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Review Article

Phantom auditory perception (tinnitus): mechanisms of generation and perception

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SUMMARY

Phantom auditory perception - tinnitus - is a symptom of many pathologies. Although there are a number of theories postulating certain mechanisms of its generation, none have been proven yet. This paper analyses the phenomenon of tinnitus from the point of view of general neurophysiology. Existing theories and their extrapolation are presented, together with some new potential mechanisms of tinnitus generation, encompassing the involvement of calcium and calcium channels in cochlear function, with implications for malfunction and aging of the auditory and vestibular systems.

It is hypothesized that most tinnitus results from the perception of abnormal activity, defined as activity which cannot be induced by any combination of external sounds. Moreover, it is hypothesized that signal recognition and classification circuits, working on holographic or neuronal network-like representation, are involved in the perception of tinnitus and are subject to plastic modification. Furthermore, it is proposed that all levels of the nervous system, to varying degrees, are involved in tinnitus manifestation. These concepts are used to unravel the inexplicable, unique features of tinnitus and its masking. Some clinical implications of these theories are suggested.

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1. INTRODUCTION

1.1 Epidemiology of phantom auditory perception

Phantom auditory perception, described as tinnitus in the clinical literature, occurs with surprisingly high frequency and affects about 35% of the general population[27,169,272], with about 15% reporting its presence as frequent or continuous[7,169]. Tinnitus has been described in association with nearly every form of ear pathology. It occurs in 85% of patients with ear problems[26,169], and afflicts nearly 36 million Americans, 7-9 million severely[26,27,169,272], with high levels of annoyance precluding normal life in about 1 million[27,169,272]. Nevertheless, the pathophysiology of tinnitus has remained obscure and its treatment therefore elusive. With respect to a cure for tinnitus, the most recent clinical information[27,56,89,248] is rather pessimistic. Although some relief has been observed in patients treated with auditory masking procedures [93,94,169,272] , electrical stimulation[8,92,141], pharmacological and other methods[27,38,166,169,243,271], most approaches seem to act on the patient's attitude toward their tinnitus rather than on the underlying mechanisms[94,199,274]. Additionally, a strong non-specific placebo effect has been observed, making simple evaluation of treatment effectiveness open for discussion[27,43,48,51,165,254]. For most sufferers, particularly the most disturbed and distressed, help remains inaccessible. Significant progress in this field can only be achieved by determining the mechanisms of different types of tinnitus generation. A better understanding of how neuronal activity related to tinnitus is processed within the nervous system is needed to comprehend possible mechanisms of tinnitus attenuation. Such information will eventually allow for mechanism-specific treatment of tinnitus patients.

1.2 An animal model of tinnitus

Until now, essentially all work on tinnitus was done on humans, with the consequential implications and restrictions thereby resulting, owing to the lack of a valid animal model of tinnitus. Recently, such a model was created in this laboratory[111-116,118,121] and is presently being used to evaluate different possible mechanisms of tinnitus and methods of

its alleviation, as well as to address the general issues of perception and hallucinations[117] This model implemented two independent strategies: (i) a behavioral paradigm, based on Pavlovian suppression technique; and (ii) an electrophysiological evaluation of the spontaneous activity of single cells recorded from the inferior colliculus.

The behavioral approach is based on the well-established observation that salicylates cause auditory phantom sensations systematically in humans[61,169,182] and the following reasoning. It is impossible to induce tinnitus in a systematic manner for short, precisely controlled periods of time. This precludes utilization of typical behavioral techniques aimed at emphasis of the relation between short, well-defined sensory stimuli, which are stronger than background, and a reinforcement. During these procedures, animals are trained to habituate to the background. To enable tinnitus detection, it is necessary to reverse this situation and to utilize training which would enhance the importance of a continuous signal (tinnitus), constituting a portion of the background.

To achieve this goal, the following procedure was developed as a modification of the approach created by Estes and Skinner[52]. This paradigm is based on the creation of antagonism between ongoing, appetitively-based behavior and aversively-based response elicited by Pavlovian training, confronting two opposite motivations: thirst and fear. The animals' continuous reactions (licking reinforced by water) are partially attenuated during the conditioned stimulus by fear, which has been previously associated with the conditioned stimulus by proper training. Since the animal licks numerous times throughout the duration of the conditioned stimulus (30 s), the thirst level is kept constant, and the balance between thirst and fear results in a different extent of reaction suppression, it is then possible to evaluate gradual changes in the animals' fear.

The main idea of the tinnitus detection paradigm was based on creating a situation in which the presence of a continuous auditory signal would be associated by the animal with safety and the absence of it (silence) with danger. To achieve this, pigmented rats were exposed 24 h/day to mild (62 dB SPL) noise and were trained to associate silence with danger by terminating 4 presentations of 30 s of noise offset with a single mild electric shock. Next, the animals went through a passive extinction period, when offset of noise was presented but without the shock. The expectation was that if during extinction the animals experienced salicylate-induced tinnitus (evoked by daily injection of sodium salicylate) while external noise was off, it would be interpreted as a substitute for background noise, hence as a signal of safety. Therefore offset of noise should suppress licking to a smaller extent, and the process of extinction should occur more rapidly than in the control group injected with saline. Conversely, if the animals were trained in a Pavlovian suppression situation when salicylate-induced tinnitus was present, the rats would be conditioned to the sound of tinnitus as the conditioned stimulus, since during offset of external noise, tinnitus would become the dominant signal. This group of animals would be expected to exhibit stronger and longer lasting suppression than the previously described groups. Thus, daily salicylate injection should have an opposite effect on the animals' behavior, depending on whether the drug was introduced before or after the day of suppression training.

The results obtained, presented, and discussed in detail elsewhere[115] fully confirmed these expectations. Relative to control subjects injected with saline, subjects starting injections prior to training exhibited more severe suppression and persistence of suppression. Conversely, subjects beginning injections after training showed less suppression and rapid recovery of drinking.

The important question to be answered was if the observed effects were due to the action of salicylate on the auditory system or perhaps due to non-specific action of the

drug. To test this, another experiment was performed paralleling the procedure outlined above but switching to a visual modality, e.g. using continuous light as background, with offset of this light serving as the conditioned stimulus. In this situation, the effects of salicylate observed previously were eliminated, indicating that the salicylate-induced effects were specifically auditory. A number of other control experiments were performed, including mimicking tinnitus with continuous external tone, which showed the same effect as salicylate[115]; decreasing the level of background noise at the same stages as salicylate introduction, to evaluate the effect of salicylate-induced increase of hearing threshold, had no effect[110].

Furthermore, we obtained analogous results using another drug, quinine[116]. Quinine presumably has a different mechanism of action on the auditory system than does salicylate[215,249], but shares with salicylate tinnitus-inducing properties in humans[61,169]. These combined results support the postulate that this paradigm detects salicylate-induced phantom auditory perception in rats.

In an electrophysiological study of tinnitus, the spontaneous activity of inferior colliculus cells was analyzed before and after salicylate administration[121]. This approach was based on Evans' report[53,54] which shows increased spontaneous activity of auditory nerve fibers and the appearance of abnormal patterns of activity after salicylate. Our results showed that the spontaneous activity of inferior colliculus cells increased after salicylate, while the spontaneous activity in the non-auditory part of the cerebellar vermis remained stable[121]. Additionally, the presence of abnormal activity was indicated. These findings support the hypothesis that tinnitus results from aberrant neural activity within the auditory pathways, which is interpreted as sound at higher auditory centers.

It was necessary to assure that the salicylate doses being used were inducing sufficient levels of the drug in perilymph to interfere with cochlear functions, and that the behavioral differences observed between groups of animals were not due to varying salicylate levels. Sampling of serum, cerebrospinal fluid, and perilymph at various time intervals after salicylate showed levels of the drug[114,119] comparable with levels reported to alter cochlear transduction functions[215], to decrease the turgor of outer hair cells (OHC)[20], and to alter their membrane properties[6,244]. Finally, different experimental treatments and paradigms were without effect on salicylate uptake, eliminating the possibility that the behavioral differences observed among groups were due to variations in salicylate levels.

Work to date has focused on developing and establishing an animal model of tinnitus using both behavioral and electrophysiological approaches. The behavioral part shows that amimals are perceiving tinnitus in a given experimental situation, while the electrophysiology elucidates possible cochlear and neural mechanisms of tinnitus generation. We are now evaluating the hypothesis, presented in more detail further in this text, regarding the involvement of calcium and calcium channels in normal functions and dysfunctions of the cochlea [111,112] .

1.3 Basic science connotation

Although virtually all data available to date were gathered clinically, the phenomenon of tinnitus is very interesting for basic science. It offers an interesting tool to study mechanisms of phantom perception in general and can be used as a starting point to study hallucinations. Analysis of the tinnitus phenomenon should provide better insight into the mechanisms of perception and the representation of external stimuli in the nervous system. The relation between a perception and the stimulus evoking it is one of the basic issues of psychological theory. Plasticity of the brain supports the possibility of phantom perception in humans, originating from the ideas of gestalt psychologists[97] and

continuing in modern theories of perception[41,77]. With respect to auditory neuroscience, tinnitus offers the challenging question of how relatively weak, continuous signals are being discriminated from the background of spontaneous activity without undergoing habituation. Tinnitus resembles phantom somatosensory and phantom pain perceptions[262]. Information obtained from tinnitus research might help to better understand these phenomena.

In the literature, the terms 'objective' and 'subjective' tinnitus are sometimes used with the meaning that the sound of 'objective' tinnitus can be detected by an observer. As tinnitus is by definition a subjective phantom sensation, use of the terms 'subjective' and 'objective' is not advisable. Some tinnitus patients may be experiencing somatosounds[27,169], the result of abnormal blood flow or myogenic activity, and these phenomena should be excluded and managed separately.

Furthermore, it is important to stress that tinnitus is a physiological disorder of the auditory system, not a psychological or psychiatrical disorder[65,169]. Unfortunately in the past, some tinnitus patients were directed to a psychiatrist for treatment of schizophrenia, for which auditory hallucinations are landmark[24,95,292]. Analysis of the psychological profile of tinnitus patients reveals the incidence of depression, which might be due to tinnitus, but the general psychosomatic profile remains normal[65].

1.4 General aims

Basic, well-established concepts of neurophysiology are being used in this paper to analyze the possible mechanisms of tinnitus generation and perception, indicating implications and predictions arising from this approach. These concepts are used to explain the puzzles of tinnitus, and to propose certain clinical implications. I would like to stress that since the current information available on tinnitus was collected under clinical or psychoacoustical pretenses, the type of information that was gathered is not appropriate for evaluating the correctness of my theories. Therefore, some of my hypotheses regarding tinnitus perception arise from theoretical predictions. Although the available data are in agreement with my proposals, more information is needed for their proof. Nevertheless, the hypotheses presented here are testable and offer a theoretical, experimental and clinical framework for work on tinnitus.

2.TINNITUS GENERATION

Several general hypotheses describing the origin of sensorineural tinnitus have been proposed[157,177,230,260,261]; however, none has been proven yet. There is consensus that tinnitus is the result of aberrant neural activity within the auditory pathways and that such activity is erroneously interpreted as sound by auditory centers, but the agreement ends here. Nevertheless, there is clearly a variety of different conceivable mechanisms of tinnitus generation.

