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Auditory thalamic circuits and $GABA_A$ receptor function: Putative mechanisms in tinnitus pathology

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ABSTRACT

Tinnitus is defined as a phantom sound (ringing in the ears), and can significantly reduce the quality of life for those who suffer its effects. Ten to fifteen percent of the general adult population report symptoms of tinnitus with 1–2% reporting that tinnitus negatively impacts their quality of life. Noise exposure is the most common cause of tinnitus and the military environment presents many challenging high-noise situations. Military noise levels can be so intense that standard hearing protection is not adequate. Recent studies suggest a role for inhibitory neurotransmitter dysfunction in response to noise-induced peripheral deafferentation as a key element in the pathology of tinnitus. The auditory thalamus, or medial geniculate body (MGB), is an obligate auditory brain center in a unique position to gate the percept of sound as it projects to auditory cortex and to limbic structures. Both areas are thought to be involved in those individuals most impacted by tinnitus. For MGB, opposing hypotheses have posited either a tinnitus-related pathologic decrease or pathologic increase in GABAergic inhibition. In sensory thalamus, GABA mediates fast synaptic inhibition via synaptic $GABA_A$ receptors ($GABA_A$Rs) as well as a persistent tonic inhibition via high-affinity extrasynaptic $GABA_A$Rs and slow synaptic inhibition via $GABA_B$Rs. Down-regulation of inhibitory neurotransmission, related to partial peripheral deafferentation, is consistently presented as partially underpinning neuronal hyperactivity seen in animal models of tinnitus. This maladaptive plasticity/Gain Control Theory of tinnitus pathology (see Auerbach et al., 2014; Richardson et al., 2012) is characterized by reduced inhibition associated with increased spontaneous and abnormal neuronal activity, including bursting and increased synchrony throughout much of the central auditory pathway. A competing hypothesis suggests that maladaptive oscillations between the MGB and auditory cortex, thalamocortical dysrhythmia, predict tinnitus pathology (De Ridder et al., 2015). These unusual oscillations/rhythms reflect net increased tonic inhibition in a subset of thalamocortical projection neurons resulting in abnormal bursting. Hyperpolarizing de-inactivation of T-type Ca2+ channels switches thalamocortical projection neurons into burst mode. Thalamocortical dysrhythmia originating in sensory thalamus has been postulated to underpin neuropathies including tinnitus and chronic pain. Here we review the relationship between noise-induced tinnitus and altered inhibition in the MGB.

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Contents

Abbreviations: AAC, auditory association cortex; AI, primary auditory cortex; Ca^{2+}, calcium; GABA, g-amino butyric acid; GBX, gaboxadol; IC, inferior colliculus; MGB, medial geniculate body; MGv, ventral division of MGB; MGd, dorsal division of MGB; MGm, medial division of MGB; PPTg, pedunculopontine tegmental nucleus; TRN, thalamic reticular nucleus

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1. Tinnitus as a significant health problem

Tinnitus is defined as a phantom sound (ringing in the ears), and can significantly affect the quality of life for those experiencing it (Norena, 2011; Tyler et al., 1993). Tinnitus affects an estimated 10–15% of the general adult population with 1.6% to 0.5% rating tinnitus between severely annoying and profoundly impacting their quality of life (Axelsson & Ringdahl, 1989; Baguley et al., 2013; Nondahl et al., 2002; Shargorodsky et al., 2010). The most common cause of tinnitus is high-level noise exposure (Axelsson & Ringdahl, 1989; Brusis, 1993; Humes et al., 2006; Kaltenbach, 2011; Nondahl et al., 2009; Salmivalli, 1977; Taylor & Williams, 1966). Helfer et al. (2005) found that soldiers deployed to battle zones were 52.5 times more likely to suffer auditory damage than non-deployed soldiers. The American Tinnitus Association (ATA) reports that 60% of all cases of auditory injury, including tinnitus, within the Iraq and Afghanistan veteran population were the result of a blast-induced mild traumatic brain injury. A Department of Defense study of Iraq service veterans found that 43% of those veterans seen one month after a blast exposure continued to report tinnitus. Noise-induced hearing loss has dramatically increased across the military such that impaired hearing acuity (hearing loss and tinnitus) is the second most common VA disability award, exceeding $1.28 billion per year (ATA). For those disabled by tinnitus, the personal sequelae may include: depression, anxiety, sleep disturbances, inability to concentrate, fatigue, and sometimes suicide (Henry et al., 2014; Roberts et al., 2010, 2013). Invariably, individuals disturbed by their tinnitus are those whose attention is bound to the sensation in their head. The magnitude of tinnitus distress may relate to attention fixed on this phantom auditory percept (Jacobson et al., 1996; see below and Roberts et al., 2013). Brain circuits that are critically involved in the control of attention, arousal and learning, project to sensory structures including the auditory cortex and auditory thalamus (medial geniculate body, MGB) and associated structures such at the thalamic reticular nucleus (Fig. 1) (Metherate, 2011; Motts & Schofield, 2010; Zikopoulos & Barbas, 2006, 2012). A main goal of the research supported by the military is to identify neural changes associated with loud-sound-induced tinnitus. These changes can then be selectively targeted by drugs that ameliorate the attentional aspects of tinnitus. Scientific advances in this area would benefit the general population as well as military personnel and veterans who experience emotional duress from their tinnitus.

