Research Article

Effect of Acute and Chronic Salicylate Induced Tinnitus on Social Interactions and Aggressive Behaviors in Male Rats

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Highlights

- Salicylate-induced tinnitus may affect social interactions and aggressive behaviors
- Chronic tinnitus increased rats' aggressive behaviors compared to acute tinnitus

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ABSTRACT

Background and Aim: Many people with tinnitus have significant difficulties in social interactions. It is not clear whether impaired social interactions are a direct consequence of tinnitus or not. Due to the possibility of controlling longitudinal data in animal studies (pre- and post-tinnitus induction and duration), this study aimed to examine the effects of acute and chronic salicylate induced tinnitus on social interactions and aggressive behaviors in rats.

Methods: In this study, 28 male Wistar rats with normal hearing were divided into two groups: acute tinnitus (7 received saline, and 7 received single dose of 400 mg/kg salicylate) and chronic tinnitus (7 received saline, and 7 received 400 mg/kg salicylate for 14 consecutive days). The auditory brainstem response, pre-pulse inhibition of acoustic startle, gap pre-pulse inhibition, and social interaction tests were conducted at baseline, 6 hours after salicylate injection in the acute group and one day after salicylate injection in the chronic group.

Results: The gap pre-pulse inhibition of acoustic startle significantly decreased after both acute and chronic salicylate toxicity. Following number and time and struggling number and time after salicylate injection were significantly different in both groups, while Sniffing, wounding, attacking and fisting numbers significantly increased only in the chronic salicylate group. Results of saline group were not significant.

Conclusion: Tinnitus caused by either acute or chronic salicylate toxicity may have an effect on social and aggressive behaviors. Since rats' aggressive behaviors increased following chronic tinnitus induction, it can be said that the duration of tinnitus is also effective.

Keywords: Tinnitus; salicylate; pre-pulse inhibition; social interaction test; aggressive behavior

Introduction

Subjective tinnitus is a frequent auditory disorder that affect 11.9–30.3% of the general populations, and 3–3.9% of those with persistent and bothersome tinnitus. Tinnitus is commonly associated with unpleasant feelings, such as stress, frustration, sleep difficulties, depression and nervousness [1-3]. It can lead to psychological distress and avoid social interactions, leaving negative impact on the quality of life [4]. Animal models can be used to facilitate the study on social and behavioral disorders in people with tinnitus, due to control over longitudinal data (before and after tinnitus induction, and induction duration) and confounding factors (age, gender, and hearing loss) [2]. In animal studies, it is more likely to examine one type of disorder [5].

The salicylate toxicity model of tinnitus has been used by scientists for several years to study potential biochemical and neurophysiological causes of tinnitus. Due to pain killing, anti-inflammatory, and antipyretic properties, salicylate is commonly prescribed for moderate headache treatment and has a long history of usage in treating rheumatoid arthritis [6, 7]. To confirm the occurrence of emotional reactions following tinnitus, we can examine the effect of tinnitus duration on emotional reactions. It can be studied with acute and chronic models of salicylate-induced tinnitus. Moreover, the animal model of salicylate-induced tinnitus, due to the induction of slight hearing loss, can be helpful to distinguish between social and behavioral disorders of people with hearing loss and tinnitus [8].

Few studies have attempted to investigate how tinnitus affects social behaviors of animals, despite the fact that tinnitus is linked to increased anxiety and psychological distress which can affect social interactions and cause aggressive behaviors [2, 4, 9]. Therefore, this study aimed to examine the effect of salicylate-induced tinnitus and duration (acute versus chronic conditions), on social interactions and aggressive behaviors of male rats.

Methods

Animals and experimental design

In this study twenty-eight male Wistar rats who were three months old and weighed between 260 and 300 g were prepared from the Experimental and Comparative Studies Center of Iran University of Medical Sciences in Tehran, Iran. All rats were kept in normal laboratory conditions [8, 10] and in small groups of 3-4 inside the cage to avoid social isolation stress. The cages were kept in a quiet room to reduce the disturbing effects of noise. Five days before the tinnitus and social and aggressive behaviors tests, the animals' hearing threshold was examined using the Auditory Brainstem Response (ABR) test.