The majority of tinnitus cases are being related to cochlear dysfunction[169]. The organ of Corti represents a very complex and delicately balanced micromechanical system. The discovery by Russell and Sellick[220,221] that hair cells have tuning curves as sharp as single auditory nerve fibers showed that there is no need to postulate neuronal sharpening of frequency response beyond the basilar membrane mechanics. This caused reconsideration of previous concepts concerning the micromechanical properties of the organ of Corti[136,159,241,290,304]. The OHC play an essential role in the frequency selectivity of the basilar membrane[37,219]. The rigid coupling of cilia to hair cells is crucial for their normal function[85,260,261,301-304]. The cilia of hair cells are stiff and brittle[60,256,257], the rigidity of

their coupling with the hair cell membrane being dependent upon the concentration of intracochlear calciun[191]. Measurement of the kinetics and transfer functions of ciliary movements has shown a strong dependence of these functions on calcium concentration[34,60,98,191]. All these findings can be used to propose mechanisms of tinnitus generation based on cochlear dysfunction.

2.1 Spontaneous otoacoustic emission

The involvement of active mechanical processes in tinnitus generation has been suggested [88,132,286-288]. These active processes, even when responsible for generating acoustic energy within the cochlea, do not seem to be simplistically related to tinnitus as initially hoped[54,132,286-287]. An analysis of the population of tinnitus sufferers revealed that there is little or no correlation between the subjective characteristics of tinnitus and spontaneous otoacoustic emission. Nevertheless, a correlation occurs in a small percentage, estimated at 4%, of all tinnitus cases[27]. Recent results by Penner indicate that spontaneous otoacoustic emission might be responsible for tinnitus[200-202]. Then salicylate, which is well known to induce tinnitus in humans [61,169,182] and was reported to abolish spontaneous otoacoustic emissions [162,167,170] and to suppress active processes in the cochlea [6,20,212,213,244], should relieve tinnitus. This has been described only in one case when, in parallel with the disappearance of initial tinnitus, salicylate-induced tinnitus appeared[202]. More data are needed to evaluate the significance of spontaneous otoacoustic emission related tinnitus. Nevertheless, active processes might be involved in tinnitus generation but in a more complex manner as described in the sections to follow.

2.2 Stereocilia decoupling

In 1980, Tonndorf suggested an alteration in the mechanical coupling between hair cells and the tectorial membrane may be the basis for the origin of tinnitus[260,261]. His hypothesis was derived from work by Harris[85], who calculated the level of thermal noise at the input of hair cells. Harris concluded that loose coupling of hair cell cilia to the tectorial membrane should result in increased thermal noise of the system, up to 30 dB above the threshold of sound perception. Tonndorf deduced that such an increase of thermal noise will be perceived as tinnitus. Due to the frequency-specific properties of segments of the basilar membrane, depending on the extent of basilar membrane involved, perception of the resulting noise varies from broad-band to very-narrow-band, the latter sounding essentially like pure tone. This theory predicts the appearance of center clipping of an auditory signal, resulting in poor speech perception and recruitment, phenomena observed in tinnitus patients[27,169,260,261]. To my knowledge, this hypothesis has not been confirmed experimentally.

It is possible to extrapolate this theory further and to propose other mechanisms of decoupling the tectorial membrane from the basilar membrane. Mechanical decoupling might occur not only at the tectorial membrane but also at the attachment of the cilia to the OHC. Decreased strength of rootlet attachments in the apical plate of OHC would introduce 'free play' of the cilia and should have the same decoupling effect as in Tonndorf's model, resulting in increased thermal noise. Interestingly, exposure to intense sound, which is known as a method to produce temporary tinnitus in humans, causes bending and disorganization of the cilia, followed by damage to the rootlets as the first morphological findings observed after noise exposure[150,156,232-235]. Such damage will result in mechanical decoupling of the tectorial membrane from the OHC system.

2.3 Discordant damage of inner and outer hair cells

Accumulated data show that a traumatic agent, such as noise or ototoxic drugs, causes cochlear damage starting its action on the basal high-frequency part of the basilar membrane, with OHC affected first, followed by damage to inner hair cells (IHC)[29,103,154-156,234,253]. Therefore on a partially damaged basilar membrane, there will be some areas with totally damaged OHC and IHC. and other regions with damaged OHC while IHC remain reasonably intact. This last area is of particular interest. The mechanical properties of the organ of Corti will be seriously affected, due to disintegration of the coupling between the basilar and tectorial membranes, while IHC will be sufficiently functional. It is possible to expect abnormal movements of the basilar membrane and perhaps local collapse of the tectorial membrane, decreasing the distance between IHC cilia and the tectorial membrane to the extent of physical contact and bending of the cilia. This might cause tonic depolarization of IHC, resulting in the appearance of abnormal activity in afferent fibers. The hypothesis outlined here was proposed by Stypulkowski[253] and might be further extended as follows to include possible loops involving efferent innervation of OHC and IHC systems.

It has been proposed that the position of the basilar membrane is adjusted to provide an optimal working point for transduction characteristics of the organ of Corti by changing the length of OHC under the influence of the efferent system innervating OHC [147,148,296]. Afferents coming from OHC should provide information describing their working point which subsequently, after processing within the brainstem, will be fed back to efferent fibers to adjust the length of OHC. Decrease or lack of input from OHC belonging to a portion of the basilar membrane might result in decreased activity within efferent fibers[18], aimed at increased negative dampening (through OHC) and decreased inhibition on afferents coming from IHC. This will yield enhanced activation of normal IHC, resulting in abnormal activity perceived as tinnitus. Since an efferent fiber branches profoundly in the cochlea, reaching as many as 100 OHC over a distance of up to 3 mm of basilar membrane[53], this will cause a release from inhibition of OHC and IHC from the neighboring normal portion of the basilar membrane. The activity due to this phenomenon can be further enhanced by edge effect, as described subsequently.

The above hypothesis can be used to explain several mysteries of tinnitus, such as: (i) why the pitch of tinnitus usually correlates with the slope of the audiogram, a common clinical observation[88]; (ii) why patients with the same audiograms might or might not have tinnitus; (iii) the mechanisms of noise-induced temporary tinnitus. Moreover, it points out a new approach for evaluation of the tinnitus patient.

The slope of the audiogram corresponds to the area on the basilar membrane where partial damage of IHC and OHC occurs. Hence this is exactly the area where one can expect to find a portion of the basilar membrane with functional IHC and damaged OHC. The difference among patients with seemingly identical hearing loss represents a different extent of OHC and IHC loss. It has been shown that exposure to the same noise might result in dissimilar patterns of cochlear damage in different subjects[39,103,158], and that the diffuse loss of OHC up to 30% might not have a significant impact on hearing threshold[15,82,225]. This observation further supports the postulate that hearing threshold predominantly depends on the integrity of the IHC and not so much on the OHC system. Therefore audiometric evaluation is insufficient for determining the status of the OHC system along the basilar membrane and might, at best, be sufficient for approximate prediction of the presence of tinnitus. Independent evaluation of the status of IHC and OHC is needed. Methods developed recently for evaluating cochlear emissions and distortion products can be used for determining the status of

OHC [17,84,131,133,134,163,168,210,211,279,285,299], whereas traditional audiometry might be used to estimate the integrity of the IHC system.

Exposure to intense sound first results in bending of the OHC stereocilia, effectively decoupling them from tectorial membrane and preventing sound-induced excitation of OHC. If the noise is not too intense and does not cause permanent threshold shift, the stereocilia return to their normal state within hours or days. Transient tinnitus is frequently reported after exposure to such noise [64,135,169], which is consistent with the proposed theory. Pemanent damage of OHC might result in permanent tinnitus, provided that there are still some functional IHC in the area. Interestingly, comparison of sound-induced tinnitus with chronic tinnitus indicated that both kinds may arise from the same auditory precesses[64].

2.4 Calcium involvement in cochlear dysfunctions

There is consensus that calcium plays a significant role in cochlear function [2,49,57,59,99,101,227,252,268,297]. There are several possible mechanisms through which calcium might influence the transduction properties of the cochlea. Calcium has been shown to influence: (i) position of the tectorial membrane[140]; (ii) hair cells' calcium-dependent potassium channels[32,35,98,100,101,227,269]; (iii) transduction properties of hair cell cilia[191]; (iv) slow motile properties of OHC[59,107,268,296,297]; and (v) release of neurotransmitter from hair cells[37,252]. Additionally, hypothyroidism with associated low calcium is affiliated with hearing 1oss[175], presumably through development of a non-functional tectorial membrane as a result of low calcium 1eve1[216].

Previously, I have hypothesized that changes in calcium ion concentration in the perilymph as well as within hair cells may be responsible for a variety of cochlear dysfunctions including tinnitus, further implying that calcium channel modulators might be useful in alleviation of cochlear and vestibular disorders[111,112]. This hypothesis is based on the following reasoning.

2.4.1 Effect on micromechanical coupling of the cochlear structures Decoupling of cilia from the tectorial membrane might result from decreased concentration of calcium in cochlear fluid, as this coupling is calcium dependent. Kronester-Frei[140] showed that removal of intracochlear calcium causes rapid swelling of the tectorial membrane, with a parallel increase in the distance between the hair cell cilia and the membrane. Further on, the ultrastructure of the tectorial membrane matrix loses its organized striated sheets, disintegrating into randomly dispersed fibrillar material and small particles[86]. Since even minor changes in the parameters of ciliary coupling with both hair cells and the tectorial membrane have a significant impact on the transduction properties of hair cells, calcium-induced changes in coupling could be a physiological basis for Tonndorf's hypothesis.

In this regard, it is interesting that subcutaneous or oral administration of 300-400 mg/kg of aspirin or sodium salicylate in rats causes a significant decrease in serum calcium[118,126,127,222], to the extent sufficient to be responsible for fetal toxicity. Moreover, this teratogenic effect of salicylate can be prevented by exogenous $CaC1_2$[267]. Our observation fully confirmed these findings, further indicating that salicylate decreases calcium levels in cerebrospinal fluid (CSF) and perilymph[118,120]. Interestingly, our experiments with another tinnitus-inducing drug, quinine, showed both behaviorally detectable tinnitus[116] and a significant decrease of serum calcium (Jastreboff, in preparation).

2.4.2 Outer hair cells In this respect, the recent report of Brownell and co-workers, analyzing electrically and chemically induced OHC volume changes, is of particular interest [20]. Brownell postulated that ' The low calcium may increase the permeability of the

cytoplasmic membrane to ions and low molecular weight molecules'. Therefore, decrease of calcium results in increase of OHC diameter and decrease of OHC length under normal conditions. This, in turn, might be responsible for the reported attenuation of cochlear active processes by salicylate due to mechanically decoupling OHC from the tectorial membrane, in addition to the direct effect of salicylate on the electrical-mechanical conversion site in the OHC membrane[6].

Other possibilities of tinnitus generation are based on the involvement of calcium in transduction processes elsewhere within the cochlea. There is consensus that calcium is required in the process of transduction of mechanical stimuli into electrical potentials[31,32,37,98,184,269]. It has been shown that acoustic transduction is mediated by calcium-sensitive potassium channels[32,100,227,269], and that calcium plays a crucial role in determining the mechanical properties of cilia[191] and the slow motile properties of OHC[294,297]. Decrease of intracellular calcium concentration within the apical part of OHC should decrease the tension of the contractive proteins attached to the cilia's rootlets, changing their mechanical characteristics particularly for small displacements of the cilia. Thus, there might be an increase of 'free play' in ciliary pivoting and a decrease of mechanical coupling between the tectorial and basilar membranes, resulting in an increase of thermal noise and tinnitus. Although calcium is not essential for fast motility of OHC[5,228,295], it is crucial for slow OHC movements[49,59,268,297], which have been postulated to be involved in adjusting the basilar membrane position to assure the most efficient sound transduction in a wide range of intensities[147,148,296]. These hypotheses predict that decrease of the intracochlear calcium level might result in non-linear, recruitment-type characteristics of cochlear microphonics (CM), particularly when recorded from OHC or from outside of the cochlea, when OHC activity predominates in CM[37]. Increase of noise in CM and cochlear action potentials (CAP) might be expected as well. Clinically, this type of tinnitus should be associated with worse speech perception than might be predicted from the audiogram, with display of disproportionately poor speech discrimination near threshold and better discrimination at higher intensities.

