Effect of Neuronal Excitability in Hippocampal CA1 Area on Auditory Pathway in a Rat Model of Tinnitus

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Abstract

Background: Tinnitus is a common disorder that causes significant morbidity; however, the neurophysiological mechanism is not yet fully understood. A relationship between tinnitus and limbic system has been reported. As a significant component of the limbic system, the hippocampus plays an important role in various pathological processes, such as emotional disturbance, decreased learning ability, and deterioration of memory. This study was aimed to explore the role of the hippocampus in the generation of tinnitus by electrophysiological technology.

Methods: A tinnitus model was established in rats through intraperitoneal injection of salicylate (SA). Subsequently, the spontaneous firing rate (SFR) of neurons in the hippocampal CA1 area was recorded with in vivo multichannel recording technology to assess changes in excitability induced by SA. To investigate the effect of excitability changes of hippocampus on the auditory pathway, the hippocampus was electrically stimulated and neural excitability in the auditory cortex (AC) was monitored.

Results: Totally 65 neurons in the hippocampal CA1 area were recorded, 45 from the SA group (n = 5), and 20 from the saline group (n = 5). Two hours after treatment, mean SFR of neurons in the hippocampal CA1 area had significantly increased from 3.06 ± 0.36 Hz to 9.18 ± 1.30 Hz in the SA group (t = −4.521, P < 0.05), while no significant difference was observed in the saline group (2.66 ± 0.36 Hz vs. 2.16 ± 0.36 Hz, t = 0.902, P > 0.05). In the AC, 79.3% (157/198) of recorded neurons showed responses to electrical stimulation of the hippocampal CA1 area. Presumed pyramidal neurons were excited, while intermediate neurons were inhibited after electrical stimulation of the hippocampus.

Conclusions: The study shows that the hippocampus is excited in SA-induced tinnitus, and stimulation of hippocampus could modulate neuronal excitability of the AC. The hippocampus is involved in tinnitus and may also have a regulatory effect on the neural center.

Key words: Auditory Cortex; Electrical Stimulation; Hippocampus; Neuronal Excitability; Tinnitus

Introduction

Tinnitus is a common disorder that causes significant morbidity; it has a prevalence ranging from 10% to 15%.¹,² Many people habituate to tinnitus, but the phantom sound severely impairs quality of life for some patients, even leads to depression and suicide. In 1993, Jastreboff and Hazell³ introduced a neurophysiological model of tinnitus, assuming that once the abnormal signal of the auditory system is perceived by the subcortical nerve center, the auditory cortex (AC) will recognize this signal as important, and enhance its perception and evaluation. The limbic system is involved in this pathway and results in the development of negative cognition and emotion, intensifying the patient’s attention to tinnitus, resulting in anxiety and fear emotions.⁴,⁵ This negative emotion further enhances the perception of tinnitus signals, causing a vicious cycle between tinnitus and negative emotion.⁶

Alterations in cortical regions involved in emotion, memory, perception, and salience functions among tinnitus patients have been reported previously.⁷,⁸ As an important component of the emotion and memory networks, the hippocampus is essential for emotional reaction, learning, and memory.⁹,¹⁰ Hippocampus could constantly update the

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tinnitus signal that is generated in the thalamocortical system preventing habituation. The CA1 area of the hippocampus is of significant importance for neurotransmission in and out of hippocampus, and the possibility of a role for this area in tinnitus is intriguing.

Neuronal excitability, recorded by direct insertion of an electrode into the targeted brain area, can provide a reliable understanding of neuronal activity. In this study, we recorded changes in the neuronal excitability in the hippocampus, to gain understanding of the possible regulatory effect of the hippocampus in tinnitus. We also electrically stimulated the hippocampus and recorded the neuronal excitability of the AC. The objective of our study was to investigate the potential role of the hippocampus, particularly the CA1 area, in tinnitus, to provide electrophysiological evidence for the pathogenesis of tinnitus.

**METHODS**

**Ethical approval**
All procedures used in this study were approved by the Institutional Animal Care and Use Committee of Peking University Health Science Center (No. 2016-0010), and were conducted in accordance with these guidelines.

**Animals**
Adult male Sprague-Dawley rats (250–350 g) were obtained from the medical experimental animal center of Peking University Health Science Center. Animals were individually housed with free access to food and water, and were maintained under environmentally controlled conditions (12-h light-dark cycles, 22 ± 1°C, and 50–70% relative humidity).