Within five days of handling, normal-hearing rats were divided into two groups: acute tinnitus (7 received saline, and 7 received salicylate) and chronic tinnitus (7 received saline, and 7 received salicylate). The ABR, tinnitus, social, and behavioral tests were performed before and 2 and 6 hours after salicylate injection (400 mg/kg per day) in the acute group and one day after salicylate injection (400 mg/kg per day) in the chronic group between 9 a.m. and 4 p.m. [8, 11]. The study's experimental setup is illustrated in Figure 1.

Tinnitus induction

To induce tinnitus, sodium salicylate (CAS 54-21-7; Merck Co., Germany) was dissolved in 0.9% saline at a concentration of 200 mg/mL and intraperitoneally injected at the dose of 400 mg/kg. In the acute group, salicylate was injected one time (8:00 a.m.). In the chronic group, to reduce the mortality from repeated injections of high doses of salicylate, a dosage of 200 mg/kg was injected twice per day (8:00 a.m. and 16:00 p.m.) for 14 consecutive days [11]. Rats in the saline subgroups received the same volume of saline.

Auditory brainstem response test

The ABR test (Bio-logic Navigator Pro, USA) was conducted to evaluate hearing threshold under anesthesia with ketamine (10%, 80 mg/kg, intraperitoneally) and xylazine (2%, 10 mg/kg, intraperitoneally) [8, 10]. The acoustic stimuli were delivered using a high-frequency loudspeaker placed 3 cm away from the right ear of the rat. These stimuli included click and tone bursts of 4, 8, 12, and 16 kHz, with a duration of 5 ms and a rise/fall time of 2 ms. Evoked potentials were recorded from the intensity of 70 dB SPL to the threshold level by subcutaneous needle electrodes placed at the vertex of right and left ears. Wave II was also monitored [8, 10].