It is noteworthy that ionic compositions are not homogenous along the cochlea and concentrations of endolymphatic calcium have been reported to increase by a factor of two between the basal and apical parts of the cochlea[105]. This finding might be partially explained by recent data showing that longitunal flow of endolymph does not exist[224]. Thus local ionic concentrations represent a dynamic balance between passive diffusion and active pumping of the ions from stria vascularis[104,124,190], which can be different for different portions of the organ of Corti. The distribution of hair cell stereocilia and their interlinking is heterogenous as well, with taller cilia and higher extent of interlinking occurring in the basal part of cochlea[63,257-259]. Given the information above, it is reasonable to postulate that a change in serum calcium level, which has been shown to be reflected in calcium concentrations in CSF and perilymph[125], might influence various parts of the basilar membrane to different extents, perhaps with the basal end of the basilar membrane affected first. Therefore, even a general change in the serum calcium level might result in tonal type of tinnitus.

2.4.3 Modulation of neurotransmitter release. Another interesting possibility is the direct influence of calcium level on the release of neurotransmitter from hair cells. Data obtained from lateral line preparation showed that gradual increase of calcium level resulted initially in suppression of spontaneous activity of the VIII nerve fibers, while evoked activity tended to increase[45,46,80,187,242]. Only when calcium level was further increased above 5 mM were both types of activity suppressed. Conversely, a decrease in

the calcium level increased spontaneous activity and decreased evoked activity. For low calcium levels, evoked activity was totally abolished while spontaneous activity remained stable, but with a change from random to regular type of discharges[45]. These data indicate the possibility of the existence of partially independent mechanisms of transmitter release for spontaneous and evoked activity, both of which are calcium-dependent, but in a different manner. This postulate is further supported by the finding that venom from the spider, *Argiope trifasciata*, a highly specific blocker of ion channels associated with glutamatergic receptors, in lower doses affects sound-evoked activity recorded from auditory nerve fiber without influencing spontaneous activity[36].

Although there is consensus that calcium is essential for transmitter release, the novelty is that modification of the calcium level might have a converse action on spontaneous versus evoked activity. Since a decrease in the calcium level results in an increase of spontaneous and a decrease of evoked activity, this should cause a decreased signal-to-noise ratio, with increased tendency to tinnitus and the appearance of a problem with speech perception and hearing in general.

In summary, it is possible to predict the following sequence of events when the calcium level decreases in the cochlea. The tectorial membrane will swell, increasing the distance between the membrane and 0HC[140], causing partial mechanical decoupling, which should increase the thermal noise of the system[85,260]. Transduction characteristics of the cilia will change in a manner indicating a more flexible attachment[191], which again should decrease the mechanical coupling between OHC and its cilia, resulting in decreased mechanical coupling between the tectorial membrane and OHC with the consequences as described above. Slow mobility of OHC will decrease[191,296], reducing the influence of feedback control extended by the efferent system on OHC-controlled micromechanical properties of the basilar membrane, which in turn might prevent active compensation for local damage of hair cell systems. The OHC membrane permeability to ions and low molecular weight molecules will increase, resulting in changes of OHC volume and turgor[20]. Spontaneous activity of the VIII nerve will increase while auditory evoked activity will decrease[45,46,242]. All those effects are proceeding in one direction - increase of the noise within the system and parallel decrease of signal-evoked activity. This will result in deterioration of the signal-to-noise ratio, which would facilitate the appearance of tinnitus. Additionally, this should reduce recognition of sounds, particularly in noise and as complex as speech.

The calcium level influence might be of interest from a clinical perspective, since abnormal increase of spontaneous activity and its increased regularity might be responsible for some types of tinnitus. Therefore by increasing the cochlear calcium level, it should be possible to suppress or eliminate tinnitus, with the further possibility of enhancing evoked activity. Thus, it might be possible to alleviate tinnitus without compromising hearing.

2.5 Calcium channels

Transmitter release, as well as slow motile properties of OHC, depend on intracellular calcium level[37,79,139]. Although extracellular calcium will influence intracellular calcium concentration, the crucial role is played by functional characteristics of the calcium channels[76]. Since calcium influx is an intermediate step in transmitter release from hair cells, and since certain types of tinnitus might result from increased spontaneous activity, it is possible to expect that by inhibiting calcium influx into hair cells, it should be possible to attenuate some cases of tinnitus originating in the cochlea.

Another possibility relates to the postulate that calcium-dependent slow movement of

OHC might be involved in adjusting basilar membrane position 1[147,148,295,296]. Therefore by affecting the function of OHC calcium channels, it is possible to expect changes of the basilar membrane position as a result of calcium channel modulator action.

This hypothesis has found preliminary confirmation in our data, where it was shown at the behavioral level that a calcium channel blocker, nimodipine (BAY e 9736), abolished salicylate-induced tinnitus in animals[111,112,116]. Nimodipine acts on L-type channels, prolonging the inactive state of the channel[96]. This substance has the interesting ability to pass through the blood-brain barrier much better than any other known calcium channel antagonist[129,239]. Possible applications for this drug focus on the described increase of the brain blood flow by nimodipine, thus suggesting its use in cases of subarachnoid hemorrhage[3,25,239] and ischemia[128,250,511].

Recently accumulated data indicate the possibility of nimodipine's interaction with CNS in a direct manner[239]. Our data, recording the characteristics of cochlear potentials from the intact cochlea[111,112] and from cochleas perfused with artificial perilymph containing different doses of nimodipine[12,13], clearly demonstrated that nimodipine exerts its action directly on the cochlea and hair cells without changing cochlear blood flow. Additionally, our data indicate that the action of the drug occurs at least at two levels, perhaps affecting slow motile processes within the OHC system and has an impact on the processes involved in transmitter release. Furthermore, another calcium channel blocker, MK-600, while in large doses has been shown to inhibit both spontaneous and evoked activity, in lower concentrations this substance suppressed spontaneous activity without affecting evoked activity [80] . Clinical data, although preliminary at this moment, support the possibility of suppression of tinnitus by nimodipine[255].

2.6 Aging, calcium and L-type calcium channels

The hypothesis relating calcium with dysfunctions of the auditory and vestibular systems has several implications. Since many of the mechanisms discussed for cochlear hair cells should exist for vestibular hair cells, one might expect similarity in mechanisms underlying normal function and malfunction between both systems. For instance, it is possible that disorders resulting in aberrant calcium levels in CSF and perilymph might increase susceptibility of both the auditory and vestibular systems to malfunction. In addition, it might explain the tendency of the elderly toward tinnitus and vestibular disorders. This postulate is based on the following observations.

It has been proposed that altered calcium homeostasis is involved in the process of aging, with modified calcium permeation across membranes a common change [21,42,71,123,143-146,206]. Available data imply that general calcium metabolism is disturbed in the elderly[149].

Salicylates, well known for increasing the threshold of hearing and inducing tinnitus in humans[61,169], cause decreased calcium levels in serum and CSF[118,120,126,127,222,267]. A report published recently on salicylate toxicity in people of various ages showed that the elderly are more susceptible to the effects of this drug, and that smaller doses per kg of body weight are sufficient to induce tinnitus[76], in spite of essentially unchanged salicylate uptake and plasma clearance in humans[183]. We reported that calcium levels decreased in serum, CSF and perilymph after salicylate[118,120]. Our data show that this decrease is highly non-linear as a function of dose and salicylate serum levels[118]. The threshold level of salicylate-induced calcium decrease corresponds to the reported level that evokes tinnitus in humans[61]. The threshold of calcium decrease is related to the animal's age, with a lower value observed in older animals (Jastreboff, in preparation).

Auditory system dysfunction in the elderly and the high frequency of tinnitus occur-

rence, affecting about 1/3 of the population above 65 years of age, has a profound effect on their life[81,223,231]. Although there are reports describing anatomical and physiological changes in animals' hearing[23,102,142,280-283], nevertheless, no theory has been presented as yet to explain why the elderly have such a high incidence of tinnitus and vestibular disorders, except to associate it with age-related noise or drug-induced cumulative hearing loss.

I postulate that disturbances in calcium metabolism and dysfunction of L-type calcium channels reported for the elderly and aging tissues[4,21,44,106,143-146,206,291] might affect cochlear function, increasing the spontaneous activity of auditory nerve fibers among other things. This might enhance changes in the auditory system due to other minor pathologies which would otherwise be subthreshold in terms of tinnitus perception. Additionally, it might enhance the severity of tinnitus already existing due to other mechanisms. The observation describing a correlation of senile hearing loss to decreased serum calcium level and disturbed calcium metabolism further support this postulate[291].

A similar effect could exist in the vestibular system where calcium ions play an important role[32-34,50,101,227,252,269], and their imbalance has been implied as being responsible for Meniere's disease and other vestibular disorder[172-174,188]. Alternatively, it has been proposed that Meniere's disease and associated tinnitus results from potassium poisoning of cochlear hair cells, due to the flow of potassium-rich endolymph to perilymph through rupture of the scala media caused by endolymphatic hydrop[138,236,293]. Nevertheless, this does not exclude the facilitatory influence of calcium imbalance, with potassium poisoning being the final step.

The loss of calcium homeostasis could also facilitate the increase of vestibular disorders seen in the elderly. Interestingly, melanocytes have been reported to act as a calcium buffer[172,173,185], and the relationship between pigmentation and susceptibility to auditory and vestibular disorders (higher pigmentation - higher resistance)[28,29] further support the possibility of calcium involvement. Relevance of melanin for pharmacological treatment of tinnitus has been proposed as well[164].

Continuing this theme, calcium channel modulators should play an important role in the function of the vestibular and auditory systems and might be useful in alleviating their disorders. The process of aging has been related to increased calcium influx into ce11s[123]. The calcium L-type channel antagonist, nimodipine, was reported to be effective in improving the performance of old animals in behavioral tasks[42], in hippocampal long-term potentiation[21,145], and in preventing deterioration of the vestibular and motor systems[73,237,239,270]. Nimodipine crosses the blood-brain barrier better than any other calcium channel antagonist, therefore therapeutic levels in CSF can be reached without toxic side-effects[129,239]. Our data support this therapeutic possibility[111,112].

Thus, it is proposed that calcium channel modulators might be effective in preventing age-related deterioration of the auditory system in a manner similar to that described for vestibular and motor systems[237,239]. Although more work is needed to prove this hypothesis, it provides a testable hypothesis for the mechanism of aging of the vestibular and auditory systems. Additionally, it proposes a new approach for treatment of auditory and vestibular disorders, indicating a possible etiology for disorders associated with aging in these systems and a strategy to alleviate or slow down some age-related processes.

2.7 Synaptic transmission

Another cause of cochlear tinnitus can be related to increased synaptic transmission between the IHC system and the VIII nerve. This might result from several factors, such as: (i) increased spontaneous release of a transmitter substance from the IHC, thus

increased spontaneous activity within the auditory nerve; (ii) increased sound-evoked release of this transmitter; (iii) increased effectiveness of the transmitter on the postsynaptic membrane; (iv) decreased inhibition caused by the efferent system.

