

# Pathophysiological Mechanisms of Tinnitus

## Mecanismos Fisiopatológicos do Zumbido

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### ABSTRACT

Tinnitus is an otoneurological symptom physically and psychologically affecting the individual which finds himself inserted in a doubtful environment. The problem is, at present, one of the challenges faced by investigators. It is estimated that 1 to 2% of the population is severely hit by the symptom, which damages the quality of life. Tinnitus may be present in at least 300 diseases seen in everyday clinics varying from obstruction of the external acoustic meatus by cerumen to serious diseases as intracranial tumors. Pathophysiological mechanisms, both peripheral and central, are suggested to explain the generation and perception of the symptom in the auditory system and the cerebral cortex. Research in clinical and mainly experimental studies was able, in the last two decades, to propose theories trying to comprehend the problem and also as a fundament to its treatment. In this context, the present paper, aims to review the several theories about the pathophysiology of tinnitus, emphasizing relevant aspects that may have implications for the treatment of this symptom.

**Key words:** tinnitus, pathophysiology of tinnitus; mechanisms in tinnitus.

### RESUMO

O zumbido é um sintoma otoneurológico que afeta física e psicologicamente o indivíduo, permanecendo envolto em inúmeras incógnitas e sendo um dos desafios dos pesquisadores na atualidade. Estima-se que 1 a 2% da população seja severamente acometida por esse sintoma, que pode trazer prejuízo à qualidade de vida das pessoas. Pode apresentar-se em uma ou mais dentre 300 patologias, podendo estar relacionado com situações clínicas cotidianas, como a obstrução do meato acústico externo por cerume, ou a patologias graves, como os tumores intracranianos. As pesquisas têm apontado para mecanismos fisiopatológicos diversos, periféricos e centrais, que poderiam explicar a geração e percepção do sintoma nas vias auditivas e córtex cerebral. Sobretudo nas duas últimas décadas, os pesquisadores puderam propor, a partir de estudos clínicos e principalmente experimentais, teorias que podem ajudar na compreensão do sintoma e fornecer alicerces para o seu tratamento. Nesse contexto, o presente trabalho visou revisar as diversas teorias sobre a fisiopatologia do zumbido, abordando aspectos relevantes que podem ter implicação no tratamento do sintoma.

**Unitermos:** zumbido, fisiopatologia do zumbido, mecanismos de zumbido.

### INTRODUCTION

Tinnitus, from the latin tinnire means "sounding as a bell". Also called "Tinido", the sound can be considered

an auditive illusion not related to external acoustical stimuli.<sup>45</sup>

It is an otoneurological symptom that causes great suffering to the patient, including suicide attempts.<sup>23</sup> The

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daily chores and sleep of nearly 1 to 2% of the population may be affected by this problem.<sup>44</sup>

About 300 disease may have tinnitus as one of its manifestations, which may be classified according to the affected region as, peripheral, central, extra -auditory or of unknown origin, the last one in 50% of the patients.

The sound, continuous or intermittent, constant and mono or polytonal is generally referred as a shrill, whistle, waterfalls or shower noises, hissing sound of pressure pans, bell ringing, insect flutter, heart pulsation or butterfly wing beating. Discomfort is not always associated to the intensity of the ringing, which is variable, but alongside disesthesia and dizziness it is one of the main otoneurological manifestations.<sup>22</sup>

Tinnitus should be considered as symptom of disease or as sequels following aggressions to the auditory system<sup>23</sup>, but it is important to distinguish it from auditory hallucinations in psychotic patients hearing voices or sounds of music.<sup>17</sup>

Several theories try to explain the physiopathology of the generation and perception of tinnitus. Current consensus is that tinnitus results from aberrant neural activity in the auditory system, generally of excitatory nature<sup>28</sup> and interpreted as sound by the auditory cortex.<sup>46</sup>

The present paper reviews theories on tinnitus physiopathology, emphasizing relevant aspects to explain this intriguing symptom.

## TINNITUS NEUROPHYSIOLOGICAL MODELS

### Participation of outer hair cells

Suffering of hypoxia-sensitive hair cells is one of the hypotheses, which try to explain tinnitus.<sup>29</sup>

Involvement of outer hair cells (OHC) in generating tinnitus has been considered since Kemp (1978)<sup>30</sup> identified and described otoacoustic emissions (OAE), although Gold (1948)<sup>26</sup> suggested that low intensity sounds could be physiologically generated in the cochlea, in absence of stimulation, constituting the so-called spontaneous otoacoustic emissions (SOAe).