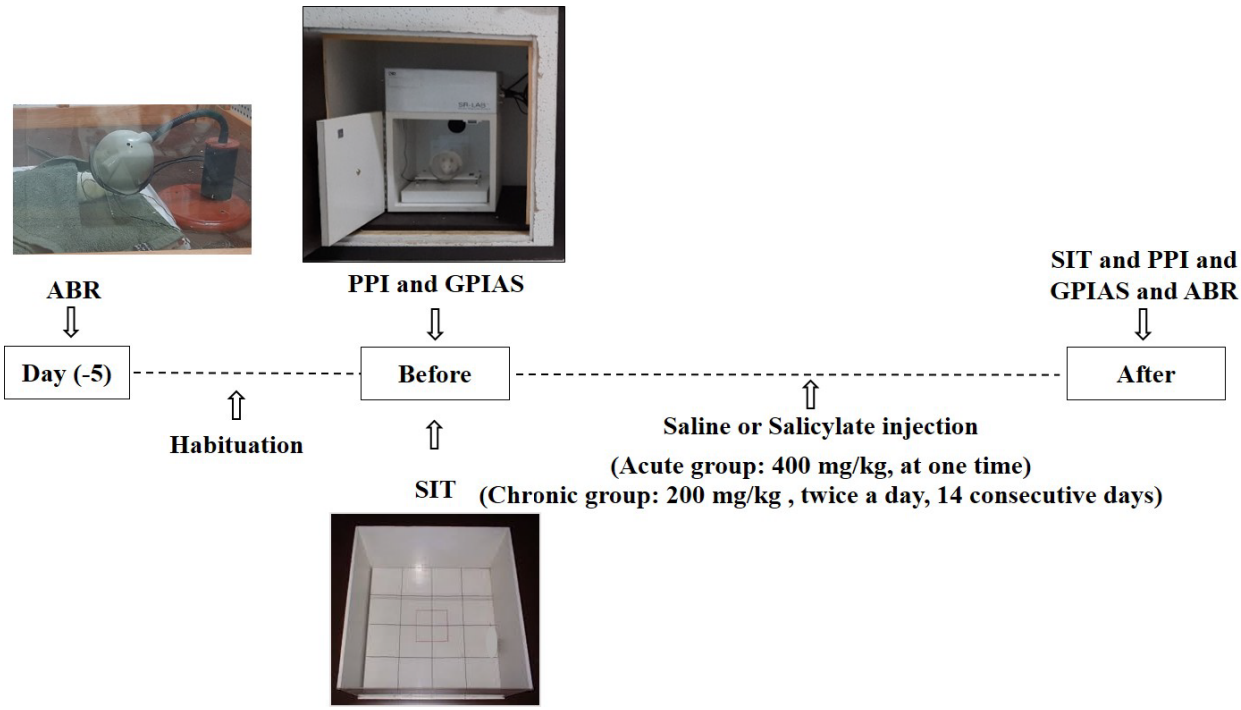

Figure 1. Schematic illustration of experimental design of study. ABR; auditory brainstem response, PPI; pre-pulse inhibition, GPIAS; gap pre-pulse inhibition of the acoustic startle, SIT; social interaction and aggressive behavior test

Tinnitus evaluation

The SR-LAB system (San Diego Instrument, USA) was utilized to administer the Pre-Pulse Inhibition (PPI) and Gap Pre-pulse Inhibition of the Acoustic Startle (GPIAS) tests for tinnitus evaluation [8, 10]. The stimuli were presented in accordance with the study by Turner and Parrish [12]. Trials (10 startle trials and 10 gap trials in the GPIAS test or pre-pulse trials in the PPI test) were conducted in a quasi-random manner with inter stimulus intervals of 15–20 s. A brief burst of 20-ms Broadband Noise (BBN) at 115 dB SPL was used to trigger startle reactions. Half of the animals were first evaluated using the PPI test, while the other half were evaluated using the GPIAS test. The mean percentages of GPIAS and PPI before and after tinnitus induction were compared in acute and chronic salicylate and saline groups. Tinnitus assessment was conducted, before social behavior tests.

Social and aggressive behaviors tests

An open field apparatus was used to administer the Social Interaction Test (SIT) for assessing social and aggressive behaviors, while a recording device was placed 100 cm above the focal point of the setup to capture the results. Thirty minutes before the test, the animals were transported and put inside the apparatus to let them adapt to the new environment. To begin, one un-manipulated male rat that matched the study rat's age and weight was placed in the open field apparatus. Then, one study rat was set free from the far left corner of the apparatus, and his moves were recorded for 20 minutes [10]. Social interaction parameters were the number and time of conspecific following, number and time of struggling, number and time of conspecific grooming, and number of conspecific sniffing. Aggressive behavior parameters were the number of biting, fisting, wounding, and attacking and first attack latency [2]. The average of each parameter before and after tinnitus induction was compared between acute and chronic salicylate groups.

Statistical analysis

We used PRISM v.9 software to conduct statistical analyses. We reported the data as mean±standard error of the mean (SEM). All four test scores (ABR, PPI, GPIAS, and SIT) were analyzed using a two-way repeated measures ANOVA, and the subgroups were compared using Tukey's or Sidak's multiple comparison tests. Statistical significance was set at 0.05.

Results

Effect of salicylate administration on hearing threshold

Two-way repeated measures ANOVA results showed that the hearing thresholds were significantly different before and after salicylate injection for all stimuli (click and 4, 8, 12 and 16 kHz) in the acute salicylate group, $F_{(1,30)}$=80.44, p≤0.0001; p=0.049, 95% CI: –9.98 to –0.02; p=0.049, 95% CI: –9.98 to –0.02; p≤0.0001, 95% CI: –14.27 to –4.31; p=0.0003, 95% CI: –13.55 to –3.59; p=0.0003, 95% CI: –13.55 to –3.59, respectively (Figure 2 A); and for 8, 12 and 16 kHz tones in the chronic salicylate group, $F_{(1,30)}$=100.3, p≤0.0001; p=0.0003, 95% CI: –12.49 to –3.23; p≤0.0001, 95% CI: –16.06 to –6.79; p≤0.0001, 95% CI: –16.78 to –7.51, respectively (Figure 2 B). There were no significant differences in the acute or chronic saline groups (p>0.05) (Figure 2 C and D).

