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Significance of Serotonin Transporter Gene Polymorphism in Tinnitus

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Objectives: To assess the role of serotonin transporter gene (*SLC6A4*) polymorphism in tinnitus.
Materials and Methods: Fifty-four consecutive patients experiencing subjective tinnitus and 174 healthy controls were allocated for the study. Psychoacoustic parameters of tinnitus were measured. Beck Depression Inventory was used to assess the depression level of the patients. Tinnitus Handicap Inventory was used to assess the severity of tinnitus. A visual analog scale was designed to measure the impact of tinnitus on quality of life of the patients. The 44-bp insertion–deletion in the promoter region (5-HTTLPR) and 17-bp variable number tandem repeats in the second intron of the serotonin transporter gene were assessed.
Results: No difference was found between the genotypes and allele frequencies of the patients and controls regarding variable number tandem repeats and 5-HTTLPR polymorphisms ($p > 0.05$). There was no association between the psychoacoustic parameters of tinnitus and *SLC6A4* polymorphism ($p > 0.05$). There was a significant association between the 5-HTTLPR polymorphism and scores from the visual analog scale of the patients ($p < 0.05$).
Conclusion: Generation of tinnitus signal is not associated with *SLC6A4* polymorphism and possibly with serotonergic mechanisms. However, the "*ll*" genotype variant of the *SLC6A4* polymorphic promoter region seems associated with the limbic and autonomic nervous system symptoms of the patients with tinnitus. Therefore, serotonergic mechanisms may help explain the neurophysiological model of tinnitus, and serotonin replacement or serotonin reuptake inhibitors may increase the success rate of tinnitus treatment modalities based on the neurophysiologic model of tinnitus. **Key Words:** Polymorphism—Serotonin—Serotonin transporter gene—Tinnitus.

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Tinnitus is a common and poorly understood disorder and a major problem for the patients and clinicians. It is defined as a sound sensation in the absence of an external stimulus. The prevalence of chronic tinnitus is almost 10 to 15% among adults (1). In 1 to 3% of the population, tinnitus affects the quality of life, causing sleep disturbances and psychiatric distress (2). Tinnitus can be classified either as objective or subjective. In objective tinnitus, the source of the sound is in the body, whereas subjective tinnitus is caused by an abnormal neural activity that is not evoked by sound (3).

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Tinnitus results from a variety of pathological conditions, but its mechanism is still unclear. Many theories and models have been proposed to explain tinnitus mechanism. The cochlear hair cells have been suggested as the origin. Releases of the excitatory neurotransmitter, glutamate, during stressful episodes, calcium imbalance, discordance in the hair cell function, and loss of outer hair cell function, and activation of cochlear *N*-methyl-D-aspartate receptors are the theories suggesting that tinnitus originates from the cochlear hair cells (4–7). Other theories point out the cochlear nerve and central auditory pathways and include spontaneous activity in the auditory nerve fibers and dorsal cochlear nucleus, cortical plasticity, and reorganization of the pathways in the central auditory system as a result of hearing loss, causing abnormal interactions between auditory and other central pathways (8–13).

Tinnitus is associated with psychiatric disorders. There are many studies to demonstrate the presence of psychopathological disorders and high depressive scores in tinnitus patients (14,15). A relation is apparent between tinnitus and depression, which coincides in 30% of the cases. For this reason, there may be a causal relationship between the molecular bases of these disorders. Because serotonin is associated with the occurrence of depression and psychiatric disorders, it may also be associated with the occurrence of tinnitus.

Serotonin is a neurotransmitter that is widely distributed in the central nervous system. The serotoninergic activity is involved in many physiological functions and in some disease states such as anxiety and depression (16). Serotoninergic fibers and terminal endings are found in most of the auditory nuclei, the inferior colliculus, the nuclei of the lateral lemniscus, and superior olivary complex (17). Modifications of serotonin neurotransmission impair inhibitory associative learning and have been proposed to contribute to tinnitus and hyperacusis (18).

