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Research paper

The effect of supplemental dietary Taurine on Tinnitus and auditory discrimination in an animal model

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ABSTRACT

Loss of central inhibition has been hypothesized to underpin tinnitus and impact auditory acuity. Taurine, a partial agonist at inhibitory glycine and γ-amino butyric acid receptors, was added to the daily diet of rats to examine its effects on chronic tinnitus and normal auditory discrimination. Eight rats were unilaterally exposed once to a loud sound to induce tinnitus. The rats were trained and tested in an operant task shown to be sensitive to tinnitus. An equivalent unexposed control group was run in parallel. Months after exposure, 6 of the exposed rats showed significant evidence of chronic tinnitus. Two concentrations of taurine in drinking water were given over several weeks (attaining average daily doses of 67 mg/kg and 294 mg/kg). Water consumption was unaffected. Three main effects were obtained: (1) The high taurine dose significantly attenuated tinnitus, which returned to near pre-treatment levels following washout. (2) Auditory discrimination was significantly improved in unexposed control rats at both doses. (3) As indicated by lever pressing, taurine at both doses had a significant group-equivalent stimulant effect. These results are consistent with the hypothesis that taurine attenuates tinnitus and improves auditory discrimination by increasing inhibitory tone and decreasing noise in the auditory pathway.

1. Introduction

Chronic tinnitus, the perception of sound without an external acoustic stimulus, affects a significant proportion of the adult population. For those who experience tinnitus, 3–5% find it to be bothersome and at times disabling (Cooper, 1994). The pathophysiology responsible for tinnitus is not completely understood. Animal models have been developed to understand the basic neuroscience of tinnitus and to screen potential therapeutics (Brozoski and Bauer, 2008). Using these models, evidence from a number of laboratories points to decreased inhibition in the auditory pathway as an important component of tinnitus pathology (Bauer et al., 2008; Kaltenbach, 2007; Salvi et al., 2000; Wang et al., 2009). We recently reported that vigabatrin, a γ-amino butyric acid (GABA) agonist, effectively and reversibly eliminated the evidence of acoustic-trauma-induced chronic tinnitus in rats (Brozoski et al., 2007a). Using a similar procedure, the present study examined the effect of taurine on psychoacoustic performance and tinnitus.

Taurine is a sulfur-containing β-amino acid found at high concentrations in mammals. As a "non-coding" amino acid, it is derived directly from food sources and indirectly from the metabolism of other common sulfur-containing amino acids such as cysteine and methionine (Birdsall, 1998; Huxtable, 1992; Oja and Saransaari, 2007). Taurine is distributed widely in the mammalian body (approximately 1 g/kg in humans) including blood plasma, heart, muscle, and brain tissue, and may beneficially participate in diverse physiological processes. Examples reported in the literature include, cell volume regulation (Hoffmann et al., 2009), weight reduction (Tsuboyama-Kasaoka et al., 2006), antioxidant action (Atmaca, 2004; Fang et al., 2002), facilitation of neural development (Aerts and Van Assche, 2002; Sturman, 1986; Sturman et al., 1986) and thermoregulation (Birdsall, 1998; Huxtable, 1992; Oja and Saransaari, 2007; Sgaragli et al., 1981, 1996). Experimentally-induced taurine depletion has been shown to exacerbate the retinopathy produced by the GABA-transaminase inhibitor, vigabatrin (Jammoul et al., 2009).

Abbreviations: ABR, acoustic brainstem-evoked response; BBN, broad-band noise; DCN, dorsal cochlear nucleus; GABA, γ-amino butyric acid; GlyR, glycine receptors; $GABA_AR$, $GABA_A$ receptors; $GABA_BR$, $GABA_B$ receptors; IC, inferior colliculus; MGB, medial geniculate body; R, suppression ratio; SPL, sound pressure level.

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Relevant to the present study, taurine has been shown to act as an inhibitory neuromodulator, although its status as a neurotransmitter is unresolved. There is evidence of taurine specific receptors (Frosini et al., 2003; Wu et al., 1992, 1990). Taurine has been shown to inhibit neural activity by acting at glycine (GlyR), $GABA_A$ ($GABA_AR$), and $GABA_B$ ($GABA_BR$) receptors (Albrecht and Schousboe, 2005), and is distributed throughout the central and peripheral auditory system (Contreras and Bachelard, 1979; Harding and Davies, 1993). In the central auditory system it has been shown to activate GlyRs in rat inferior colliculus (IC) (Xu et al., 2004, 2006), and may act similarly in the auditory midbrain and brainstem, including the cochlear nucleus, superior olivary complex, and nuclei of the lateral lemniscus (Friauf et al., 1997). Although the inhibitory role of taurine is widespread in the CNS, it may have an excitatory role in the periphery. Liu et al. (2006, 2008) have shown that increased taurine elevates cochlear outer hair cell and spiral ganglion neuron Ca^{2+} influx.