The first two possibilities are related to a dysfunction within the hair cells. It is possible to envision several mechanisms which might, in turn, enhance spontaneous release of the transmitter. Perhaps the simplest mechanism involves the effect of modulation of calcium concentration as discussed previously. Modification of calcium concentration within the hair cells depends on its concentration in the perilymph[124] and in the kinetic properties of calcium channels. Alteration in calcium concentration within the perilymph indicates only the possibility of changes within the hair cells, while modification of the calcium channel should have a direct impact on the intracellular calcium level. Thus, one may speculate that increased calcium influx into the hair cells through dysfunctioning calcium channels should result in increased spontaneous release of transmitter, causing increased spontaneous activity within the VIII nerve. The observation that calcium decrease has an opposite effect on spontaneous and evoked activity [45,46,242] suggests the possibility of separate mechanisms governing evoked versus spontaneous transmitter release.

Modification in transduction parameters resulting in increased transmitter release from the same mechanical stimuli (displacement of the cilia) might be related to higher sensitivity of calcium-controlled potassium channels involved in the first stage of transduction, or in increased sensitivity of calcium channels involved in the second stage of transduction.

The third possibility involves increased sensitivity of the postsynaptic site. Tonic partial depolarization of the postsynaptic membrane, or decreased activity of a catabolic enzyme digesting a neurotransmitter, which will result in accumulation of the neurotransmitter and its prolonged action on the receptor, might produce such a effect. This can be tested and discussed in more detail once the afferent neurotransmitter and its catabolic enzymes in the cochlea are positively determined[1,10,11,47,58,79,122,139,187,214,242]. However, it might be predicted that dysfunction of this kind should be reflected in elevated characteristics of CAP as compared to CM, particularly for close-to-threshold stimuli. A faster saturation of CAP as compared to the control situation can be envisaged. At the clinical level, patients with decreased loudness discomfort level might belong to this category, together with patients with decreased efferent inhibition, which is described below.

The fourth category concems the decreased efferent inhibition of the afferent fibers coming from IHC. Again, this should result in relatively larger afferent excitation after the same amount of neurotransmitter is released. Possible effects resulting from dysfunction of the interaction of efferent fibers with the OHC system are discussed separately. It should be stressed that in addition to general disinhibition involving all IHC or OHC, tinnitus might result from even relatively small changes occurring only in a limited (frequency-specific) portion of the efferent system, which might be further enhanced by the 'edge effect', as discussed below.

2.8 Edge effect

In the visual system, the enhancement of contrast in the transition between patterns of different density has been documented[245]. There is consensus that the major factor responsible for this phenomenon is lateral inhibition, and that the edge effect exists for modalities other than vision[78]. It has been postulated that a decrease of activity in only a subpopulation of neurons, further enhanced by lateral inhibition, could be responsible for tinnitus[137,226]. Observation of local decrease in the activity of some auditory nerve fibers

after cochlear damage was used to support this postulate. Furthermore, it has been indicated that tinnitus patients frequently report the pitch of tinnitus as corresponding roughly to the transition point from normal hearing to that of an adjacent frequency of elevated threshold.

This hypothesis can be extended further by saying that any localized change in cochlear function or VIII nerve activity might result in tinnitus, since a lateral inhibition-based edge effect will act on both a decrease and an increase in activity. This local change might result from mechanical damage, e.g. noise-induced or age-related effects. The point is that due to the edge effect, either an increase or decrease of local neuronal activity, presenting even small variations along the cochlea's partition, may have a great impact after being enhanced by edge effect.

This should be true for both modified spontaneous or evoked activity, synchronization of that activity, or abnormal temporal patterns of discharges, as long as the change is localized. In other words, if the activity of abnormal hair cells, VIII nerve fibers, or cluster of neurons within a nucleus shows an abnormal pattern of activity with a clear border from normally functioning units, one might expect that this difference will be further enhanced by an edge effect. Although physical closeness is easiest to imagine, it can be postulated that functional interrelation might act in the same way. If cells which are even physically distant but which project to the same part of a higher center (the same group of neurons), or are part of a neuronal network performing a specific function, exhibit an abnormal type of activity, then edge effects could occur. This will be further discussed in Section 3.

2.9 Efferent system

Efferent innervation exerts a clear effect on the OHC system [152,247,276], IHC afferents[71,72,277,278,289], otoacoustic emission[186,189], and on cochlear evoked potentials[71]. Hazell suggested a mechanism of tinnitus generation which involves control of active processes in the cochlea by the efferent system[88]. The cochlear efferent system affects both classes of afferent fibers coming from IHC and OHC. The OHC play a crucial role in sharpening the tuning of the basilar membrane through active mechanical processes and results in negative dampening of the basilar membrane[147]. The possibility that an overreaction of this active system might yield tinnitus has already been proposed[87,88,132,200,286-288].

Motile activity may occur in a cycle-by-cycle manner controlled by stress-activated ion channels acting in phase with basilar membrane displacement. The efferent system may act in a tonic manner, adjusting the working point (e.g. the initial tension exerted by the OHC) as proposed by Lepage[47]. The efferent system is, in turn, under the control of feedback from auditory information provided by the afferents exhibiting a high degree of frequency selectivity, frequently having equally low threshold of response and equally sharp tuning as afferent fibers[18]. When damage of a group of outer and/or inner hair cells occurs, there is decreased auditory information from this region. This might result in a localized reduced efferent discharge rate. Since efferent innervation is diffuse[18,19,151,153], the ensuing disinhibition would affect normal undamaged hair cells adjacent to the damaged area, resulting in increase of negative overdampening[88]. These, in turn, will yield enhancement of the ambient or thermal noise of the system at a frequency corresponding to the position of the border of the damaged area on the basilar membrane. The effect may be further enhanced by higher centers, the overall result being the perception of tinnitus.

At the experimental level, it should be possible to detect increased noise in both the

CM and CAP, as well as non-linearity of the CM and psychological perception for tones very close to the frequency(ies) of tinnitus. To detect this phenomenon, it would be necessary to measure these potentials for close-to-threshold perception in very small frequency increments. An increased response and a decreased threshold would indicate the presence of a section of basilar membrane with negative overdampening. Interestingly, decreased threshold of hearing for frequencies close to tinnitus has been reported[266].

The clinical prediction is that this type of tinnitus would be very difficult to mask using external auditory signals because negative overdampening would result in decreased discomfort levels and increased perception of the external signal with a pitch close to that of tinnitus. Total auditory masking of tinnitus, defined as total suppression of tinnitus perception by external sound, should occur on the basis of two-tone inhibjtion, therefore for tones being some distance from the perceived pitch of tinnitus. Masking frequencies close to the tinnitus pitch should be effective only at relatively higher levels, if at all.

2.10 Cross-talk between hair cells or VIII nerve fibers

Most views on the origin of tinnitus are based on the assumption that the location of active neurons, as well as the mean activity of their discharges, are the principal determinants of auditory processing. Alternatively, Moller[177] postulated that tinnitus is based on the occurrence of 'cross-talk' between demyelinated auditory nerve fibers or hair cells where there was breakdown of electrical insulation between them. Such a loss of insulation could occur following acoustic neuroma, vascular compression syndrome, and other retrocochlear pathologies [108,109,178-181]. This could result in increased phase correlation of the spontaneous activity of different fibers, which ultimately become phase-locked with each other, leading to abnormal pulse generation.

2.11 Analogy with pain

Recently, Tonndorf proposed a mechanism of tinnitus based on an analogy with pain perception[262]. According to this theory, tinnitus results from an imbalance between the activity of large fibers innervating IHC and small OHC fibers, caused by partial damage of one or both of the systems. This model was further extended to imitate Melzack's Gate Control Theory of pain, arguing the similarity of IHC fibers to somatosensory, large-diameter fibers and OHC fibers to small-diameter, pain-related fibers. It remains to be shown that the interaction mediated by the fibers' innervation of OHC and IHC occurs in the manner of presynaptic inhibition, as required in Melzack's and this model.

The relationship of changes between cochlear dysfunction and tinnitus outlined above represents only an example of possible scenarios. Practically any local modification of cochlear transduction properties might produce tinnitus due to a contrast enhancement between altered and normal areas which might be amplified by further central processing within the nervous system, as discussed below.

2.12 Hyperactivity within the auditory pathways

It is generally agreed that the CNS compensates for a decreased information input in any modality by increasing the sensitivity of centers involved in perception. The action of the CNS is oriented to homeostasis, with excitatory and inhibitory influences interacting at all levels, thus increasing its flexibility and control and providing fine balance, as well as adaptation and habituation. Total absence of input disturbs such a balance and might result in abnormal activity of centers involved in the processing of this information. I am proposing a hypothesis that even for tinnitus originating in the cochlea, processing of tinnitus-related information within the auditory pathways is of crucial significance, rather than assigning to those pathways a role that is one of purely passive transmission.

Gerken and co-workers reported that after sound-induced hearing loss, sensitivity of the cochlear nuclei and inferior colliculi neurons to electrical stimulation increased and recruitment emerged[14,66-69]. This observation was strengthened further by Sasaki et al[229,230], who reported a relative increase of 2-deoxy glucose uptake into cochlear nuclei and inferior colliculi after damage of the cochlea and auditory nerve starting a few days after the surgery. Salvi and Ahroon[226] presented results similar to those of Gerken and co-workers, while increased neural excitability in inferior colliculus related to noise-induced hearing loss has been reported by Willott and Lu[284]

The mechanism of this phenomenon is unknown. One may speculate that decreased input from the periphery causes contraction from the neuronal assembly involved in automatic gain control within the auditory nervous system causes plastic, long-lasting changes in synaptic weight. These finally result in increased sensitivity of those nuclei to any input, including spontaneous activity which, in turn, might yield the perception of tinnitus. Another explanation is presented in Section 3.

It is possible to induce tinnitus in some people by attenuation of an external acoustic signal and to decrease it by enhancing the auditory input (e.g. by hearing aids)[94,169]. This might be partially explained by peripheral auditory masking provided by amplified environmental sounds, but the fact remains that for many patients this effect is not instantaneous and might take days[93], indicating the need to consider plastic changes in the CNS. From this point of view, the surprising and unexplained clinical phenomenon is that of total deafness with no tinnitus whatsoever.

All tinnitus, whether generated peripherally or centrally, finally results in abnormal cortical activity, as this is where it is perceived. However, cortical tinnitus occurs in the absence of an abnormal subcortical input. At the present moment, the only certain model of tinnitus other than the cochlear type is where both acoustic nerves have been sectioned. This is obviously not a proper model of cortical tinnitus, since such an operation will result in increased subcortical sensitivity, as discussed previously.

Theoretically, it is possible to envision significant differences between the hyperactivity occurring at the cortical level as compared with that in the more peripheral pathways. One might expect very complex, hallucinatory-like perceptions of tinnitus, which may be then categorized as auditory hallucinations. Involvement of other cortical areas becomes more likely (hypersensitivity to light or tactile stimuli may be evident)[90].

Summarizing possible mechanisms of tinnitus generation, it is hypothesized that changes in cochlear micromechanics, and more generally in dysfunctions within the cochlea, could produce tinnitus through several intermediate steps. Of particular importance might be extra- and intracellular calcium levels. Dysfunctions of the efferent system and active processes occurring in the cochlea could be another important cause of tinnitus. Tinnitus might result from abnormal hyperactivity of the higher levels of the auditory pathways, including the auditory cortex. I realize that it is possible to propose a wide variety of detailed hypotheses based on micromechanical, biochemical or even molecular abnormalities, but rather the intent was to outline classes of possible tinnitus generators.