Currently, it is known that OHCs increase middle ear sensitivity by amplifying sounds through energy dependent

active processes.<sup>8</sup> They concern electromobile cells, able to contract and produce vibrations affecting the mechanical properties of the organ of Corti. These vibrations are manifested by very low sounds, emitted as SOAes by the cochlea and able to be detected by sensitive microphones located in the external acoustic meatus, in normal and tinnitus -affected individuals.<sup>38</sup>

As an average, 28% men and 56% women show measurable SOAes, although it can explain very few tinnitus cases<sup>29</sup>. According to Baskill & Coles (1992)<sup>2</sup>, the correlation between tinnitus and SOAes could be seen in only 2% of the cases, this index being less than 10% in several studies<sup>29</sup>.

In this context, Penner & Burns(1987)<sup>40</sup> observed that in individuals affected by tinnitus, only in rare instances there were coincident frequencies between SOAes and tinnitus, a finding which contradicts the direct relationship of OHCs motor activity and the symptom. Further more, masking tinnitus should suppress SOAes or inversely, the symptom disappears when SOAes are abolished.<sup>1</sup> It is known that salicylates abolish SOAes, but tinnitus perception does not decrease when OHC activity is interrupted. Rather, according to Penner (2000)<sup>41</sup> salicylate ototoxicity increases the risk of auditory loss and consequently an increased tinnitus perception.

### Participation of inner hair cells

Internal hair cells (IHC) being functionally afferent have been focused in several tinnitus models. Disturbed cochlear functions by mechanical trauma or blood supply modify the biophysical properties of hair cells, changing ionic conductivity and increasing spontaneous neurotransmissions<sup>53</sup>.

Glutamate is the presumed neurotransmitter in IHC<sup>10</sup>. Synaptic transmission alterations between IHC and the cochlear nerve could increase the spontaneous activity of the neural fibers, generating tinnitus. This would be due to increased effective transmission in the post-synaptic fibers or inhibition by increased efferent activity.<sup>28</sup>

Experimental studies using glutamate blockers, like caravornine<sup>12</sup> or glutamic acid diethylester<sup>13</sup> indicated protective effects against ototoxicity and some forms of tinnitus in humans<sup>29</sup>; another glutamate antagonist, memantine, when injected in guinea pig cochlea reduced the spontaneous activity of the auditory nerve fibers.<sup>39</sup>

## Disproportion between inner and outer hair cells

Another tinnitus theory addresses the disproportional damage to OHCs and IHCs in auditory traumatic situations. Ear exposure to noise or to ototoxic drugs cause alterations in the cochlear structure, starting with lesions in the high frequency region basal membrane, by damaging initially the OHCs and later the IHCs. Thus, the damaged basal membrane will have areas showing totally lesioned OHCs and IHCs and others with lesioned OHCs and intact IHCs<sup>28</sup>. According to a proposal by Stypulkovski (1989)<sup>50</sup> in relation to the afferent system, the basal membrane, in the absence of hair coupling by lesioned OHCs, would have higher amplitude contractile movements. In addition, the partial uncoupling of the tectorial membrane, would shorten the distance between the membranes allowing OHC hairs to be close to the tectorial membrane, thus promoting a tonic OHC depolarization and resulting in abnormal activity in the afferent fibers.

As to the efferent system, Hazell (1987)<sup>27</sup> proposed that OHC positions in relation to the tectorial membrane is an information afferently conveyed to superior centers which after processing regulates the length of the cell efferent systems. As the inhibitory efferent impulse results from the summated afferent impulses, there is a decreased efferency as there are OHCs that do not respond to sonorous stimuli. Considering that one efferent fiber may innervate about 100 OHCs, the inhibitory reduction could affect areas of the basal membranes where OHCs are normal, thus freely contracting and stimulating IHCs in these regions. The resulting anomalous electric activity could be related to tinnitus<sup>28</sup>.

This theory would explain some of the tinnitus mysteries as the existence of individuals with very similar audiograms but not necessarily having tinnitus; as the possibility of audiometrically normal individuals showing tinnitus since diffused lesions of up to 30% OHCs could not be detected in audiometry; as the tinnitus frequency very close to the area of representation of audiometric loss.<sup>28</sup>

## The involvement of calcium

A variety of cochlear dysfunctions may be caused by calcium concentration changes in the perilymph or within

hair cells. Several possible mechanisms suggest that cochlear transduction is calcium dependent.<sup>11</sup>

Lower intracochlear calcium may rapidly change the tectorial membrane permeability causing edema, and also increase OHC diameter. and decrease its length thus shortening the distance hair-tectorial membrane. In addition, decrease of calcium concentration alters hair cells depolarization capacity by interfering in potassium intracellular regulation. Cell hair mobility and contractions are disturbed by intracellular decrease of calcium in the hair roots.<sup>28</sup>