Effect of salicylate administration on tinnitus

As shown in Figure 3 A, two-way repeated measures ANOVA results showed that the GPIAS test scores were significantly different before and 6 hours after salicylate injection in the acute salicylate group ($F_{(2,24)}$=7.086, p=0.0038; p=0.0009, 95% CI: 11.47–45.23), while it was not significant two hours after in this group (p>0.05). As shown in Figure 3 B, the GPIAS test scores significantly decreased in the chronic salicylate group after salicylate injection, $F_{(1,12)}$=102.9, p≤0.0001; p≤0.0001, 95% CI: 42.71–63.23. Regarding results for the PPI test (Figure 3 C and D), the scores were not significantly different in the acute and chronic salicylate groups (p>0.05). In the acute and chronic saline groups (Figure 3 A-D), the GPIAS and PPI test results were not significantly different (p>0.05)

Effect of salicylate administration on social interactions and aggressive behaviors

Based on the two-way repeated measures ANOVA, conspecific following number and time significantly reduced after salicylate injection in the acute salicylate group, ($F_{(1,12)}$=21.95, p=0.0005; p=0.0378, 95% CI: 0.23–8.05; $F_{(1,12)}$=28.92, p=0.0002; p=0.0218, 95% CI: 5.312-65.26) and in the chronic salicylate group ($F_{(1,12)}$=21.95, p=0.0005; p=0.0041, 95% CI: 2.09–9.91;