An emergent hypothesis supported by recent studies suggests that altered balance between excitatory and inhibitory neurotransmission within central nervous system circuits may underpin chronic human neuropathies including tinnitus and chronic pain (Kaltenbach, 2011; Leaver et al., 2011; Norena, 2011; Auerbach et al., 2014; Rauschecker et al., 2015; Roberts et al., 2010; Sedley et al., 2015). The MGB is an obligate auditory brain center well-positioned to gate the percept of sound as it travels to the auditory cortex and to limbic structures. Recent functional models of tinnitus pathology suggest that individuals most affected by tinnitus demonstrate abnormal function in limbic and thalamocortical circuits (Leaver et al., 2011; Rauschecker et al., 2010; Winer et al., 1999). These reviews by Rauschecker and colleagues strongly implicate the MGB and its ascending and descending connections as key components of the tinnitus network (Leaver et al., 2011; Rauschecker et al., 2010; Shinonaga et al., 1994).

2. Auditory thalamus (MGB)

The MGB transforms the ascending sensory code while gating the relative salience of sensory signals, in part, through adjustments in thalamocortical rhythmicity (Cope et al., 2005; Goard & Dan, 2009; Hughes et al., 2008; Wafford et al., 2009). The MGB receives lemniscal and extralemniscal ascending inputs as well as inputs from the brainstem, thalamic reticular nucleus, limbic structures and descending inputs from auditory and nonauditory cortices (Fig. 1) (Bajo et al., 1995; Lee & Winer, 2008a, 2008b, 2008c; Rouiller & Ribaupierre, 1990; Rouiller & Welker, 1991; Winer & Larue, 1987; Winer et al., 1999). The ventral division (MGv) is believed to be primarily auditory/lemniscal receiving tonotopically-aligned primary ascending excitatory and inhibitory projections from inferior colliculus (Peruzzi et al., 1997; Saint Marie et al., 1997a). The dorsal (MGd) and medial (MGm) divisions of the

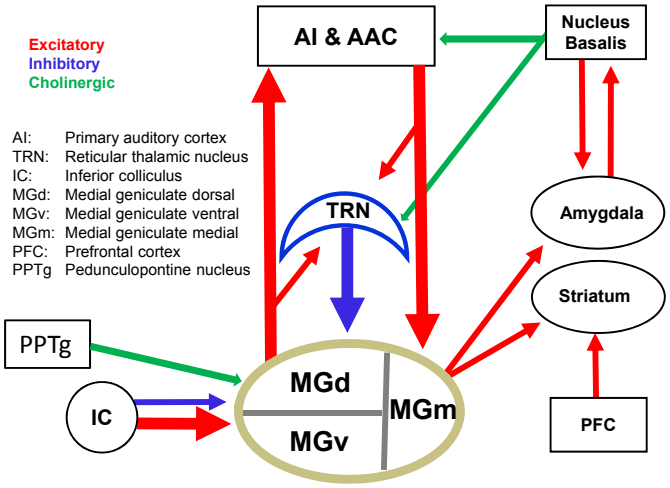

Fig. 1. Major connection of the Medial Geniculate Body (MGB). Ascending projections from the Inferior Colliculus (IC) and descending projections from auditory cortex (AI, AAC) and reticular thalamic nucleus (TRN) include glutamatergic and GABAergic components. Connections to the amygdala, striatum and the TRN are likely important in the tinnitus network.

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