The synaptic serotonin is inactivated by presynaptic reuptake, which is mediated by the serotonin transporter (16,19). Blockage of the serotonin transporter leads to increased extracellular serotonin (20). The gene for serotonin transporters is located on chromosome 17q12. There are 2 polymorphic regions on the serotonin transporter gene (*SLC6A4*) including a 44-bp insertion–deletion in the promoter region (5-HTTLPR) and a 17-bp variable number tandem repeats (VNTR) in the second intron of the gene. Two alleles, termed long (*l*) and short (*s*), are found in 5-HTTLPR, which is a functional polymorphism. In vitro studies showed that the "*l*" allele variant has a greater transcriptional activity than the "*s*" allele (21). Thus, presence of "*l*" allele results in the synthesis of more serotonin transporters and, in turn, higher presynaptic uptake and depletion of serotonin in the neural synapses. Ogilvie et al. (22) identified the existence of polymorphisms of the *SLC6A4* gene and identified 3 novel alleles of the VNTR region, namely STin2.9, STin2.10, and Stin2.12, containing 9, 10, and 12 copies of the VNTR element, respectively. The function of VNTR is not well known.

The literature is lacking studies to demonstrate association of serotonin with tinnitus. Because the *SLC6A4* variants can alter the amount of serotonin in the synapse, assessment of *SLC6A4* polymorphism might show the association of serotonin with tinnitus. In this study, we aimed to assess association of *SLC6A4* polymorphism with tinnitus.

MATERIALS AND METHODS

Seventy-five consecutive patients experiencing subjective tinnitus were allocated for the study. After taking patients' history, thorough otolaryngologic examination and audiologic evaluation were performed to determine whether the patients were appropriate for the study. Of 75 patients, 65 consented to provide a blood sample for genetic analyses for *SLC6A4* and 54 patients were appropriate for inclusion in the study. The tinnitus group included 33 women (61%) and 21 men (39%). The age range was between 20 and 51 years. Tinnitus was bilateral in 31 patients (57%) and unilateral in 23 patients (43%). All patients were experiencing chronic tinnitus (>1 yr). Blood samples were also obtained from 174 healthy volunteers as controls. The patients and control subjects were from the same population. The study was approved by the Ethical Committee of the Faculty of Medicine.

The exclusion criteria were the presence of one or more of the following: objective tinnitus, air-bone gap on pure-tone audiometry, sensorineural hearing loss worse than 30 dB in the frequency range of 250 to 6,000 Hz on pure-tone audiometry, middle or external ear problem, otosclerosis, chronic otitis media, vestibular schwannoma, Ménière's disease, otorrhea, history of previous ear and neurotologic surgery, history of temporal bone trauma, endocrinologic disease, psychiatric disorder, and history of ototoxicity.

Psychoacoustic parameters of tinnitus, including duration, frequency, loudness, threshold, minimal masking level, and residual inhibition, were measured. Beck Depression Inventory (BDI), which included 21 questions, was used to assess the depression level of the patients. Tinnitus Handicap Inventory (THI), which included 25 questions, was used to assess the severity of tinnitus. A visual analog scale (VAS) was designed to measure the impact of tinnitus on quality of life of the patients. The impact of tinnitus on quality of life of the patients was scored using VAS, which evaluated the following: severity of tinnitus (VAS-1), frequency and duration of tinnitus (VAS-2), discomfort level (VAS-3), attention-deficit (VAS-4), and sleep disorders (VAS-5).

Blood samples were collected in tubes containing ethylenediamine tetra-acetic acid and were stored at −20°C until isolation procedure was performed. The polymorphisms of *SLC6A4* (VNTR and 5-HTTLPR) were analyzed in the DNA obtained from leukocytes of the patients and healthy controls by using polymerase chain reaction (PCR). Polymerase chain reaction was performed twice for all samples. Distilled water not including DNA was used as a negative control.