3.1 DETECTION OF TINNITUS-RELATED ACTIVITY

3.1 Unusual psychoacoustical features of tinnitus

Perception of tinnitus exhibits a number of features which are quite different from the perception of external sound of similar intensity and frequency spectrum. Contrary to masking of external sounds, tinnitus can be masked by pure tones or band-pass noise of a

wide range of frequencies, often contralaterally with the same effectiveness and with intensity of masker, frequently abnormally great or small as compared to the signal-to-noise ratios required by external signals and maskers[55,94,169,192,195,197,198,203,204,265,272]. Indeed, masking of tinnitus resembles central masking of external sounds. Contrary to masking external sounds, tinnitus requires increased intensity of masker over a period of minutes[193,197,198,265], while external sound does not require this increase. Sometimes it is impossible to mask tinnitus, disregarding intensity of external sound[273]. Furthermore, it is impossible to create beats by interference of tinnitus with external tone, and tinnitus does not exhibit phase-related phenomena[169]. Cessation of masker is frequently followed by a period of residual inhibition when tinnitus disappears or is reduced in magnitude [27,169,199,203,273]. Additionally, tinnitus does not habituate even when its perceived loudness is weak.

3.2 Abnormality of tinnitus-related patterns

These observations suggest that the representation of tinnitus within the auditory pathway may be different from the representation of external sounds. I hypothesize that, in the majority of cases, tinnitus results from the perception of abnormal activity within the auditory pathways which cannot be evoked by any combination of external sounds. Additionally, I propose that detection of the tinnitus signal occurs in a pattern-detection manner by neuronal assemblies, and that this detection process undergoes plastic changes. In the remaining part of this section, I will attempt to show how those two postulates can untangle otherwise unexplained puzzles of tinnitus.

The simplest situation with abnormal activity occurs in the condition when neighboring fibers fire in synchrony[77]. Under normal conditions, it is possible to partially synchronize a group of fibers by low-frequency tones (each fiber will fire with higher probability within a given phase range), but the phase will be different for each fiber. Even then, this synchronization will not include physically close fibers, since even fibers innervating the same IHC exhibit different thresholds of activation and different phase relations in reference to an external tone. Since tonotopic organization is preserved at each level of the auditory system, physically close fibers will also be close in characteristic frequency and should project in a like manner to higher-order neurons. Synchronized, even weak activity will evoke much higher excitation of the goal cells than stronger but diffused tone-induced activity. Such synchronized activity might be much more difficult to attenuate because of its unusual pattern. Any other abnormal temporal and/or spatial patterns of activity within the auditory system might induce disproportionally strong excitation of higher-order neurons. Lateral inhibition and pattern-enhancing features of neuronal assemblies could produce further enhancement.

Although there is only very limited information available on neuronal activity which might be related to tinnitus, nevertheless these data are in agreement with the proposed hypothesis of abnormal patterns of discharges[53,54,121,226]. Moreover, an analysis of tinnitus-related abnormal patterns of activity should provide interesting information for work on auditory prostheses, when electrical stimulation of the auditory nerve (cochlear implants) or cochlear nuclei complex, which results in abnormal patterns of excitation, is used to induce perception of sound in a deaf ear.

3.3 Deciphering tinnitus puzzles

Initially, a totally new tinnitus-related signal has to be classified and categorized. This stage might follow the process of self-organization of recognition categories[22] in a manner described for a self-organizing recognition system able to build codes for speech signals, as proposed by Grossberg[78]. This theory incorporates adaptivity of the networks involved,

development of codes for new input patterns with stress on the necessity of attentional and orienting subsystems to process familiar and unfamiliar events, code stabilization with its involvement in suppression of noise in input patterns, postulate rescaling of noise criterion to each pattern context, and stresses the importance of two-way interaction of the subsystems involved[22,78]. The detailed description of this interesting mathematical theory is beyond the scope of this paper. Only implications for tinnitus recognition and perception theory are incorporated in this text.

3.3.1 Detection After crossing the threshold of pattern detection, tinnitus-related weak signals, immersed in the noise of spontaneous activity, are processed by neural assemblies. The initial newness and persistence of the signal, combined with the alarm that tinnitus usually generates, enhances the recognition of this particular pattern and induces plastic modification of adaptive filters. This assures that future appearance of this particular pattern, even if contaminated by noise, will be recognized. The process requires some period of time and repetition of the initial signal, but unfortunately for patients, tinnitus is persistent and the initial anxiety induced by its presence very strong, reinforcing tuning of the system to the tinnitus signal and effectively improving detection of tinnitus. *

The initial process of recognition involves crossing a detection threshold of a relatively weak tinnitus-related signal and separating it from spontaneous activity. The threshold--crossing phenomenon might contribute to the very rapid onset of tinnitus reported by patients. Typically, patients describe the onset of tinnitus as a rapid phenomenon, appearing in full strength from the very beginning. Due to the abnormal pattern of this activity, it might be much more difficult to suppress (or habituate to) than to external sounds. Furthermore, if tinnitus detection is carried on by neuronal assemblies in a manner related to neuronal networks or a holographic neuronal network[22,62,78,160,208,209,240,275], even incomplete or weaker patterns similar to the original one will evoke nearly the same perception.

This hypothesis might explain the persistence of tinnitus perception even when a peripheral generator produces a transitory, fluctuating or intermittent signal. The remaining weaker signal is still sufficient to induce detection in a network which has been 'tuned' to the tinnitus pattem by creating a recognition category for tinnitus-related activity[22,78.]

Moreover, if the tinnitus-related pattern, as I postulate, cannot be imitated by any combination of external sounds, its masking, attenuation and habituation should be quite different from that of external applied sounds. As has been pointed out, the simplest example of such an abnormal pattern will result from electrical stimulation of the cochlea. Reports of patients with unilateral deafness who have undergone electrical stimulation of the deaf ear support the proposed hypothesis of abnormality of tinnitus-related activity.

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* This process can be illustrated by the observation of a person exposed to a totally new language. Initially, it is impossible to detect any words or even familiar sounds, and the language sounds like a strange noise or melody. After the initial learning stage has been accomplished, suddenly it is possible to divide phrases into fragments and recognize familiar repetitive patterns, even without the slightest understanding of the meaning of the phrases. This stage represents the transition from treating new sound patterns as a non-specific noise, to pattern recognition of crucial features of the language. Once this is achieved, it is usually never lost. A new pattern of excitation within the nervous system, if weak, is treated as part of the noise of spontaneous activity and ignored. When the signal is stronger or more persistent (even though still weak), it is detected as a new significant pattern, and attenuation of its perception becomes difficult, e.g. it requires strong masking by an external noise source.

The same problems encountered in reconstructing the sound of tinnitus with the use of a music synthesizer appeared when trying to imitate electrical stimulation-evoked perception by providing the hearing ear with a wide variety of synthesized sounds. Even for simple, sinusoidal electrical stimulation, perceived sound is complex and practically impossible to imitate[90] . The psychoacoustical data obtained in evaluation of patients with cochlear implants show that even with most advanced multichannel implants, and with elaborated sound processors, the quality of the perceived sound is poor, with a small dynamic range and very limited frequency and intensity discriminations[30,92,207]. In only 5% of the cases is speech recognition without lip reading possible, and an appreciable number of patients with implants (2-15%) choose to discontinue the use of their prostheses[30]. These observations are in agreement with data from single fiber recordings from the auditory nerve, with electrical stimulation of the cochlea showing abnormal histograms of activity and compressed, steep rate-intensity functions[14,207,246]. Furthermore, when contralateral acoustical masking of electrically evoked sensation was evaluated, typical flat characteristics of tinnitus masking were obtained[90].

I would like to stress that as tinnitus results from a variety of causes, there is a continuum of tinnitus-related activity from such causes, which can be closely imitated by external sounds to activity which cannot be induced by any combination of external sounds. Depending upon the extent of abnormality, it should be easier or more difficult to mask or otherwise lessen tinnitus. I postulate that tinnitus resulting from only slightly abnormal activity will have undergone habituation, as external signals do. Therefore in practice, cases are seen of tinnitus resulting from significantly abnormal activity.

3.3.2 Masking One of the puzzles of tinnitus is the observation that in different patients reporting tinnitus of the same loudness and pitch, sometimes it was necessary to use much higher levels of external noise to mask the tinnitus than would be expected from the psychoacoustical masking level of a comparable external tone: in others, for practically the same sensation of tinnitus, a very low level of external noise is sufficient to suppress the perception of tinnitus completely [55,94,193,197-199,203,264,265,273]. This phenomenon can be explained by proposing that, in the first case, tinnitus results from neuronal activity which is highly different from any activity induced by sound, while in the second case, tinnitus-related activity is close to patterns of activity induced by sound. Therefore, it is possible to retune the neuronal assembly detecting tinnitus by increasing the system noise, thus retuning the neural assembly away from a tinnitus pattern. This phenomenon cannot be explained by peripheral masking of tinnitus. The problems involved with masking will be discussed in detail elsewhere (Jastreboff and Hazell, in preparation).

3.3.3 Residual inhibition Recognition of patterns of variable complexity in noise[22] and plasticity scheme may also explain a phenomenon known as 'residual inhibition'[26,27,55,94,198,199,203,272,273] e.g. total disappearance of tinnitus perception (commonly for seconds, minutes, hours, or occasionally days) after masking by external sounds, yet another mystery of tinnitus. When tinnitus results from relatively normal neuronal activity, detection of even relatively loud tinnitus may occur at the border of the 'detection space' in a metastable, adaptive network. Hence when the equilibrium of the network is disturbed by increasing the level of additional external noise (the prerequisite for residual inhibition to occur), the system switches to another metastable state in which the same tinnitus signal is below the threshold of detection. After switching off external noise, this metastate can be sustained for some period of time, up to the moment when the system switches back to its previous preferred state, with resultant tinnitus detection. Residual inhibition is the time needed to restore equilibrium. Repetitive masking might

cause gradual shifting in the tuning of the neuronal assembly, resulting in prolonged periods of residual inhibition, in some cases suppressing the detection of tinnitus totally.

3.3.4 Distributed involvement of entire auditory system I would like to stress that the process of recognition and classification of an activity within the auditory pathways might play a very significant role in the process of tinnitus generation and in the reported increased excitability of auditory pathways in a situation of abnormally low input from the periphery [14,66-69,161,229,230,284]. The same principles of adaptive filtering and of distinguishing signal from noise by neuronal networks[22] should apply. An imbalance in the activity, intensified by lateral inhibition and contrast-enhancement schemes, might result in abnormally amplified activity in the auditory pathways. Dysfunction of neuronal networks involved in pattern recognition and classification, including, for example, abnormally high feedback from attentional and orienting subsystems[22], might aberrantly enhance an otherwise ignored anomaly in neuronal activity, yielding tinnitus perception. This points out that classification of tinnitus as peripheral, cochlear and central is superficial and is not advisable, since even if the initial cause of tinnitus can be traced to the cochlea, neuronal processing can be dominant. Therefore, the same cochlear damage in different humans might or might not produce tinnitus.

One implication from this model is that although tinnitus may appear very rapidly, its disappearance (at least for periods in excess of a few hours or days) is much more difficult to achieve and may require longer periods of time for treatment to be effective. Another aspect, discussed in the next section, is the importance of emotional factors and attitudes toward tinnitus for final tinnitus evaluation.

4. PERCEPTION OF TINNITUS

Up to this point, the possible mechanisms of tinnitus generation and the detection of tinnitus-related abnormal patterns of activity within the auditory pathways have been discussed. From both theoretical and clinical points of view, the next step - tinnitus perception - is of importance. Tinnitus has been described as generated in the cochlea, undergoing pattern recognition within the auditory pathway, and becoming reinforced by processing within subcortical centers. The next step is perception, psychological evaluation, and classification of this pattern.

4.1 Previous experience and emotional state

Presumably, associative cortical areas are involved in this process, relating the perceived pattern to previous experience and to biological significance of a signal. The interpretation of an auditory pattern has a profound impact on the reaction it invokes and on the threshold of its detection and recognition during repetitive presentation. The cry of a baby can be perceived as insignificant and easily ignored by a stranger, while for the baby's mother, this auditory signal can be very powerful and wake her from sleep. In this example, contrasting this effect to the same sound depends on the relation of a sound to the history of its evaluation.