**Experimental design**

**Experiment 1**
Rats were randomly divided into a saline group (n = 5) and a salicylate (SA) group (n = 5). Rats in the SA group were injected with SA (350 mg/kg, i.p.), which has previously been shown to induce tinnitus. This tinnitus model has been widely used in experimental studies and its reliability has been verified by both audiology and behavioral testing. The saline group rats received an injection of an equal volume of saline.

Rats were anesthetized with isoflurane (3.0–5.0% during induction for 3 min and then 1.5–2.5% for maintenance) through a gas pump (RWD R520IP, Shenzhen, China). When full-depth anesthesia was reached, as assessed by foot withdrawal in response to a foot pinch, the rats were placed in a stereotoxic apparatus (RWD 68026R, Shenzhen, China) for surgery. The body temperature of the rats was maintained at 37.0°C by means of an animal heating pad. The CA1 area (AP = −4.56 mm, ML = 1.90 mm, DV = −2.80 mm) was confirmed according to the rat brain stereotactic coordinates (Paxinos and Watson, 2007). The hippocampal CA1 area of the left hemisphere was exposed as mentioned above. The dura of the brain was removed with a surgical microscope, and a 16-channel silicon electrode was implanted in the dorsal hippocampus to record the neuronal activity in the CA1 area.

The basal spontaneous firing rate (SFR) of the CA1 area was recorded before treatment with saline or SA. The SFR was also recorded at six time points after the treatment: 0.5, 1.0, 1.5, 2.0, 2.5, and 3.0 h.

**Experiment 2**
Twelve rats were anesthetized and placed in stereotaxic head frame on a heating pad. The hippocampal CA1 area of the left hemisphere was exposed as in experiment 1 and a stimulating electrode was inserted into the CA1 area for delivering electrical stimulation. The AC (AP = −3.96 mm, ML = −6.50 mm, DV = −[4.40–5.40] mm) of the right hemisphere was exposed as previously described. The dura mater was removed and the recording electrode was then advanced along the dorsoventral axis into the AC.

Electrical stimulation was performed using a custom-made bipolar tungsten electrode. Electrical stimuli were delivered as shock trains (pulse duration: 0.1 ms, train duration: 1 min, rate 50 Hz). The SFR of the AC was recorded before and immediately after delivering electrical stimulation to the CA1 area. For each time point, the recording duration was more than 3 min.

**Spike train analysis**
The electrophysiological techniques used in this study are similar to those described in previous publications. The iridium oxide electrode was composed of two shanks, each of which had eight recording sites (100 µm each site, 0.2–0.4 MΩ impedance), with an intershank distance of 200 µm. Recordings sites were staggered to provide a two-dimensional arrangement. Three stainless steel screws, threaded into the cranium, were used as ground electrodes during recordings. The electrode was moved slowly to the target region using stereotaxic coordinates.

The output of the electrode was connected to a 16-channel preamplifier (Plexon Inc, Dallas, TX, USA) using a flexible low-noise cable. Signals were sent to a multichannel acquisition processor and recorded. Signals were analyzed using Offline Sorter (Plexon Inc, Dallas, TX, USA) and NeuroExplorer (Nex Technologies, Madison, AL, USA) for spike sorting. The valley-seeking scan algorithm was used for principal component analysis and K-mean scan was selected for automatic neuron clustering. Then, manual verification of automatic clusters was performed. Abnormal waveforms such as interference waveforms and waveforms occurring within the refractory period (1 ms) were removed. Timestamps of neuronal spiking were imported to NeuroExplorer for comparison of crosscorrelations to prevent cell data duplication.

**Histological studies**
At the end of recordings, rats were deeply anesthetized and perfused with 4% paraformaldehyde solution. Rat brains
were removed for histological analysis. The locations of the electrodes were confirmed by microscope observation. Only rats with correctly implanted electrodes were included in the data analysis.

**Statistical analysis**

Statistical analysis was performed with SPSS 24.0 (SPSS Inc., Chicago, IL, USA). Data were expressed as mean ± standard error. The Shapiro-Wilk test was used to verify whether the data conformed to a Gaussian distribution. Mean values of normally distributed continuous variables were compared using the independent sample t-test, while those with a nonnormal distribution were compared with the Mann-Whitney U-test. Paired sample t-tests were used to identify the significance of pairwise comparisons. A $P < 0.05$ was considered as significantly different.

**Results**

**Effect of salicylate on neuronal firing rate of hippocampal CA1 area**

We were able to record the firing activity of 65 neurons in the hippocampal CA1 area, 45 from the SA group ($n = 5$) and 20 from the saline group ($n = 5$) [Figure 1a]. The mean SFR was 3.06 ± 0.36 Hz before SA injection and 3.60 ± 0.37 Hz at 3.0 h after SA administration, while the mean SFR of the saline group was 2.66 ± 0.36 Hz and 2.06 ± 0.41 Hz before and 3.0 h postsaline treatment, respectively. However, t-tests indicated no statistical difference at the time point of 0 h and 3.0 h in both the saline group ($t = 1.009$, $P > 0.05$) and SA group ($t = -1.023$, $P > 0.05$).