Genetic Analysis

Insertion–deletion polymorphism in the promoter region was typed by PCR amplification of DNA, using flanking primers 5′-GGCGTTGCCGCTCTGAATGC-3′ (forward) and 5′GAGGGACTGACTGAGCTGGACAACCCAC-3′ (reversed). In PCR of insertion–deletion polymorphism, 50 μl of reaction mixture contained 1 μl of each primer, 5 μl (25 mmol/L) of $MgCl_2$, 2 μl (10 mmol/L) of dNTP, 5 μl of PCR buffer, 0.3 μl of Taq DNA polymerase, 4 μl of DNA, and 28.7 μl of distilled water. DNA was initially denaturated at 94°C for 5 minutes and subjected to a 30-cycle/min denaturation at 94°C for 30 seconds, annealing at 61°C for 30 seconds and extension at 72°C for 1 minute, and then final extension at 72°C for 5 minutes. Variable number tandem repeat polymorphism in the second intron of the *SLC6A4* was typed by PCR by using 5′-GTCAGTATCACAGGCTGCGAG-3′ (forward) and 5′TGTTCCTAGTCTTACGCCAGT-3′ (reversed). In PCR of VNTR polymorphism, 50 μl of reaction mixture contained 2 μl of each primer, 2 μl (25 mmol/L) of $MgCl_2$, 1 μl (10 mmol/L) of dNTP, 5 μl of PCR buffer, 0.3 μl of Taq DNA polymerase, 5 μl of DNA, 32.7 μl of distilled water. DNA was initially denaturated at 94°C for 5 minutes and subjected to a 35-cycle/min denaturation at 94°C for 45 seconds, annealing at 52°C for 1 minute and extension at 72°C for 1.5 minutes, and then final extension at 72°C for 5 minutes. Amplification products were resolved by electrophoresis (90 V, 110 min) on 3% agarose gels.

TABLE 1. *Comparison of VNTR and 5-HTTLPR polymorphisms of patients and controls*

	VNTR variants			5-HTTLPR variants			
	12/12	12/10	10/10	*ll*	*ls*	*ss*	Total
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Controls	98 (56.3)	63 (36.2)	13 (7.5)	36 (20.7)	80 (46)	58 (33.3)	174 (100)
Patients	30 (55.6)	20 (37)	4 (7.4)	12 (22.2)	26 (48.1)	16 (29.6)	54 (100)
Total	128 (56.1)	83 (36.4)	17 (7.5)	48 (21.1)	106 (46.5)	74 (32.5)	228 (100)

DNA bands were generated by Taq polymerase and photographed under ultraviolet light.

Statistics

One-way analysis of variance and χ^2 tests were used for the statistical analyses. The population was in Hardy–Weinberg equilibrium.

RESULTS

There was no difference between genotypes of patients and controls regarding VNTR (χ^2= 0.012 and $p = 0.994$) and 5-HTTLPR ($\chi^2 = 0.262$, $p = 0.877$) polymorphisms (Table 1).

In the patients, the pure-tone averages (average of pure tones in 500, 1,000, 2,000, and 4,000 Hz) on the right and left ears were 10.3 ± 5 dB (ranged from 2 to 22 dB) and 11 ± 6 dB (ranged from 2 to 25 dB), respectively. There was no association between the psychoacoustic parameters of tinnitus with VNTR and 5-HTTLPR polymorphisms (one-way analysis of variance, $p > 0.05$). (Tables 2 and 3). The mean THI and BDI scores of the patients were 38.8 ± 24 and 45 ± 10, respectively. There was no association between the THI and BDI scores of the patients with VNTR and 5-HTTLPR polymorphisms ($p > 0.05$).

There was no association between the VAS scores of the patients and VNTR polymorphism ($p > 0.05$; Table 4). There was an association between the VAS scores of the patients and 5-HTTLPR polymorphism (Table 5). For the first VAS parameter (severity), the scores of patients with "*ll*" genotype were significantly higher than the scores of patients with "*ls*" ($p = 0.004$). For the third VAS parameter (tinnitus discomfort level), the scores of patients with "*ll*" genotype were significantly higher than the scores of patients with "*ls*" and "*ss*" genotypes ($p = 0.002$ and $p = 0.03$, respectively). For the fourth (attention-deficit) and the fifth VAS parameters (sleep disorder), the scores of patients with "*ll*" genotype were significantly higher than the scores of patients with "*ls*" and "*ss*" genotypes ($p = 0.04$ and

TABLE 2. *Psychoacoustic parameters of tinnitus versus 5-HTTLPR variants of patients*