Recognition strategies involve different processing of various signals resulting in their preferential recognition. The cortical evaluation of a signal involves its association with patterns stored in auditory memory. Any such pattern can be and often is related to some emotional state. Tinnitus may recall the sound of traffic, aircraft or central heating -most patients actually start with a search for a source of real sound[90]. Signals perceived within any sensory system can be related to signals in different systems. Perception of those signals which evoke strong emotional states (positive or negative), as being of

particular importance and increasing attention to this particular signal, will be preferentially enhanced[22].

Depending on associations with an emotional state, the same pattern of neuronal activity initiating tinnitus at the periphery might be perceived quite differently in various individuals, or in the same person in different situations[9091]. * This brings to mind the importance of evaluating tinnitus in relation to other patterns in memory and their emotional associations. Initially, tinnitus is predominantly associated by sufferers with something unpleasant, dangerous, or anxiety-provoking[90,169]. This negative image of tinnitus strongly enhances the attention placed on it which, in turn, enhances the detection and perception of the particular tinnitus-related pattern. Through positive feedback involving short- and long-term memory[22,78], the pattern recognition mechanism is further intensified, making discrimination of this particular pattern from spontaneous and external sound-evoked activities all the easier. Thus even weak, only partially preserved patterns can be recognized as tinnitus due to previous network training.

Intuitively, it appears that the louder the perceived tinnitus is, the higher the level of annoyance it should induce. In reality, the situation is more complex. First of all, there is the problem of how to evaluate tinnitus loudness. Fowler introduced the comparison of tinnitus to contralateral sound of frequency matching pitch of tinnitus and concluded that in the majority of cases, tinnitus has very low loudness, below 10 dB sensation level[27,94,196,266]. Others argue that this approach is misleading and that, rather, scales corresponding to subjective loudness perception, taking into account the recruitment phenomenon, should be use[194-196,218,264,266]. Even with this approach, correlation of annoyance and loudness exhibits abnormalities[266]. The patient's data show rather large within-session and between-session variability and indicate that factors other than loudness contribute to perceived tinnitus annoyance. Therefore, association of the perceived sound of tinnitus with a patient's history and emotional state might play an important role. From this perspective, the possible involvement of the prefrontal cortex is of importance.

4.2 Prefrontal cortex

The prefrontal cortex has been proposed as being unique among cortical areas in its relationship with interoceptive, as well as exteroceptive, sensory domains and, therefore, the foremost structure that could synthesize the inner and outer sensory worlds[74]. Studies performed since the middle of the eighteenth century have established an anatomical basis for common beliefs: that the prefrontal cortex stands at the 'common endpoint' for diverse afferent channels and is 'privy' to all incoming information[74,75]. This attribute of the prefrontal cortex makes it a candidate for the integration of sensory and emotional aspects of tinnitus postulated above.

* A clinical example is seen in one patient with a pronounced social conscience for whom the hissing sound of tinnitus was in itself not particularly loud or troublesome, but evoked very strong images of prisoners being tortured with continuous noise[90] . Another patient with a very similar type of tinnitus found it particularly intrusive during the day, affecting concentration markedly. Paradoxically, although before the appearance of tinnitus this patient had had a problem with sleeping, at night his sleep actually improved, as it evoked memories of a happy carefree childhood and of the water cistern which had often produced a loud hissing noise in his attic bedroom as he drifted off to sleep![91]

This last example is of particular interest because it indicates that the same tinnitus pattern can induce different associations in the same person when combined with other stimuli, resulting in an opposite effect of tinnitus on the patient's life. Additional complementary signals (presumably darkness, the time of day, and other factors associated with going to sleep), together with the patient's previous experience, were necessary to change the evaluation and assignment of the same perceived signal.

In the 1950s, a lobotomy operation was performed on 20 patients exclusively because of tinnitus[9]. One might expect that disconnecting the prefrontal cortex should result in disassociation of sensory and emotional aspects of tinnitus, and similarly to its effect on pain perception, and should cause a decreased level of annoyance produced by tinnitus. The data not only confirmed this obvious prediction (all 19 patients who survived reported decreased annoyance of tinnitus) but out of those, 8 patients reported a decrease in the perceived loudness of tinnitus as well. The remaining 11 patients reported tinnitus to be the same but that it was not bothering them to the previous extent, and none reported increase in tinnitus loudness.

This result shows that disconnecting the prefrontal cortex from the system evaluating tinnitus actually interfered with the process of psychophysical tinnitus estimation or with its generation. Perhaps the simplest explanation is that lobotomy removed the emotional reinforcement of tinnitus pattern detection, removed the attentional and orienting subsystems from networks involved in the recognition of tinnitus-related activity, thus facilitating partial habituation of its signal.

Another possible mechanism of involvement of the prefrontal cortex is related to the observation that it is necessary to sustain a reaction[75]. Considering the possibility of similar interaction of the prefrontal cortex with reactions of the autonomic system as with the motor system, decreased activity of the prefrontal cortex might result in decreased autonomic responses to tinnitus, whereas enhanced activity of the prefrontal cortex might produce continuous enhanced anxiety, which through a positive feedback loop might further tune the nervous system into perception of tinnitus, as discussed previously.

4.3 Parallel systems approach

The traditional hierarchical model of cortical organization postulates a stepwise hierarchical sequence, proceeding from relatively raw sensory input at the primary sensory cortices through several stages of processing, to polymodal zones for cross-modal interchange of information, to paralimbic and limbic areas for investment with emotional tone, and to the frontal association area where both sensory and limbic data are integrated[74]. According to the classical model, the flow of information is mainly unidirectional, from the sensory through the associative and motor centers. Recently, Goldman-Rakic emphasized a different aspect, focusing on the functions distributed between several parallel, interconnected systems [74]. She outlined the brain as a 'highly integrated but distributed machine whose resources are allocated to several basic parallel functional systems that bridge all major subdivisions of the cerebrum[74] and further stated: 'it may in the future be more useful to study the cortex in terms of information processing functions and systems rather than traditional but artificially segregated sensory, motor, or limbic components and individual neurons within only one of these components.'

This parallel distributed network concept implies the possibility of the creation of loops enhancing or suppressing the perception of a given pattern in a much more flexible manner than allowed by the hierarchical organization model, and is in accordance with Grossberg's mathematical approach to neuronal pattern recognition and classification[22,78]. A distributed, highly interconnected network offers the possibility of creating loops which under the conditions of a continuous sensory signal (tinnitus), with significant emotional tone (concern, fear, inability to control it), further amplify the perception of tinnitus by creating positive feedback within the cortical networks.

4.4 Clinical 'masking'

On the other hand, the reason why masking and biofeedback or even a placebo are so effective in some patients is that even a partial (but sufficiently prolonged) change in the

emotional component may reorganize the functions of the distributed network, thus changing the psychological significance of the tinnitus. The loudness and pitch of tinnitus might remain the same, but the tinnitus is no longer so intrusive and can be 'ignored'.

Indeed, analysis of patients undergoing masking revealed that the psychoacoustical characteristics of tinnitus, such as its loudness or masking threshold, have not been changed either immediately after cessation of masker[199] nor after 6 months of its use[94]. These results support the postulate that so-called 'tinnitus maskers' are effective through facilitating re-evaluation of tinnitus and retraining of cortical networks, and are not actually altering psychoacoustical characteristics of tinnitus in the direction of its attenuation.

The above postulate has obvious theoretical and clinical significance. 'Masking' should be seen as retraining of the higher processing centers involving a gradual reorganization of the recognition of tinnitus, particularly its association with emotional state. As a result, the tinnitus becomes less threatening, and there are changes in the associations of tinnitus with positive emotional states. Another important clinical implication is that during 'tinnitus masking', one should not attempt to eliminate totally the perception of tinnitus, and that a certain amount of time, measured rather in weeks than in hours, is needed for the 'masker' to be effective. The best approach is to use the 'masker' as weak as possible, which only interferes with the perception of tinnitus and provides a patient with the feeling of the possibility of even temporal control of tinnitus, without inducing anxiety by too loud a sound of 'masker'. The additional justification for the partial masking approach is that since in the 'masking procedure' behavioral retraining of the association of a sensory signal (tinnitus) with a negative emotional state is actually performed, the basic requirement for such a procedure is the presence of stimulus undergoing retraining.

Hazell[90,91,94] showed that partial masking of tinnitus could be as effective as total or complete masking in reducing tinnitus-related complaints. It is hard to interpret this response in terms of a peripheral masking effect. It is much more likely that the masker, which in this case is simply introducing a competing signal, is facilitating retraining of tinnitus evaluation occurring at a higher cortical level. The psychological components related to the evaluation of tinnitus and the type of emotion it evokes are of particular importance, and procedures which affect this evaluation are likely to be effective in tinnitus alleviation.

5. CONCLUSIONS

Tinnitus is not a single, well-defined disease. It is a symptom of many pathologies - even in one patient, several different~types of tinnitus might coexist[83,201,202]. The approach to tinnitus presented above proposes a new view of mechanisms of its generation and perception and provides physiological interpretation of its features which have not been explained previously. Furthermore, this approach implies that tinnitus should not be simply categorized into peripheral and central, as is presently done, but that all levels are involved in each case to varying degrees, and all parts (generator, pattern recognition neural networks, and association circuits), are essential. However, dominance of a given level may exist.

Association cortices, the limbic system, and prefrontal cortex are involved in tinnitus perception and its classification and assignment of certain emotional states. Signal recognition and classification networks, which through plastic modification are able to change the recognition of a pattern of neuronal activity, are assumed to be involved in tinnitus perception. These assumptions may explain residual inhibition, rapid onset of

tinnitus but its much slower attenuation, effectiveness of contralateral masking and tinnitus masking by tones from a wide range of frequencies, its resistance to masking, and long-term effectiveness of masking tinnitus by sounds which do not 'cover' or mask it in the auditory sense.