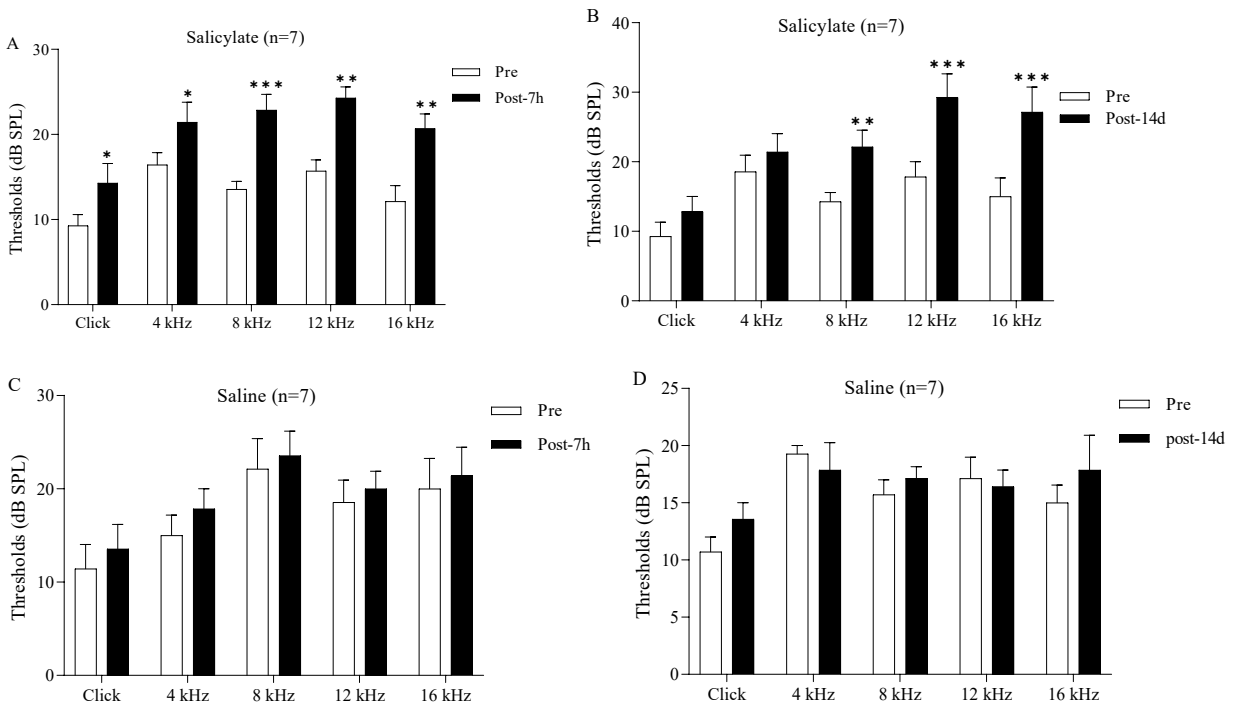

Figure 2. Effect of acute and chronic salicylate administration on hearing threshold of auditory brainstem response. The results are presented as mean±SEM. The differences between groups were determined by two way repeated measures ANOVA followed by Sidak test
* p≤0.05, ** p≤0.001 and, *** p≤0.0001.

$F_{(1,12)}$=28.92, p=0.0002; p=0.0012, 95% CI: 24.03–83.97). There was no significant difference between two groups after salicylate injection (p>0.05) (Table 1).

The conspecific grooming number and time were not significant in both groups before and after salicylate injection (p>0.05) (Table 1). The struggling number and time increased significantly after salicylate injection in the acute salicylate group ($F_{(1,12)}$=75.14, p≤0.0001; p=0.0055, 95% CI: –15.36 to –2.92; $F_{(1,12)}$=91.14, p≤0.0001; p=0.0004, 95% CI: –74.2 to –25.8) and in the chronic salicylate group ($F_{(1,12)}$=75.14, p≤0.0001; p≤0.0001, 95% CI: –26.93 to –14.5; $F_{(1,12)}$=91.14, p≤0.0001; p≤0.0001, 95% CI: –102.2 to –53.8). Also, there were significant differences between the two groups after salicylate injection, $F_{(1,12)}$=75.14, p≤0.0001; p=0.0002, 95% CI: –17.38 to –5.76 for struggling number and $F_{(1,12)}$=91.14, p≤0.0001; p=0.0138, 95% CI: –50.61 to –5.39 for struggling time (Table 1). Moreover, the sniffing number, wounding number, attacking number, first attack latency, and fisting number significantly increased only in the chronic salicylate group ($F_{(1,12)}$=13.5, p=0.0032; p=0.002, 95% CI: –2.27 to –0.59; $F_{(1,12)}$=7.2, p=0.0199; p=0.0163, 95% CI: –1.29 to –0.14; $F_{(1,12)}$=47.3, p≤0.0001; p≤0.0001, 95% CI: –20.33 to 9.67; $F_{(1,12)}$=11.11, p=0.006; p=0.0014, 95% CI: –427.9 to –119.2; $F_{(1,12)}$=27.84, p=0.0002; p≤0.0001, 95% CI: –14.35 to –5.94, respectively). As well as, there were significant differences between two groups after salicylate injection in these variables, $F_{(1,12)}$=13.5, p=0.0032; p=0.004, 95% CI: –1.93 to –0.36 for sniffing number; $F_{(1,12)}$=7.2, p=0.0199; p=0.0364, 95% CI: –1.11 to –0.03 for wounding number; $F_{(1,12)}$=47.3, p≤0.0001; p=0.0002, 95% CI: –14.69 to –4.74 for attacking number; $F_{(1,12)}$=11.11, p=0.006; p=0.0004, 95% CI: –406.3 to –117.9 for first attack latency; $F_{(1,12)}$=27.84, p=0.0002; p=0.0001, 95% CI: –11.93 to –4.07 for fisting number (Table 1). Furthermore, number of biting significantly increased only in the chronic group ($F_{(1,12)}$=6, p=0.0306); while there was no difference between groups after salicylate injection (p>0.05) (Table 1). There was no significant difference in the acute or chronic saline groups in all of the social interaction tests (p>0.05) (Table 1).