Tinnitus parameter	Genotype	Mean	SD	Minimum	Maximum
Duration (mo)	*ll*	45.5	53.4	5	180
	ls	27.2	28.9	1	120
	ss	40.4	78.6	3	340
	Total	34.7	53.7	1	340
Frequency (Hz)	*ll*	3,931.3	3,236.5	0	8,000
	ls	3,868.1	3,670.9	0	8,000
	ss	4,279.4	3,559.7	0	8,000
	Total	4,009.3	3,532.3	0	8,000
Loudness (dB)	*ll*	23.4	9.5	0	37
	ls	19.8	17.5	0	65
	ss	21.5	17.3	0	75
	Total	21	16.3	0	75
Threshold (dB)	*ll*	11.5	6.7	0	25
	ls	19.8	17.2	0	65
	ss	16.2	15.5	0	65
	Total	17.1	15.5	0	65
Minimal masking level	*ll*	25.2	14.7	0	54
	ls	25.5	22	0	77
	ss	21.5	18.1	0	55
	Total	24.1	19.6	0	77
Residual inhibition	*ll*	0.4	0.6	0	2
	ls	0.9	1	0	2
	ss	0.8	0.9	0	2
	Total	0.8	0.9	0	2

TABLE 3. *Psychoacoustic parameters of tinnitus versus VNTR variants of patients*

Tinnitus parameter	Genotype	Mean	SD	Minimum	Maximum
Duration (mo)	10/10	12	7.8	6	24
	10/12	29.9	32.3	3	120
	12/12	40.3	64.8	1	340
	Total	34.7	53.7	1	340
Frequency (Hz)	10/10	3,546.9	3,768.3	0	8,000
	10/12	2,899.4	3,443.6	0	8,000
	12/12	4,691.4	3,438.3	0	8,000
	Total	4,009.3	3,532.3	0	8,000
Loudness (dB)	10/10	19.6	16.4	0	52
	10/12	20.5	17.3	0	65
	12/12	21.4	16	0	75
	Total	21	16.3	0	75
Threshold (dB)	10/10	20.7	8.3	10	35
	10/12	16.7	16.1	0	55
	12/12	16.9	16.1	0	65
	Total	17.2	15.5	0	65
Minimal masking level	10/10	19	3.3	14	22
	10/12	23.7	21.1	0	77
	12/12	24.8	20.1	0	69
	Total	24.1	19.6	0	77
Residual inhibition	10/10	1	1	0	2
	10/12	0.64	0.95	0	2
	12/12	0.8	0.93	0	2
	Total	0.78	0.94	0	2

TABLE 4. *Correlation of VAS scores with VNTR polymorphism in the patients*

VAS (tinnitus)	Genotype	No. of patients	Mean	SD	Minimum	Maximum
VAS-1 (severity)	10/10	4	7.5	2.6	4	10
	10/12	18	5	2.3	2	10
	12/12	32	4.6	2.1	1	8
	Total	54	5	2.3	1	10
VAS-2 (frequency and duration)	10/10	4	9.5	1	8	10
	10/12	18	7.3	2.7	2	10
	12/12	32	8.1	2.9	1	10
	Total	54	7.9	2.7	1	10
VAS-3 (discomfort level)	10/10	4	7	2.1	4	9
	10/12	18	5.9	2.7	3	10
	12/12	32	5.5	2.8	1	10
	Total	54	5.7	2.7	1	10
VAS-4 (attention-deficit)	10/10	3	3	3.4	1	7
	10/12	18	4	3.5	0	10
	12/12	32	3.3	3.2	0	10
	Total	53	3.5	3.3	0	10
VAS-5 (sleep disorder)	10/10	4	4	4.1	0	8
	10/12	18	4.5	3.8	0	10
	12/12	32	2.5	2.7	0	8
	Total	54	3.3	3.3	0	10

$p = 0.03$, respectively). There was no significant difference between the VAS scores and genotypes of the patients with unilateral and bilateral tinnitus ($p > 0.05$).

DISCUSSION

There is an association between tinnitus and various psychological problems such as depression (23,24). Almost 6 to 25% of the patients with chronic tinnitus report a substantial amount of psychological problems (25–28). The incidence of comorbid depressive disorders in patients with chronic and disabling tinnitus has been reported range from 48 to 60% (29). In a study in which the patients with disabling tinnitus and healthy controls were compared, Sullivan et al. (30) found a life time prevalence of major depression in 78% of patients (versus 21% of controls), and they concluded that tinnitus disability is strongly associated with major depression. This strong association suggests a causal relationship between the molecular bases of tinnitus and depression. Serotonin seems one of the potential molecules that may be involved in the occurrence of these disorders.