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REFERENCES

1. Adams, J.C., Mroz, E.A. and Sewell, W.F., A possible neurotransmitter role for CGRP in a hair-cell sensory organ, *Brain Res.*, 419 (1987) 347-351.
2. Aitkin, L., Brain stem lesions and sound localization. In *The Auditory Midbrain: Structure and Function in the Central Auditory Pathway*, Humana Press, Clifton, N.J., 1986, pp. 24-30.
3. Allen, G.S., Ahn, H.S., Preziosi, T.J., Battye, R., Boone, S.C., Chou, S.N., Kelly, D.L., Weir, B.A., Crabbe, R.A., Lavik, P.J., Rosenbloom, S.B., Dorsey, F.C., Ingram, C.R., Mellits, D.E., Bertsch, L.A., Boisvert, D.P.J., Hundley, M.B., Johnson, R.K., Storm, J.A. and Transou, C.R., Cerebral arterial spasm - a controlled trial of nimodipine in patients with suarachnoid hemorrhage, *N.Engl.J.Med.*, 308 (1983) 619-624.
4. Ash, S.L. and Goldin, B.R., Effects of age and estrogen on renal vitamin D metabolism in the female rat, *Am.J.Clin.Nutr.*, 47 (1988) 694-699.
5. Ashmore, J.F., A fast motile response in guinea-pig outer hair cells: The cellular basis of the cochlear amplifier, *J.Physiol.*, 388 (1987) 323-347.
6. Ashmore, J.F., Effect of salicylate on a rapid charge movement in outer hair cells isolated from the guinea-pig cochlea, *J.Physiol.*, 412 (1989) 46P-46P. (Abstract)
7. Axelsson, A. and Ringdahl, A., Tinnitus - A study of its prevalence and characteristics, *Brit.J.Audiol.*, 23 (1989) 53-62.
8. Battmer, R.D., Heermann, R. and Laszig, R., Suppression of tinnitus by electric stimulation in cochlear implant patients, *HNO.*, 37 (1989) 148-152.
9. Beard, A.W., Results of leucotomy operations for tinnitus, *J.Psychosomat.Res.*, 9 (1965) 29-32.
10. Bledsoe, S.C., Jr., Bobbin, R.P. and Puel, J.-L., Neurotransmission in the inner ear. In A.F. Jahn and J.R. Santos-Sacchi (Eds.), *Physiology of the Ear*, Raven Press, New York, 1988, pp. 385-406.
11. Bobbin, R.P. and Ceasar, G., Kynurenic acid and gamma-D-glutamylaminomethylsulfonic acid suppress the compound action potential of the auditory nerve, *Hearing Res.*, 25 (1987) 77-81.
12. Bobbin, R.P., Jastreboff, P.J., Fallon, M. and Littman, T., Nimodipine, a calcium channel antagonist, reverses the summating potential, *Soc.Neurosci.*, 15 (1989) 210-210. (Abstract)
13. Bobbin, R.P., Jastreboff, P.J., Fallon, M. and Littman, T., Nimodipine, an L-channel calcium antagonist, abolishes the negative summating potential recorded from guinea pig cochlea, *Assoc.Res.Otolaryngol.*, (1990) (Abstract)
14. Bock, G.R., Horner, K. and Steel, K.P., Electrical stimulation of the auditory system in animals profoundly deaf from birth, *Acta Otolaryngol.(Stockh.)*, Suppl 421 (1985) 108-113.
15. Bohne, B.A. and Clark, W.W., Growth of hearing loss and cochlear lesion with increasing duration of noise exposure. In R.P. Hamernik, D. Henderson and R. Salvi (Eds.), *New Perspectives on Noise-induced Hearing Loss*, Raven Press, New York, 1982, pp. 283-302.
16. Bonfils, P., Spontaneous otoacoustic emissions: clinical interest, *Laryngoscope*, 99 (1989) 752-756.
17. Bonfis, P., Uziel, A. and Pujol, R., Evoked oto-acoustic emission from adults and infants: Clinical applications, *Acta Otolaryngol.*, 105 (1988) 445-449.
18. Brown, M.C., Morphology and response properties of single olivecochlear fibers in the guinea pig, *Hearing Res.*, 40 (1989) 93-110.
19. Brown, M.C., Liberman, M.C., Benson, T.E. and Ryugo, D.K., Brainstem branches from olivocochlear axons in cats and rodents, *J.Comp.Neurol.*, 278 (1988) 591-603.

20. Brownell, W.E., Shehata, W.E. and Imredy, J.P., Slow electrically and chemically evoked volume changes in guinea pig outer hair cells. In N. Akkas (Ed.), *Biomechanics of Active Movement and Deformation of Cells*, Springer-Verlag, ,1990, 493-498..
21. Campbell, L.W., Hao, S-Y. and Landfield, P.W., Aging-related increases in L-like calcium currents in rat hippocampal slices, *Soc.Neurosci.*, 15 (1989) 106.10. (Abstract)
22. Carpenter, G.A. and Grossberg, S., Neural dynamics of category learning and recognition: Attention, memory consolidation, and amnesia. In S. Grossberg (Ed.), *The Adaptive Brain I: Cognition, Learning, Reinforcement, and Rhytm*, Elsevier Science Publishers B.V., Amsterdam, 1987, pp. 239-286.
23. Casey, M.A. and Feldman, M.L., Aging in the rat medial nucleus of the trapezoid body. II. Electron microscopy, *J.Comp.Neurol.*, 232 (1985) 401-413.
24. Cloninger CR, ;.Martin RL ; Guze SB ; Clayton PJ., Diagnosis and prognosis in schizophrenia, *Arch.Gen.Psychiatry*, 42 (1985) 15-25.
25. Cochen, R.J. and Allen, G.S., Cerebral arterial spasm: the role of calcium in vitro and in vivo analysis of treatment with nifedipine and nimodipine. In R.H. Wilkins (Ed.), *Proceedings of the 2nd International workshop on Vasospasm*, Williams and Wilkins, Baltimore, 1980, pp. 527-532.
26. Coles, R.R.A., Epidemiology of tinnitus. In J.P.W. Hazell (Ed.), *Tinnitus*, ChurchillLivingstone, Edinburgh, 1987, pp. 46-70.
27. Coles, R.R.A., Tinnitus and its management. In Scott-Brown and S.D.G. Stephens (Eds.), *Otolaryngology*, Butterworth, Guildford, 1987, pp. 368-414.
28. Conlee, J.W., Abdul-Baqi, K.J., McCandless, G.A. and Creel, D.J., Differential susceptibility to noise-induced permanent threshold shift between albino and pigmented guinea pigs, *Hearing Res.*, 23 (1986) 81-91.
29. Conlee, J.W., Gill, S.S., McCandless, P.T. and Creel, D.J., Differential susceptibility to gentamicin ototoxicity between albino and pigmented guinea pigs, *Hearing Res.*, 41 (1989) 43-52.
30. Consensus Development Panel, National Institutes of Health consensus development conference statement on cochlear implants, *Arch.Otolaryngol.Head.Neck.Surg.*, 115 (1989) 31-104.
31. Corey, D.P. and Hudspeth, A.J., Response latency of vertebrate hair cells, *Biophys.J.*, 26 (1979) 499-506.
32. Corey, D.P. and Hudspeth, A.J., Ionic basis of the receptor potential in a vertebrate hair cell, *Nature*, 281 (1979) 675-677.
33. Corey, D.P. and Hudspeth, A.J., Analysis of the microphonic potential of the bullfrog's sacculus, *J.Neurosci.*, 3 (1983) 942-961.
34. Corey, D.P. and Hudspeth, A.J., Kinetics of the receptor current in bullfrog saccular hair cells, *J.Neurosci.*, 3 (1983) 962-976.
35. Corey, D.P., Smith, W.J., Barres, B.A., Koroshetz. and W.J., Calmodulin inhibitors block adaptation in vestibular hair cells, *Soc.Neurosci.*, 13 (1987) 538-538. (Abstract)
36. Cousillas, H., Cole, K.S. and Johnstone, B.M., Effect of spider venom on cochlear nerve activity consistent with glutamatergic transmission at hair cell-afferent dendrite synapse, *Hearing Res.*, 36 (1988) 213-220.
37. Dallos, P., Cochlear physiology, *Ann.Rev.Psychol.*, 32 (1981) 153-190.
38. Davies, E. and Donaldson, I., Tinnitus, membrane stabilizers and taurine, *Practitioner*, 232 (1988) 1139-1139.
39. Davis, R.I., Ahroon, W.A. and Hamernik, R.P., The relation among hearing loss, sensory cell loss and tuning characteristics in the chinchilla, *Hearing Res.*, 41 (1989) 1-14.
40. DeBartolo, H.M., Jr., Zinc and diet for tinnitus, *Am.J.Otol.*, 10 (1989) 256-256.
41. DeValois, R.L. and DeValois, K.K., Spatial perception, *Ann.Rev.Psychol.*, 31 (1980) 309-341.
42. Deyo, R.A., Straube, K.T. and Disterhoft, J.F., Nimodipine facilitates associative learning in aging rabbits, *Science*, 243 (1989) 809-811.
43. Dobie, R.A., Hoberg, K.E. and Rees, T.S., Electrical tinnitus suppression: a double-blind crossover study, *Otolaryngol.Head Neck Surg.*, 95 (1986) 319-323.
44. Draznin, B., Sussman, K.E., Kao, M. and Sherman, N., Relationship between cytosolic free calcium concentration and 2-deoxyglucose uptake in adipocytes isolated from 2- and 12-month-old rats, *Endocrinology*, 122 (1988) 2578-2583.
45. Drescher, D.G. and Drescher, M.J., Spontaneous neural activity of a mechanoreceptive system is undiminished by replacement of external calcium with equimolar magnesium in the presence of EGTA, *Life Sci.*, 40 (1987) 1371-1377.
46. Drescher, D.G. and Drescher, M.J., Calcium and magnesium dependence of spontaneous and evoked afferent neural activity in the lateral-line organ of Xenopus laevis, *Comp.Biochem.Physiol.*, 87 (1987) 305-310.
47. Drescher, M.J., Drescher, D.G. and Medina, J.E., Effect of sound stimulation at several levels on concentrations of primary amines, including neurotransmitter candidates, in perilymph of the guinea pig inner ear, *J.Neurochem.*, 41 (1983) 309-320.

48. Duckert, L.G. and Rees, T.S., Placebo effect in tinnitus management, *Otolaryngol.Head Neck Surg.*, 92 (1984) 697-699.
49. Dulon, D., Aran, J.M. and Schacht, J., Potassium-depolarization induced motility in isolated outer hair cells by an osmotic mechanism, *Hearing Res.*, 32 (1988) 123-130.
50. Eatock, R.A., Corey, D.P. and Hudspeth, A.J., Adaption of mechanoelectrical transduction in hair cells of the bullfrog's sacculus, *J.Neurosci.*, 7 (1987) 2821-2836.
51. Erlandsson, S., Ringdahl, A., Hutchins, T. and Carlsson, S.G., Treatment of tinnitus: a controlled comparison of masking and placebo, *Brit.J.Audiol.*, 21 (1987) 37-44.
52. Estes, W.K. and Skinner, B.F., Some quantitative properties of anxiety, *J.Exp.Psychol.*, 29 (1941) 390-400.
53. Evans, E.F. and Borerwe, T.A., Ototoxic effects of salicylates on the responses of single cochlear nerve fibers and on cochlear potentials, *Brit.J.Audiol.*, 16 (1982) 101-108.
54. Evans, E.F., Wilson, J.P. and Borerwe, T.A., Animal models of tinnitus, *CIBA Found.Symp.*, 85 (1981) 108-138.
55. Feldmann, H., Homolateral and contralateral masking of tinnitus by noisebands and by pure tones, *Audiology(Basel)*, 10 (1971) 138-144.
56. Feldmann, H., Proceedings III International tinnitus seminar, Muenster 1987, Harsch Verlag, Karlsruhe, 1987, 1-467 pp.
57. Ferrary, E., Tran Ba, H.uy P., Roinel, N., Bernard, C. and Amiel, C., Calcium and the inner ear fluids, *Acta Otolaryngol.Suppl.(Stockh.)*, 460 (1988) 13-17.
58. Fex, J. and Altschuler, R.A., Neurotransmitter-related immunocytochemistry of the organ of Corti, *Hearing Res.*, 22 (1986) 249-263.
59. Flock, A., Flock, B. and Ulfendahl, M., Mechanisms of movement in outer hair cells and a possible structural basis, *Arch.Otorhinolaryngol.*, 243 (1986) 83-90.
60. Flock, A. and Orman, S., Micromechanical properties of sensory hairs on receptor cells of the inner ear, *Hearing Res.*, 11 (1983) 249-260.
61. Flower, R.J., Moncada, S. and Vane, J.R., Analgesic-antipyretics and anti-inflammatory agents. In A.G. Gilman, L.S. Goodman and A. Gilman (Eds.), *The Pharmacological Basis of Therapeutics*, Macmillan, New York, 1980, pp. 682-728.
62. Freeman, W.J., Yao, Y. and Burke, B., Central pattern generating and recognizing in olfactory bulb: A correlation Learning Rule, *Neural Networks*, 1 (1988) 277-288.
63. Furness, D.N., Richardson, G.P. and Russell, I.J., Stereociliary bundle morphology in organotypic cultures of the mouse cochlea, *Hearing Res.*, 38 (1989) 95-110.
64. George, R.N. and Kemp, S., Investigation of tinnitus induced by sound and its relationship to ongoing tinnitus, *J.Speech Hearing Res.*, 32 (1989) 366-372.
65. Gerber, K.E., Nehemkis, A.M., Charter, R.A. and Jones, H.C., Is tinnitus a psychological disorder, *Int.J.Psychiatry Med.*, 15 (1985) 81-87.
66. Gerken, G.M., Central denervation hypersensitivity in the auditory system of the cat, *J.Acoust.Soc.Am.*, 66 (1979) 721-727.
67. Gerken, G.M., A systems approach to the relationship between the ear and central auditory mechanisms, *Adv.Audiol.*, 1 (1984) 30-52.
68. Gerken, G.M., Saunders, S.S. and Paul, R.E., Hypersensitivity to electrical stimulation of auditory nuclei follows hearing loss in cats, *Hearing Res.*, 13 (1984) 249-259.
69. Gerken, G.M., Simhadri-Sumithra, R. and Bhat, K.H.V., Increase in central auditory responsiveness during continous tone stimulation or following hearing loss. In R.J. Salvi, D. Henderson, R.P. Hamernik and V. Colletti (Eds.), *Basic and Applied Aspects of Noise-Induced Hearing Loss*, Plenum Publishing Corporation, New York, 1986, pp. 195-211.
70. Gibson, G.E. and Peterson, C., Calcium and the aging nervous system, *Neurobiol.Aging*, 8 (1987) 329-343.
71. Gifford, M.L. and Guinan, J.J., Effects of crossed-olivocochlear-bundle stimulation on cat auditory nerve fiber responses to tones, *J.Acoust.Soc.Am.*, 74 (1983) 115-123.
72. Gifford, M.L. and Guinan, J.J., Jr., Effects of electrical stimulation of medial olivocochlear neurons on ipsilateral and contralateral cochlear responses, *Hearing Res.*, 29 (1987) 179-194.
73. Gispen, W.H., Schuurman, T. and Traber, J., Nimodipine and neural plasticity in the pheripheral nervous system of adult and aged rats. In Morad, Nayler, Kazda and Schramm (Eds.), *The Calcium Channel: Structure, Function and Implications*, Springer-Verlag, Berlin, Heidelberg, 1988, pp. 491-502.
74. Goldman-Rakic, P.S., Topography of cognition: Parallel distributed networks in primate association cortex, *Ann.Rev.Neurosci.*, 11 (1988) 137-156.
75. Goldman-Rakic, P.S., Circuitry of primate prefrontal cortex and regulation of behavior by representational memory. In *Handbook of Physiology vol V: The Nervous System - Higher Functions of the Brain*, American Physiological Society, Bethesda, M.D., 1989, pp. 373-417.