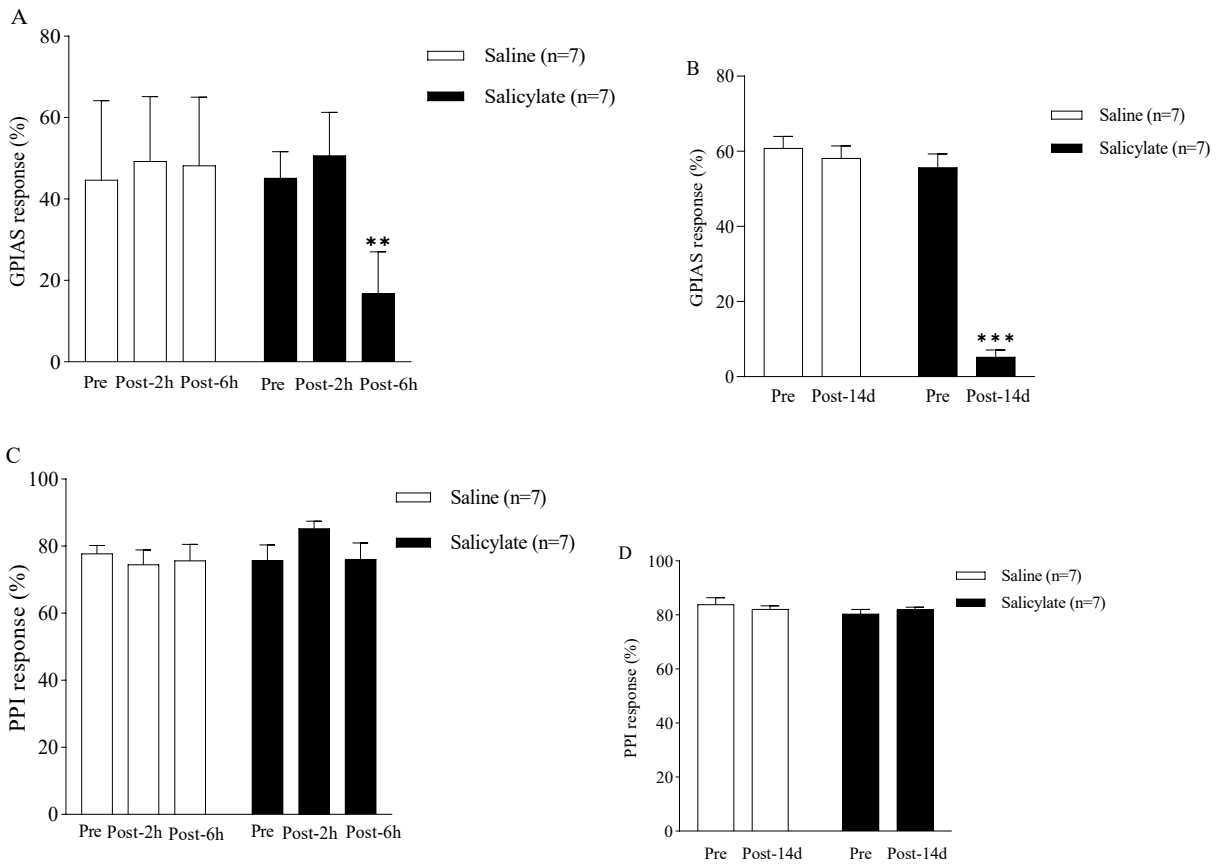

Figure 3. Effect of acute and chronic salicylate administration on gap pre-pulse inhibition of the acoustic startle and pre-pulse inhibition tests. The results are presented as mean±SEM. The differences between groups were determined by two-way repeated measures ANOVA followed by Tukey test. GPIAS; gap pre-pulse inhibition of the acoustic startle, PPI; pre-pulse inhibition
** p≤0.001 and, *** p≤0.0001.