In addition to its action at strychnine-sensitive GlyRs, taurine has been shown to activate extrasynaptic $GABA_ARs$, producing a long-lasting tonic Cl^- current. This has been shown in mouse ventrobasal thalamus (Jia et al., 2008). Recently we have identified a dose-dependent tonic inhibition of neurons in the rat medial geniculate body (MGB), mediated by extrasynaptic δ-subunit containing $GABA_ARs$ (Richardson et al., 2009). Extrasynaptic $GABA_ARs$ have high ligand selectivity, low benzodiazepine sensitivity, and are slow to desensitize. These receptors are responsible for a long-lasting tonic Cl^- influx that decreases cellular excitability. This stabilizing effect has been well documented in thalamic (Cope et al., 2005; Jia et al., 2005) neurons, the dentate gyrus of the hippocampus (Stell and Mody, 2002; Yeung et al., 2003), and cerebellar granule cells (Belelli et al., 2009; Brickley et al., 1996; Nusser and Mody, 2002). In thalamus, a number of electrophysiological and molecular studies have shown extrasynaptic $GABA_ARs$ contain α_4 and δ subunits (Chandra et al., 2006; Herd et al., 2009; Sur et al., 1999; Wisden et al., 1992). $GABA_ARs$ containing α_4 and δ subunits may be particularly important for the central inhibitory effect of taurine.

Not only can taurine in the brain be derived from sulfur-containing amino acids, but it can also enter by crossing the blood brain barrier via a Na^+/Cl^- dependent taurine transporter, TauT (Chung et al., 1994; Kang et al., 2002; Ohtsuki, 2004; Ramanathan et al., 1997; Tamai et al., 1995). It has been shown that performance on various behavioral tasks is significantly altered by supplemental dietary taurine as well as taurine administered by gastric lavage (El Idrissi, 2008; Vohra and Hui, 2000). Long-term continuous taurine administration is likely more effective than acute dosing since brain levels of taurine were not significantly altered before and after a single gastric lavage (Sved et al., 2007).

In the present experiment it was hypothesized that increasing systemic taurine levels through dietary supplement, would modulate neural activity in the central auditory pathway through either GlyR activation or increasing tonic inhibition mediated by extrasynaptic $GABA_ARs$. Enhanced inhibition, in the thalamus and elsewhere, would significantly modulate auditory sensation and may be capable of attenuating ascending activity that comprises the tinnitus signal.

2. Method

2.1. Subjects

Seventeen adult male Long–Evans rats, 4 months old at the start of the experiment, were individually housed and maintained at 25 °C with a 12/12 h reversed light/dark schedule. One subject was discarded at the beginning of the experiment because of failure to acquire basic operant skills necessary for auditory testing. The sixteen remaining subjects were trained, exposed, and tested in parallel throughout the study.

The methods used in the present study were similar to those reported in previous studies investigating the effect of drugs on tinnitus in rats (Bauer and Brozoski, 2001; Brozoski et al., 2007a). A summary of the experimental time line appears in Table 1.

2.2. Acoustic exposure and calibration methods

Eight randomly selected subjects were exposed once to loud sound before operant training and pre-drug testing. These subjects will be referred to as “exposed”. The eight unexposed control subjects will be referred to as “unexposed”. All subjects were anesthetized to an areflexive state with an isoflurane/O_2 mixture (Aerrane, Baxter Healthcare Corp., Deerfield, IL, USA) placed in a masked head holder, and had hearing thresholds determined using auditory brainstem-evoked potentials (ABR, described below). The exposed subjects were then exposed once unilaterally for 90 min to band-limited noise (similar to Bauer and Brozoski, 2001; Brozoski et al., 2007a,b). The exposure stimulus was produced using a noise generator (Grayson-Stadler 1724, Eden Prairie, MN 55344, USA), bandpass filter (KrohnHite 3384, 8 pole Butterworth filter, Brockton, MA, USA), audio amplifier (55ES, Sony, New York, NY, USA), delivered monaurally using a speaker driver (FT17H, Fostex, Tokyo, Japan) in a custom enclosure funneling to a 2 cm flexible tube that fits into the auditory canal. Peak stimulus level, centered at 16 kHz, was 116 dB sound pressure level (SPL), with an approximately linear decay to ambient levels at 6 and 24 kHz. Acoustic values were calibrated using a Brüel & Kjaer (Norcross, GA, USA) Pulse sound measurement system (Pulse 13 software), equipped with a 3560C high-frequency module, and a 4138 pressure-field microphone (Brüel & Kjaer) coupled to the transducer using rubber tubing with the internal dimensions of an adult rat external auditory canal. The sound measurement system permitted linear sound level measurements between 0 and 140 dB (re 20 μPa) and spectral analysis between 6.5 Hz and 100 kHz. Calibrations were carried out as unweighted linear SPLs. All sound levels reported in the present experiments are unweighted measures.

Sound levels were calibrated in the operant test chambers using the Brüel & Kjaer Pulse system described above, equipped with a Brüel & Kjaer 4191-L free-field microphone. This system permitted linear sound level measurements to be made between 0 and 140 dB (re 20 μPa) with spectral resolution between 3.15 Hz and 40 kHz. The microphone was positioned in each test chamber at a location 10 cm below the lid-mounted speaker, in the approximate location of a rat’s head during testing. A cloth bundle approximating the volume of a rat was placed in the test chamber

Table 1
The experimental time line.

Phase	Arrive	Sound exposure	Initial training	Tinnitus test	Taurine 0 mg	Taurine 1 mg	Taurine 4 mg	Washout1	Washout 2
Study Week		1	15	22	39	42	44	50	57
Subject Age (mo)	3.0	3.1	6.4	8.0	11.9	12.6	13.0	14.4	16.0