JOURNAL OF
OTOLOGY

ACOUSTIC STARTLE RESPONSE AFFECTED BY AGING AND CHOLINERGIC NEUROTRANSMITTERS

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Abstract

The acoustic startle response has been used to evaluate tinnitus and hyperacusis in animal models. Gap induced prepulse inhibition of the acoustic startle reflex (gap-PPI) is affected by tinnitus and loudness changes. Since tinnitus and reduced sound tolerance are commonly seen in elderly, we measured gap-PPI in Fischer 344 rats, an aging related hearing loss model, at different ages: 3-5 months, 9-12 months, and 15-17 months. The startle response was induced by three different intensity of sound: 105, 95 and 85 dB SPL. Gap-PPI was induced by different duration of silent gaps from 1 to 100 ms. When the startle was induced by 105 dB SPL sound intensity, the gap-PPI induced by 50 ms silent gap was significantly lower than those induced by 25 or 100 ms duration, showing a "notch" in the gap-PPI function. The "notch" disappeared with the reduction of startle sound, suggesting the "notch" may be related with hyper-sensitivity to loud sound. As the intensity of the stimulus decreased, the appearance of the hyperacusis-like effect decreased more quickly for the youngest group of rats. We also tested scopolamine, a muscarinic acetylcholine receptor antagonist, and mecamylamine, a nicotinic acetylcholine receptor antagonist, on the effect of gap-PPI. When scopolamine was administered, the results indicated no addition effect on the hyperacusis-like phenomenon in the two older groups. Mecamylamine, the nicotinic antagonist also showed effects on the appearance of hyperacusis on rats in different ages. The information derived from the study will be fundamental for the further research in determining the cause and treatment for hyperacusis.

Key words: startle reflex, hyperacusis, acetylcholine, scopolamine

Introduction

Hyperacusis, an unusual intolerance to environmental sound seen in children and adults, is a commonly reported disorder that has received very little attention[1]. This disorder has been described in a variety of pathologies including acoustic trauma, stapedectomy, Williams syndrome in children, migraine attacks, facial paralysis, autistic spectrum disorder and tinnitus[2]. Currently, the prevalence of hyperacusis is 9-15% in the general population and markedly increased in the tinnitus population [3]. The limited attention to hyperacusis in the literature greatly contrasts the large number of hyperacusis patients who suffer from this disorder[2]. The lack of attention may be partly due to the lack of animal model in which the neuromechanism of this disorder can be studied [4].

Currently, in the clinical setting, the Loudness Discomfort Level (LDL) is the most widely used subjective method of measuring hyperacusis in human subjects. However, some studies found the LDL did not match the patient's complains on hyperacusis[5]. Loudness growth function is another subjective measure whereby the subject uses a fractionation method of adjustment procedure to adjust the loudness level in the test ear to equal two times the loudness level of the reference ear [6]. However, both these tests can be severely affected by the patients' subjective factors.

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The acoustic startle reflex is a contraction of muscles in response to a sound of high intensity which can be used to measure the behavioral response to sound in animals. Previous studies have indicated that individuals complaining of suprathreshold hyperacusis with a probable neurochemical etiology, show abnormally low acoustic reflex thresholds when compared to normal subjects. With more study in this area, acoustic reflex testing could become more critical in the evaluation of hyperacusis and its origin. Ison et al. recently reported that aging induced hyperacusis could be measured using the startle reflex facilitation in mice [7]. The idea of facilitation of startle reflex is the founding principle for measuring hyperacusis through use of startle reflex testing. Facilitation occurs when the animal responds more to the startle stimulus as they age or as the intensity of the startle stimulus increases[7]. When preceding the startle stimuli by another stimulus, either a narrowband noise or a silent interval, the startle reflex is suppressed[8]. This phenomenon is known as prepulse inhibition and is seen through narrowband prepulse inhibition (NB-PPI) testing and gap prepulse inhibition (Gap-PPI) testing. The Gap-PPI paradigm allows us to see an interaction between facilitation and inhibition to the startle stimulus (reaction to the stimulus) when the intensity of the startle stimulus decreases.

Fischer 344 rats have been shown to develop aging related hearing loss much more quickly than other strains of rats. According to Bielefeld et al., Fischer 344 rats begin to develop an aging related hearing loss at 12 months. Auditory brainstem response (ABR) results indicate a significant hearing loss of 50-60 dB SPL for 20 to 40 kHz and a 20 dB SPL loss for 5-10 kHz in 24 months old Fischer 344 rats. The facilitation of the startle reflex at 50 ms and the progression of hearing loss in Fischer 344 rats provide an exemplary animal model for testing aging induced hyperacusis (or tinnitus) through the use of startle reflex. With the possibility of a novel and valid method of detecting hyperacusis in an animal model, there are endless possibilities for discovering the site, cause and treatments for this disorder.

Hyperacusis can be found in several different populations. Considering that hyperacusis is often related to tinnitus and tinnitus is often associated with sensorineural hearing loss, research involving aging-related hearing loss could provide insight into the etiology of hyperacusis. Sensorineural hearing loss is associated with reorganization in the central auditory system and this reorganization is thought to be associated with the development of tinnitus and hyperacusis. Dr. Ison's study pertaining to hearing loss showed hyperacusis like behavior in old mice in the low frequencies. The hyperacusis effect was pronounced by a delayed exaggeration of the acoustic startle reflex in these mice with age-related hearing loss. This suggests a useful model for detecting tinnitus and central hyperacusis in animals with age-related hearing loss may be through acoustic startle reflex testing[7].

In the auditory system, when a hearing loss is present, the signal sent through neurotransmitters is reduced and some synapses are no longer stimulated. This reduction in stimulation leads to reorganization of the central system to which these signals were previously sent. When hyperacusis or tinnitus presents as a possible result of this reorganization, it is plausible to relate the change in neurotransmitter release to the development of tinnitus or hyperacusis. Some of the most common neurotransmitters related to the auditory system are found in cholinergic receptors[9]. A current area of interest in tinnitus research is the cholinergic receptor influence on tinnitus behavior. Previous studies have found that tinnitus may be related to spontaneous activity in the dorsal cochlear nucleus[10,11]. Cholinergic receptors have been found in the cochlear nucleus[12,13] indicating that changes in acetylcholine receptors may affect spontaneous activity at this region and therefore affect symptoms such as tinnitus and hyperacusis. Acetylcholine receptor antagonists could block the effects found in the cochlear nucleus that occurs in conjunction with tinnitus and hyperacusis whereby eliminating the perception of these disorders. As the prevalence of hyperacusis in patients with continuous tinnitus is as high as 80% [2], the apparent link between these two disorders has led to the speculation of common mechanisms.

Materials and methods

Animals: Fischer 344 rats, both male and female, were assigned into three groups: rats ages 3-5 months old (n = 6), rats ages 9-12 months old (n = 5), and rats ages 15-17 months old (n = 5). Each group of rats went through the same series of testing. Acoustic startle reflex testing included NB-PPI and gap-PPI at a normal presentation level (105 dB SPL) and two reduced intensity presentations levels (10 dB SPL reduced and 20 dB SPL reduced). Drug testing included three consecutive days of subcutaneous injections of Scopolamine (0.5 mg/kg). On a separate occasion, at least one week after scopolamine injections, three consecutive days of subcutaneous injections of mecamylamine (3 mg/kg) were administered. Scopolamine was diluted to 2 mg/ml and mecamylamine was diluted to 1 mg/ml.

Acoustic Startle Reflex Testing Apparatus: Gap in-

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