Considering that the onset time of tinnitus is usually about 2.0 h after SA treatment, we also evaluated changes in the SFR at 2.0 h after SA injection. As shown in Figure 1b, 2.0 h after SA injection, the SFR of 29 neurons increased and that of 16 neurons decreased. However, the SFR of nine neurons increased and that of 11 neurons decreased in the saline group. More specifically, 2.0 h after treatment, the mean SFR of neurons in the hippocampal CA1 area had significantly increased from 3.06 ± 0.36 Hz to 9.18 ± 1.30 Hz in the SA group ($t = -4.521$, $P < 0.05$), while no significant difference was noticed in the saline group (2.66 ± 0.36 Hz vs. 2.16 ± 0.36 Hz, $t = 0.902$, $P > 0.05$). The Mann-Whitney U-test revealed significant differences between the SA group and the saline group at the time points of 0.5 h, 1.5 h, 2.0 h, 2.5 h, and 3.0 h, indicating an elevation of the overall SFR of the CA1 area by SA treatment, as shown in Figure 2. As compared with basal SFR, neuronal discharges changed significantly at the time point of 0.5 h, 2.0 h, and 2.5 h in the SA group ($t$-test, $P < 0.05$) as shown in Figure 3.

**Effect of electrical stimulation of the CA1 area on firing rate of auditory cortex**

A total of 198 neurons from 12 rats in the AC were recorded; their basal SFR was 8.04 ± 0.19 Hz. As shown in Figure 4, 157 (79.3%) neurons in the AC showed responses to electrical stimulation of the hippocampal CA1 area, and the remaining 41 neurons (20.7%) showed no obvious changes (N-neurons). The SFR of 90 neurons significantly increased after hippocampal stimulation (E-neurons), while 67 neurons showed a reduction in SFR, as compared to the basal level (I-neurons). The SFR of E-neurons was significantly lower than that of I-neurons. The SFR of E-neurons increased significantly, while that of I-neurons decreased markedly after electrical stimulation, as shown in Figure 5.

Neurons were classified into two main types according to the discharge characteristics: excitability of the presumed pyramidal neurons increased significantly ($t = -3.632$, $P < 0.01$), while intermediate neuronal excitability decreased significantly after electrical stimulation of the CA1 area ($t = 5.869$, $P < 0.01$), as shown in Figure 6a. The majority of presumed pyramidal neurons were E-neurons ($n = 85$, 55.9%), followed by N-neurons ($n = 40$, 26.3%), and I-neurons ($n = 27$, 17.8%; Figure 6b). Most intermediate neurons were I-neurons ($n = 40$, 87.0%), followed by E-neurons ($n = 4$, 8.7%), and N-neurons ($n = 2$, 4.4%; Figure 6b).

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**Figure 1:** Effects of SA on the neuronal SFR of the hippocampal CA1 area. (a) Example of neuronal discharges recorded with the silicon electrode. Upper panel: continuous recording of discharges from a single channel. Lower panel: sorting results of different types of neurons from a single channel. (b) Scatter diagram of discharges at the time point of 0 and 2.0 h after SA/saline treatment (SA group, $n = 45$; saline group, $n = 20$). Each dot indicates the spike rate of a single neuron. SA: Salicylate; SFR: Spontaneous firing rate.
Tinnitus is a common clinical symptom; however, the underlying mechanism is not well understood. To gain a better understanding of the pathophysiology of tinnitus, we used the SA-induced tinnitus animal model, developed by Jastreboff et al., which has a tinnitus pattern akin to a 70 dB pure tone at 10 kHz. Many tinnitus patients also experience negative emotions, such as anxiety, nervousness, and insomnia which implicate a role for the limbic system in this condition. According to Jastreboff’s model of tinnitus, the limbic system is involved in the development of tinnitus and gives rise to negative cognition and emotion, intensifying the patient’s attention to tinnitus, and resulting in a mutual enhancement between tinnitus and negative emotion. Rauschecker et al. proposed that the limbic system acts as a switch for cognition of tinnitus. In this study, we focused on the hippocampus as a target for intervention, if limbic–auditory interactions could be shown in tinnitus, and found that SA significantly increased the SFR of the hippocampus, indicating involvement of the hippocampus in tinnitus.

