limbic dysfunctions by measuring anxiety and cognitive impairment. Immunocytochemically, we measured Fos-like immunoreactivity (FLI) in both auditory and non-auditory brain structures of rats with behavioral evidence of tinnitus. Electrophysiologically, we measured neural activity changes in the AC and AMG of rats with noise-induced tinnitus.

2. Psychophysical correlates of tinnitus and its associated limbic dysfunctions

2.1. Testing behavioral evidence of tinnitus

Although tinnitus can be induced by many factors, it may only manifest in certain individuals or time points (Cave et al., 2007; Griest and Bishop, 1998). Consequently, numerous behavioral paradigms have been established to determine the perception and characteristics of tinnitus in animals (Bauer and Brozoski, 2001; Berger et al., 2013; Guitton and Dudai, 2007; Heffner, 2011; Heffner and Harrington, 2002; Jastreboff et al., 1988; Kizawa et al., 2010; Lobarinas et al., 2004; Longenecker and Galazyuk, 2012; Luo et al., 2014; Norman et al., 2012; Pace and Zhang, 2013; Ruttiger et al., 2003; Sederholm and Swedberg, 2013; Stolzberg et al., 2013; Turner et al., 2006; Yang et al., 2011; Zheng et al., 2011c). Over the past 15 years, our lab has adopted several paradigms, including conditioned suppression/avoidance (Heffner and Harrington, 2002; Zhang et al., 2003b), gap-detection (Luo et al., 2012; Pace and Zhang, 2013; Zhang et al., 2011), and a recently developed conditioned licking suppression paradigm (Pace et al., 2015).

For the conditioned suppression/avoidance paradigm, water-deprived hamsters were trained to drink water from a spout during the presentation of broadband noise and/or tones (Heffner and Harrington, 2002). Attempts to drink water during silence were suppressed by punishment with a mild electrical shock. Following intense tone exposure, shocks were removed and hamsters that spent a lower average percentage of time drinking during sound trials and not drinking during silent trials were considered tinnitus positive. Hamsters were tested for at least 5–10 days following tone exposure. Key advantages for this early behavioral model were that sufficient data could be collected in a single testing session, and that individual animals could be assessed for tinnitus. The drawbacks, however, were that animals required 32–35 testing sessions to reach baseline criteria and they could not be tested for long-lasting tinnitus.

As an alternative to operant conditioning models, gap-detection has evolved over the past decade into a widely used tool for tinnitus assessment in rodents. The strengths of the gap-detection test are that food/water-deprivation and shock punishments can be avoided, enabling shorter training periods. Additionally, the frequency range of tinnitus can be determined. In our studies using gap-detection, we have found evidence of acute and lasting noise-type and tonal-type tinnitus following noise exposure (Luo et al., 2012; Pace and Zhang, 2013; Zhang et al., 2011). We were also able to identify tinnitus manifestation and frequencies in individual rats, as detailed in our recent report (Pace and Zhang, 2013) (Fig. 1). In addition, we have demonstrated suppression of behavioral evidence of tinnitus using electrical stimulation of the auditory cortex (Zhang et al., 2011) and dorsal cochlear nucleus (Luo et al., 2012). While these findings are collectively in line with the literature (Bauer et al., 2008; Brozoski et al., 2002; De Ridder et al., 2006a; Seidman et al., 2008; Zhang and Kaltenbach, 1998), it is important that multiple behavioral models of tinnitus are used to validate results, especially since tinnitus may not always impair certain measurements like gap-detection (Campolo et al., 2013).

Recently, we have developed a tinnitus paradigm that utilizes conditioned licking suppression (Pace et al., 2015). The benefits of