Modifications of serotonin neurotransmission have been proposed to contribute to tinnitus (17). It was also shown that the variants of 5-HTTLPR are associated with differences in auditory evoked potentials in healthy controls (31). The 5-HTTLPR, a functional serotonin polymorphism, is associated with a variety of neuropsychiatric disorders as well as depression (32). These findings in the literature suggest an association among serotonergic mechanisms, depression, and tinnitus.

Experimental data have shown that serotoninergic fibers are present in the cochlear nucleus, inferior colliculus, nucleus of the lateral lemniscus, and superior olivary complex (17). Some indirect evidence also suggested that serotonin could be present within the cochlea (33). Serotoninergic fibers are involved in modulatory functions in the cochlear nucleus, inferior colliculus, and amygdala (34–36). In the inferior colliculus, serotonin regulates both neural firing activity and frequency tuning (37). Simpson and Davies (17) suggested that dysfunction of serotoninergic activity in the auditory pathway inhibits habituation among neural networks and contributes to tinnitus. Therefore, tinnitus generation or perception could be linked to dysfunction of serotonin in the central auditory system.

In this study, no difference was found between genotypes of patients and controls regarding VNTR and

TABLE 5. *Correlation of VAS scores with 5-HTTLPR polymorphism in the patients*

VAS (tinnitus)	Genotype	No. of patients	Mean	SD	Minimum	Maximum	*p*
VAS-1 (severity)	*ll*	10	6.9	1.7	5	10	<0.05
	Ls	27	4.3	2.2	1	10	
	ss	17	5	2.2	1	8	
	Total	54	5	2.3	1	10	
VAS-2 (frequency and duration)	*ll*	10	9.2	1.7	5	10	>0.05
	ls	27	7.9	2.9	1	10	
	ss	17	7.3	2.9	1	10	
	Total	54	7.9	2.7	1	10	
VAS-3 (discomfort level)	*ll*	10	8.1	1.8	5	10	<0.05
	ls	27	5	2.5	1	10	
	ss	17	5.6	2.7	1	10	
	Total	54	5.8	2.7	1	10	
VAS-4 (attention-deficit)	*ll*	9	6.3	3.3	0	10	<0.04
	ls	27	3.2	3	0	10	
	ss	17	2.6	3	0	9	
	Total	53	3.5	3	0	10	
VAS-5 (sleep disorder)	*ll*	10	5.8	3	1	9	>0.05
	ls	27	2.9	3.4	0	10	
	ss	17	2.5	2.6	0	8	
	Total	54	3.3	3.3	0	10	

VAS-1 (severity of tinnitus), $p = 0.004$ for *ll* and *ls* comparison; VAS-3 (discomfort level of tinnitus), $p = 0.002$ for *ll* and *ls* comparison, $p = 0.03$ for *ll* and *ss* comparison; VAS-4 (attention-deficit due to tinnitus), $p = 0.04$ for *ll* and *ls* comparison, $p = 0.03$ for *ll* and *ss* comparison.