Table 1. Effect of acute and chronic saline and salicylate injection on social interaction and aggressive behaviors tests

Group/test			Partner following number and time	Partner grooming number and time	Struggling number and time	Partner sniffing number	Wounding number	Attacking number	Latency time to first attack	Fisting number	Biting number
Acute	Saline	Pre	7.00±1.40	0.43±0.30	0.28±0.18	0.14±0.14	0	0.14±0.14	4.29±4.28	0.29±0.18	0
			45.29±9.42	0.71±0.47	0.43±0.30						
		Post	7.71±1.21	0.57±0.20	0.29±0.18	0.28±0.18	0	0	0	0.14±0.14	0
			45.71±5.15	0.86±0.59	0.57±0.43						
	Salicylate	Pre	7.71±1.27	0.71±0.47	0	0.14±0.14	0	0	0	0	0
			51.57±8.50	1.43±1.02	0						
		Post	3.57±0.92[!]	0.71±0.18	9.14±1.47[*]	0.43±0.20	0.14±0.14	5.58±0.94	11.43±5.03	2.14±0.63	0.29±0.18
			16.29±4.38[!]	1.43±0.61	50.00±9.04[♪]						
Chronic	Saline	Pre	8.86±1.70	0.71±0.47	0.14±0.14	0.29±0.18	0	0.14±0.14	5.71±5.71	0.14±0.14	0
			51.71±14.54	1.14±0.77	0.57±0.57						
		Post	7.71±1.73	0.57±0.30	0.29±0.18	0.43±0.30	0	0.14±0.14	13.86±13.86	0.14±0.14	0
			57.14±16.31	0.57±0.57	0.71±0.47						
	Salicylate	Pre	9.00±1.67	0.14±0.14	0	0.14±0.14	0	0	0	0	0
			62.00±14.52	0.57±0.57	0						
		post	3.00±0.62[*]	1.00±0.30	20.71±3.11[♫]	1.57±0.37[*]	0.71±0.29[!]	15.00±2.80[♫]	273.60±85.36[*]	10.14±2.24[♫]	0.57±0.30
			8.00±1.59[*]	2.86±1.03	78.00±9.90[♫]						
p					[###]	[##]	[#]	[###]	[###]	[###]	
					[#]						

[*] Pre vs post-acute or chronic saline or salicylate injection. [!]p≤0.05, [*]p≤0.01, [♪]p≤0.001, [♫]p≤0.0001

[#] Post-acute vs chronic salicylate induced tinnitus. [#]p≤0.05, [##]p≤0.01 and, [###]p≤0.001

Discussion

In the present study, the ABR test results showed a significant increase after salicylate injection in the acute group (in all stimuli) and chronic group (in 8, 12 and 16 kHz tones). However, similar to other studies [8, 13], hearing thresholds increased nearly 0–20 dB in rats, which did not affect behavioral assessments. The PPI test results showed no significant change after salicylate injection, which showed the appropriate hearing sensitivity of rats during the behavioral assessments, consistent with previous studies [8, 12]. Furthermore, the GPIAS test results significantly decreased after acute and chronic toxicity by salicylate, confirming tinnitus induction. However, the decrease was observed only 6 hours after salicylate injection (no significant change two hours after). Previous studies have demonstrated that GPIAS test results significantly decline 30 minutes to 14 hours after acute toxicity by salicylate [8, 14-16].

Findings of this study demonstrated the SIT parameters including number and time of conspecific following and struggling were significantly different in both acute and chronic salicylate groups. However, number of conspecific sniffing as well as aggressive behaviors (number of biting, punching, notching and attacking and first attack latency) significantly increased only in the chronic salicylate group. The increase in the rats' aggressive behaviors suggests that the duration of tinnitus was effective. The saline group did not show any significant behavioral changes, indicating that the injection had no effect on the test.