Fast OHC contractions are not affected by calcium as are the slow contractions which in conditions of low calcium would result in an increase in fast contractions and a possible source of tinnitus generation. Low levels of calcium also affect liberation of neurotransmitters by hair cells.<sup>3</sup>

## The involvement of zinc

Zinc participation in central neurotransmission has been indicated in several studies. The element was first detected in the hippocampus but today it is known to participate in some neural circuits, and that it is related to glutamatergic excitatory synaptic nets.<sup>4</sup> It is also present in amygdala neurons<sup>6</sup>, corpus striatum<sup>51</sup>, olfactory bulb<sup>21</sup>, dorsal cochlear nucleus<sup>20</sup>, spinal cord<sup>7</sup> and layers 1, -3 and 5 of the cerebral cortex and pineal gland<sup>19</sup>.

Cochlear anti-oxidant defenses contain zinc as an essential element and superoxide dismutase (Cu/Zn, SOD) is a first rate defense line against chemical generated free radicals. It is attributed to the enzyme a prominent role in cochlear protection.<sup>32</sup>

The protector effects of zinc in ischemia and against ototoxic drugs, were respectively described by Seidman et al., (1993)<sup>49</sup> and Clerici (1996)<sup>5</sup>.

Zinc physiology has been correlated to tinnitus generation<sup>19</sup> and systemic administration of the oligoelement as an alternative treatment of tinnitus<sup>25</sup> in the elderly was suggested specially because they require diets with six times the minimal amount of zinc present in normal diets.<sup>9</sup>

As a participant of vital body reaction systems, like the maintenance of the Na-K-ATPase bond, zinc deficiency may change endocochlear potential altering its electrophysiology and generating tinnitus.<sup>34</sup>

### **Cross-talk between fibers**

Cross-talk between demyelinated fibers in the VIII cranial nerve pair could produce tinnitus consequent to a real short-circuit between fibers not electrically protected. This condition could arise by vascular compression syndrome within the inner acoustic meatus or another retrocochlear pathology leading to the generation of abnormal neural impulses interpreted as tinnitus by the cerebral cortex.<sup>35</sup>

Moller (1995)<sup>36</sup> hypothesized that tinnitus could be generated in the central auditory pathways due to compression of the VIII nerve pair, interrupting the electric flux between the peripheral system and the central auditory nuclei. The central hyperactivity would result from a reduction in the inhibitory neuronal activity in the nuclei.

### **Increased spontaneous activity**

Sound signaling in the auditory system goes normally through an increased rate of neural depolarizations; tinnitus may arise from auditory system hyperactivity, with increasing spontaneous activity induced by pathological alterations. This theory is being studied in animal models by electrophysiological techniques and in humans employing imaging techniques<sup>29</sup>.

Evans et al., (1981)<sup>15</sup> demonstrated increased spontaneous activity in the cochlear nerve in cats treated with high dosages of sodium salicylates (400 mg/Kg). The same alteration was registered in pigeons cochlea infused with the drug.<sup>48</sup>

NMR functional studies in tinnitus patients showed an increased blood flux in auditory cortex areas colliculus inferior and dorsal cochlear nucleus.<sup>29</sup>

### **Bursting activity**

Another theory addresses alterations in the neural discharge patterns in the auditory system. Usually in the absence of sound stimuli, impulses are generated in random and irregular ways. However, during stimulation impulses become highly regular showing uniform intervals between discharges. The uniformity produces periodic patterns of neural discharge, resulting from synchronization and producing cycles, which are represented by a property called "phase locking", able to codify low frequency sounds (generally lower than 5000Hz) in the auditory system.<sup>14</sup>

"Phase locking" similar periodicity may be induced in animals treated with salicylates, exposed to noise or to induced endolymphatic hydropsy, a condition usually associated to the Meniere syndrome. In this condition there is a bursting increase in which two or more impulses occur in rapid succession and regular intervals.<sup>29</sup> However, some observations in patients with salicylate or quinine induced tinnitus seem to disclaim this mechanism as the symptom generator. In these patients frequencies at peak tinnitus are around 7000 to 9000 Hz<sup>33</sup>, way above the presumed limit of 5000Hz of the "phase locking" in the auditive system.<sup>14</sup>

### **Coincidental neural discharges**

Although neurons depolarize asynchronously in absence of sound stimuli, acoustic stimulation generates synchronized discharges between fibers.