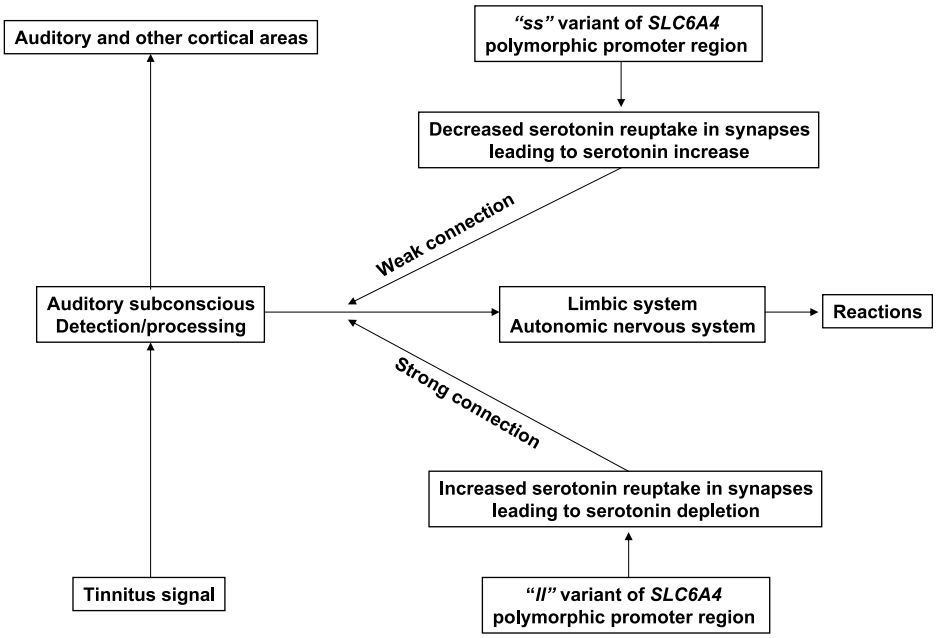

FIG. 1. Schematic demonstration of the association of 5-HTTLPR polymorphism of SLC6A4 with tinnitus.

5-HTTLPR polymorphisms. In addition, there was no association between the psychoacoustic parameters of tinnitus and *SLC6A4* polymorphism. There was no relationship between BDI and THI scores of the patients and *SLC6A4* polymorphism. The *SLC6A4* is not associated with tinnitus lateralization because there was no significant difference between the genotypes of the patients with unilateral and bilateral tinnitus. However, there was an association between the VAS scores and the functional polymorphism of *SLC6A4*, that is, 5-HTTLPR. The presynaptic reuptake of serotonin is faster in the presence of "*ll*" variant of 5-HTTLPR than in the presence of "*ls*" or "*ss*" variants. That is, "*ll*" variant leads to decreased serotonin levels in the neural synapses compared with other variants. The patients who had "*ll*" genotype had significantly higher VAS scores, which is possibly mediated by the fast presynaptic serotonin reuptake. This finding suggests that *SLC6A4* polymorphism, especially "*ll*" variant of the 5-HTTLPR polymorphism, is associated with the limbic and autonomic system symptoms such as tinnitus discomfort, attention-deficit, and sleep disorder. When we relate this finding with the neurophysiological model of tinnitus, it can be postulated that the people who have "*ll*" genotype are vulnerable to develop "the conditioned reflex arc" between the tinnitus signal and limbic and autonomic nervous system (Fig. 1). Thus, serotonin replacement or serotonin reuptake inhibitors may help restore this depletion and may be used as an adjunct to the treatment modalities that are based on neurophysiological model of tinnitus such as tinnitus retraining therapy or neuromonics.

After release, serotonin is actively cleared from synaptic spaces by *SLC6A4*, a high-affinity, Na(+)- and Cl(−)-dependent transporter localized in presynaptic neuronal membranes. This brain serotonin transporter seems to be a principal site of action of many tricyclic antidepressants, such as imipramine, and may mediate behavioral and/or toxic effects of cocaine and amphetamines. After serotonin release in brain synapses, it is taken up into the presynaptic neuron by *SLC6A4*, which thus terminates the synaptic actions of serotonin and recycles it into the neurotransmitter pool (38). This presynaptic reuptake is faster when the subject has "*l*" allele of 5-HTTLPR. In patients with depression, presence of "*ll*" variant of 5-HTTLPR polymorphism is associated with a significantly better response to serotonin reuptake inhibitor treatment when compared with the "*s*" allele carriers (39,40). Serotonin reuptake inhibitors represent one category of tools that can be used to help patients with severe tinnitus and depression (41). On the basis of our results, we can speculate that the patients with "*ll*" variant may respond better to serotonin reuptake inhibitor treatment.

Finally, because *SLC6A4* polymorphism can change attitude of the patient against tinnitus signal by altering serotonin level, it can be a cause for tinnitus distress. In addition, *SLC6A4* polymorphism may be a marker in tinnitus to show how much tinnitus distress will be in the patient.

CONCLUSION

Generation of tinnitus signal is not associated with *SLC6A4* polymorphism and possibly with serotonergic mechanisms. However, the "*ll*" genotype variant of the *SLC6A4* polymorphic promoter region seems associated with the limbic and autonomic nervous system symptoms of the patients with tinnitus. Therefore, serotonergic mechanisms may help explain the neurophysiological

model of tinnitus, and serotonin replacement or serotonin reuptake inhibitors may increase the success rate of tinnitus treatment modalities based on the neurophysiological model of tinnitus.

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