When animals exhibited fewer social interactions and more aggressive behaviors, it disrupted their ability to communicate, particularly with opposite sex, which can lead to stressful situations. Despite the high prevalence of negative emotions associated with tinnitus, the underlying mechanism is still poorly understood. Also, it is challenging to distinguish the emotional implications of hearing loss from those of tinnitus [2, 5]. The diversity of the tinnitus population is a major drawback of clinical studies and maybe an advantage for animal studies. Since the causative conditions can be more easily and precisely controlled in animal studies, only one type of the disease can be investigated in these studies [5]. Impaired social interaction and aggressive behaviors are common feature of anxiety in rodents. In a study, it was shown that the SIT results were abnormal after acoustic over-exposure or salicylate injection [2]. Guitton showed that salicylate-induced tinnitus caused profound social interaction impairment in mice. However, in contrast to our findings, salicylate-treated mice showed an irrational increase in the frequency of the following of conspecifics, even though their total social conspecifics were much lower. Moreover, consistent with our study, mice with tinnitus had greater frequency of conspecific grooming [4]. Zheng et al. discovered that animals with noise-induced tinnitus were more aggressive when interacting with other animals while sham animals were also aggressive towards tinnitus animals. This is consistent with our study. Their findings imply that rats with tinnitus are more likely to initiate interactions with conspecifics, but these interactions may be inappropriate, leading to being more aggressive towards their counterpart. Therefore, sham animals often escape from animals with tinnitus. Evidence from their study suggests that tinnitus causes complicated alterations in rats' social interactions more than in those with elevated anxiety alone [9]. However, sound exposure may be the method of choice for producing hearing impairment in studies to examine the mechanisms behind psychological distress, while tinnitus can cause psychological distress in 30–80% of cases [2, 5, 6, 8]. Lauer et al. demonstrated that social interactions decreased in almost all rats with noise exposure and acute salicylate toxicity [2]. However, they did not screen rats with induced tinnitus due to the limited duration of the effect of single-dosage salicylate, while the onset time of tinnitus induced by acute salicylate toxicity is different in previous studies (from 30 min to 6 hours) [8, 14-16]. Moreover, some studies did not found any behavior related signs of tinnitus after acute salicylate toxicity [11]. In investigating the potential mechanisms of salicylate-induced tinnitus, it is vital to know the differences between the effects of acute and chronic salicylate treatment [6]. Most of studies have focused on tinnitus induced by acute salicylate toxicity; however, the result of various studies supports the idea that tinnitus develops over time, and that the auditory system reacts differently to a single dose of salicylate compared to its multiple doses [6, 11]. Yi et al. demonstrated that the response to acute salicylate toxicity is mostly a short-term stress than a permanent one. The transition from acute to chronic tinnitus and role of non-auditory areas during tinnitus is not well understood [11]. Tinnitus develops as a result of

maladaptive plasticity of the central nervous system that includes parts of the auditory system as well as direct and indirect interconnections with other parts of the brain linked to alertness, nervousness, aggression, and concentration [1, 2, 11].

Animal studies cannot be generalized to human studies due to inherent differences in the etiologies of tinnitus, the duration of tinnitus (acute and chronic), and other relevant factors. Our findings support the notion that the psychological and social disorders experienced by tinnitus patients should not be disregarded, but rather treated as an integral part of the condition. Through the implantation of social behavioral tests, it is feasible to investigate the impact of different treatments or interventions on tinnitus-related behavioral and mood disorders, in addition to evaluating tinnitus itself. Given the potential impact of tinnitus on interpersonal communication with the opposite sex, it is recommended that this factor be explored in future studies.

Conclusion

Tinnitus caused by either acute or chronic salicylate toxicity may have a negative effect on social interactions and cause aggressive behaviors. Since aggressive behaviors increased following tinnitus induction by chronic salicylate toxicity in male rats, it can be claimed the duration of tinnitus is also effective.

Ethical Considerations

Compliance with ethical guidelines

This study was approved by the Ethics Committee of Iran University of Medical Sciences (IR.IUMS.REC.1400.842) and conducted in accordance with the guide for the care and use of laboratory animals.

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Authors' contributions

MR: Study design, acquisition of data, interpretation of the results, statistical analysis, drafting and revision the manuscript; MF: Acquisition of data; MA: Study design, interpretation of the results, statistical analysis, revision the manuscript.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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