In the first part of our study, we observed that the excitability of the hippocampus in the SA group was significantly increased compared to the saline group. The Mann-Whitney U-test showed a significant difference at the time point of 0.5 h (Z = −2.331, P = 0.020), 1.5 h (Z = −2.139, P = 0.032), 2.0 h (Z = −3.802, P < 0.001), 2.5 h (Z = −2.928, P = 0.003), and 3.0 h (Z = −2.601, P = 0.009) posttreatment between saline group and SA group. *P < 0.05; †P < 0.01. SFR: Spontaneous firing rate; SA: Salicylate.

In the second part of our study, we observed that the excitability of the hippocampus in the SA group was significantly increased compared to the saline group. The Mann-Whitney U-test showed a significant difference at the time point of 0.5 h (Z = −2.716, P = 0.035), 2.0 h (Z = −4.521, P < 0.001), and 2.5 h (Z = −1.203, P = 0.006) after SA injection. *P < 0.05; †P < 0.01. SFR: Spontaneous firing rate; SA: Salicylate.

In the third part of our study, we observed that the excitability of the hippocampus in the SA group was significantly increased compared to the saline group. The Mann-Whitney U-test showed a significant difference at the time point of 0.5 h (Z = −2.716, P = 0.035), 2.0 h (Z = −4.521, P < 0.001), and 2.5 h (Z = −1.203, P = 0.006) after SA injection. *P < 0.05; †P < 0.01. SFR: Spontaneous firing rate; SA: Salicylate.
We delivered electrical stimulation to the hippocampus and recorded the neuronal activity of rats under anesthesia, considering the complicated functions of hippocampus, particularly as a key regulator of the hypothalamic-pituitary-adrenal axis. As the crux of the auditory system, the AC has been extensively studied in animals and humans with tinnitus. A functional imaging study showed that neural activity was increased in regions involved in the neural pathway of the auditory system, such as AC, inferior colliculus, and medial geniculate body. However, resting state fMRI showed increased functional connection between the AC and hippocampus. We delivered electrical stimulation to the hippocampus and recorded the neuronal excitability of the AC, to gain insight into the possible regulatory effect of the hippocampus on the AC.

In summary, neuronal excitability in the hippocampus increased after SA treatment, indicating the potential involvement of the hippocampus in tinnitus. Electrical stimulation of the hippocampus could induce neuronal excitability changes in the AC, implying possible regulation of the central auditory system by the limbic system during tinnitus. Our study provides useful electrophysiological evidence related to the pathogenesis of tinnitus. The hippocampus may be a target region for treatment of emotion, learning and memory disorders in tinnitus. However, the neuronal activity of rats was evaluated under anesthesia, that might affect the electrophysiological results, and similar studies should be performed in awake animals.

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Conflicts of interest
There are no conflicts of interest.

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大鼠耳鸣模型中海马CA1区神经元兴奋性对听觉传导通路的影响

摘要

背景：耳鸣是听觉系统疾病的常见症状。耳鸣的病因复杂，其发生的神经生理学机制尚不明确。边缘系统参与学习、记忆和情绪反应，既往研究发现，边缘系统与耳鸣发生有关。海马是边缘系统的重要组成部分，在情绪障碍、学习和记忆能力减退等许多病理过程中起到关键作用。本研究旨在为海马参与耳鸣发生提供电生理实验证据。

方法：本研究通过腹腔注射水杨酸盐构建耳鸣模型，并利用在体多通道记录技术记录海马CA1区神经元兴奋性变化情况。通过电刺激海马CA1区记录听皮层神经元兴奋性变化，进一步研究海马CA1区神经元兴奋性改变对听觉传导通路的影响。

结果：本研究共记录到65个海马CA1区神经元，其中水杨酸盐组（n = 5）记录到45个，生理盐水组（n = 5）记录到20个。腹腔注射后2 h，水杨酸盐组海马CA1区神经元平均自发放电率从3.06 ± 0.36 Hz升高至9.08 ± 1.30 Hz（t = −4.521，P < 0.05），而生理盐水组未见显著变化（2.66 ± 0.36 Hz vs. 2.16 ± 0.36 Hz，t = 0.902，P > 0.05）。79.3 %（157/198）的听皮层神经元对海马CA1区电刺激有反应。电刺激海马CA1区后，听皮层锥体神经元兴奋性增加，中间神经元兴奋性降低。

结论：水杨酸盐可引起海马区神经元兴奋性增加。海马CA1区电刺激可调节听皮层神经元的兴奋性。海马可能参与耳鸣发生，并参与耳鸣信号的调控。