Based on these properties the theory of coincidental discharges considers that tinnitus would be generated in a pathological condition where two or more neurons show increased synchronized discharges. Since discharge synchronization is a normal neuron property, generation of tinnitus would involve increased levels of synchronization between neurons in the same area or auditory structure, or even between different structures in the system.<sup>35</sup>

### **Reorganization of tonotopic maps**

Changes in the tonotopic organization of central auditory structures are the basis of another theory that has attracted considerable attention.<sup>36</sup>

Tonotopic organization concerns the disposition of the cells within the auditory system nuclei according to frequency selectivity, reflecting the cochlear organization.<sup>29</sup>

Animal studies have demonstrated tonotopical reorganization in guinea pig auditory cortex,<sup>43</sup> and in the colliculus inferior of cats and guinea pigs<sup>42</sup>. The tonotopical reorganization seen in the auditory cortex after cochlear injury is similar to the reorganization of the somatosensorial cortex after loss of the limbic function. Clinical studies in tinnitus patients through magnetic imaging suggest that areas of the tonotopic map are reorganized.<sup>37</sup>

### **Jastreboff neurophysiological model**

According to Jastreboff (1990)<sup>28</sup>, the dynamic

interaction of some areas of the nervous central system including or not the auditory systems results in tinnitus. Thus, an initial cochlear source would not be fundamental to the gravity of tinnitus, but merely a trigger to other nervous system processes, even including participation of the limbic system.

Emotional conditions, specially humor fluctuations or anxiety may increase global stimulation and result in greater awareness of potential treats in the environment. These emotional alterations, in some cases, may increase the apparent "intensity" and irritation to sounds to which the person is already hypersensitive. In some individuals it results in an increased perception of all stimuli, visual, auditory, olfactory or painful<sup>47</sup>.

Therefore, tinnitus may be sensitizing or habit-forming depending on associations made between the auditory pathway and other centers in the central nervous system. It could be modulated or originated by stimulation of the somatosensory system.<sup>46</sup>

## DISCUSSION

Otolaryngologists always considered tinnitus as a symptom of difficult control. During decades, scarce research prejudiced by the symptom's subjectivity and lack of knowledge of its physiopathological mechanisms consolidated the concept of a non-treatable disease, leaving doctors and patients insecure and sometimes despairing.

However, recent work by some investigators and advances in new technological tools, like microscopy, tissue culture and electrophysiological studies in animal experimental research allowed the understanding of some of the peculiarities in neural physiology, fundamental for the knowledge of processes of generation and perception of tinnitus.

*Currently, it is known that tinnitus inducing agents are capable of damaging auditory system structures, mainly cochlear hair cells. In this scenario, neurophysiology studies have shown that salicylates, quinine and exposition to intense noise cause anomalous neural activity. This includes increased spontaneous activity, increased bursting and/or predisposition to coincidental neural discharges, which disturb neural physiology by changing frequency representation and relating to the physiopathology of*

*tinnitus.*<sup>29</sup>

Although we already know a lot about the physiopathological mechanisms of tinnitus it still is little compared to the vertiginous advances of research in general. However, we are able to characterize the symptom, at least, as resulting of a neural aberration, which includes multiple auditory and non-auditory paths, peripheral and central structures in a complex synaptic disarrangement.<sup>28</sup>

Any neurophysiological model considering the cochlea as an isolated generator of tinnitus is not adequate although in some situations its damage may be responsible for the symptom. It is important that the treatment of tinnitus with its complex physiopathological mechanisms, be started by the diagnostic of the triggering pathology. From 1990 on, Jastreboff neurophysiological model amplified the tinnitus concept, including in its genesis and perception the participation of nonauditory structures, allowing for new strategies and forms of treatment.

Based on the Jastreboff model, Flor et al. (1995)<sup>18</sup> emphasized the importance of the limbic system in the functional reorganization of nervous system processes to which tinnitus may be related.

Levine (1999)<sup>31</sup> considered the somatosensory system of importance in tinnitus perception, following observations that patients could modulate the symptom by fast movements, like cervical moving or biting. These patients reported changes in tinnitus intensity (increase or decrease) during these procedures, relating somatic modulation to the symptom by the interaction of its perception to the somatosensory system.

Current knowledge of different theories and neural plasticity empowers the professional with a scientifically based evaluation, to design a therapy, with drugs or not, for the improvement of this still involved in mystery symptom.

## CLOSING COMMENTS

All theories trying to explain the genesis of tinnitus converge to the existence of an aberrant excitatory activity in the auditory pathways. It is obvious, as already discussed, that more than one complex mechanism may be involved in the generation and perception of the symptom. The understanding of these mechanisms and the multiple systems involved besides the auditory one, is crucial to therapeutic

success. Experimental research has helped to attain this goal and as in any nosological situation, the physician should be aware of the theories dealing with the physiopathological mechanisms of tinnitus and with this solid foundation avoid the concepts of "impossible" or "insurmountable". Creation of more humane conditions would prevent statements like "there is nothing that can be done" or "tinnitus is not curable" or "you will have to get used to it" which unfortunately are still a reality in tinnitus strategies.

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