76. Grigor, R.R., Spitz, P.W. and Furst, D.E., Salicylate toxicity in elderly patients with rheumatoid arthritis, *J.Rheumatol.*, 14 (1987) 60-66.
77. Grossberg, S., How does a brain build a cognitive code?, *Psychol.Rev.*, 87 (1980) 1-51.
78. Grossberg, S., The adaptive self-organization of serial order in behavior: Speech, language, and motor control. In S. Grossberg (Ed.), *The Adaptive Brain II: Vision, Speech, Language, and Motor Control*, Elsevier Science Publishers B.V., Amsterdam, 1987, pp. 313-400.
79. Guth, P.S. and Melamed, B., Neurotransmission in the auditory system: A primer for pharmacologists, *Ann.Rev.Pharmacol.Toxicol.*, 22 (1982) 383-412.
80. Guth, S.L. and Drescher, D.G., Effect of calcium channel blocker D-600 on neural activity in the lateral line of xenopus, *Soc.Neurosci.*, 14 (1988) (2)799-(2)799.
81. Hale, W.E., Perkins, L.L., May, F.E., Marks, R.G. and Stewart, R.B., Symptom prevalence in the elderly. An evaluation of age, sex, disease, and medication use, *J.Am.Geriatr.Soc.*, 34 (1986) 333-340.
82. Hamernik, R.P., Patterson, J.H., Turrentine, G.A. and Ahroon, W.A., The quantitative relation between sensory cell loss and hearing thresholds, *Hearing Res.*, 38 (1989) 199-212.
83. Hammeke, T.A., McQuillen, M.P. and Cohen, B.A., Musical hallucinations associated with acquired deafness, *J.Neurol.Neurosurg.Psychiatry*, 46 (1983) 570-572.
84. Harris, F.P., Lonsbury-Martin, B.L., Stagner, B.B., Coats, A.C. and Martin, G.K., Acoustic distortion product in humans: Systematic changes in amplitude as a function of f_2/f_1 ratio, *J.Acoust.Soc.Am.*, 85 (1989) 220-229.
85. Harris, G.G., Brownian motion in the cochlear partition, *J.Acoust.Soc.Am.*, 44 (1968) 176-186
86. Hasko, J.A. and Richardson, G.P., The ultrastructural organization and properties of the mouse tectorial membrane matrix, *Hearing Res.*, 35 (1988) 21-38.
87. Hazell, J.W.P., Spontaneous cochlear acoustic emissions and tinnitus. Clinical experience in the tinnitus patient, *J.Laryngol.Otol.*, Suppl. 9 (1984) 106-110.
88. Hazell, J.W.P., A cochlear model for tinnitus. In H. Feldmann (Ed.), *Proceedings III International tinnitus seminar, Muenster 1987*, Harsch Verlag, Karlsruhe, 1987, pp. 121-128.
89. Hazell, J.W.P., Tinnitus, Churchill Livingstone, Edinburgh, 1987, 1-207 pp.
90. Hazell, J.W.P., Personal communication, (1989)
91. Hazell, J.W.P. and Jastreboff, P.J., Tinnitus I: Auditory meachanisms: A model for tinnitus and hearing impairment, *Canad.J.Otolaryngol. Head Neck Surg.*, (1990) (In Press)
92. Hazell, J.W.P., Meerton, L.J. and Conway, M.J., Electrical tinnitus suppression (ETS) with a single channel cochlear implant, *J.Laryngol.Otol.*, Suppl 18 (1989) 39-44.
93. Hazell, J.W.P., Sheldrake, J.B. and Meerton, L.J., Tinnitus masking - Is it better than counseling alone?. In H. Feldmann (Ed.), *Proceedings of the III International tinnitus seminar, Muenster 1987*, Harsch Verlag, Karlsruhe, 1987, pp. 239-250.
94. Hazell, J.W.P., Wood, S.M., Cooper, H.R., Stephens, S.D.G., Corcoran, A.L., Coles, R.R.A., Baskill, J.L. and Sheldrake, J.B., A clinical study of tinnitus maskers, *Brit.J.Audiol.*, 19 (1985) 65-146.
95. Heilbrun AB, J.r ; Diller R ; Fleming R ; Slade L., Strategies of disattention and auditory hallucinations in schizophrenics, *J.Nerv.Ment.Dis.*, 174 (1986) 265-73.
96. Hess, P., Lansman, J.B. and Tsien, R.W., Different modes of Ca channel gating behavior favored by dihydropyridines $Ca2^+$ agonist and antagonists, *Nature*, 311 (1984) 538-544.
97. Hilgard, E.R. and Bower, G.H., Theories of Learning, Prentice-Hall, Englewood Cliffs, NJ, 1975,
98. Hudspeth, A.J., Mechanoelectrical transduction by hair cells in the acousticolateralis sensory system, *Ann.Rev.Neurosci.*, 6 (1983) 187-215.
99. Hudspeth, A.J., The cellular basis of hearing: The biophysics of hair cells, *Science*, 230 (1985) 745-752.
100. Hudspeth, A.J., The ionic channels of a vertebrate hair cell, *Hearing Res.*, 22 (1986) 21-27.
101. Hudspeth, A.J. and Corey, D.P., Sensitivity, polarity and conductance in the response of vertebrate hair cells to controlled mechanical stimuli, *Proc.Natl.Acad.Sci.USA*, 74 (1977) 2407-2411.
102. Hunter, K.P. and Willott, J.F., Aging and the auditory brainstem response in mice with severe or minimal presbycusis, *Hearing Res.*, 30 (1987) 207-218.
103. Hunter-Duvar, I.M., Suzuki, M. and Mount, R.J., Anatomical changes in the Organ of Corti after acoustic stimulation. In R.P. Hamernik, D. Henderson and R. Salvi (Eds.), *New Perspectives on Noise-Induced hearing Loss*, Raven Press, New York, 1982, pp. 3-22.
104. Ikeda, K. and Morizono, T., Electrochemical profile for calcium ions in the stria vascularis: cellular model of calcium transport mechanism, *Hearing Res.*, 40 (1989) 111-116.
105. Inamura, N., Salt, A.N., Arakawa, E. and Thalmann, R., Ionic gradients within the endolymphatic space of the guinea-pig, *Assoc.Res.Otolaryngol.*, 120 (1989) 128-129. (Abstract)
106. Ishikawa, Y., Gee, M.V., Ambudkar, I.S., Bodner, L., Baum, B.J. and Roth, G.S., Age-related impairment in rat parotid cell alpha 1-adrenergic action at the level of inositol trisphosphate responsiveness, *Biochim.Biophys.Acta*, 968 (1988) 203-210.
107. Jabboury, K., Frye, D., Holmes, F.A., Fraschini, G. and Hortobagyi, G., Phase II evaluation of gallium nitrate by continuous infusion in breast cancer, *Invest.New.Drugs*, 7 (1989) 225-229.

108. Jannetta, P.J., Microvascular decompression of the cochlear nerve as treatment of tinnitus. In H. Feldmann (Ed.), *Proceedings III International Tinnitus Seminar, Muenster 1987*, Harsch Verlag, Karlsruhe, 1987, pp. 348-352.
109. Jannetta, P.J., Moller, M.B. and Moller, A.R., Disabling positional vertigo, *N.Eng.J.Med.*, 310 (1984) 1700-1705.
110. Jastreboff, P.J., An animal model of tinnitus: Development, present status, perspectives, *Hearing J.*, 42 (1989) 58-63.
111. Jastreboff, P.J. and Brennan, J.F., Specific effects of nimodipine on the auditory system, *Ann.NY.Acad.Sci.*, 522 (1988) 716-718.
112. Jastreboff, P.J., Brennan, J.F. and Sasaki, C.T., Behavioral and electrophysiological animal model of tinnitus. In H. Feldmann (Ed.), *Proceeding of the III International Tinnitus Seminar, Muenster*, Harsch Verlag, Karlsruhe, 1987, pp. 95-99.
113. Jastreboff, P.J., Brennan, J.F. and Sasaki, C.T., An animal model for tinnitus, *Laryngoscope*, 98 (1988) 280-286.
114. Jastreboff, P.J., Brennan, J.F. and Sasaki, C.T., Pigmentation, anesthesia, behavioral factors and salicylate uptake, *Arch.Otolaryngol.Head.Neck.Surg.*, 114 (1988) 186-191.
115. Jastreboff, P.J., Brennan, J.F. and Sasaki, C.T., Phantom auditory sensation in rats: An animal model for tinnitus, *Behav.Neurosci.*, 102 (1988) 811-822.
116. Jastreboff, P.J., Brennan, J.F. and Sasaki, C.T., Animal model of tinnitus: Quinine effects, *Assoc.Res.Otolaryngol.*, 11 (1988) 260-260. (Abstract)
117. Jastreboff, P.J., Brennan, J.F. and Sasaki, C.T., An animal model of tinnitus: Perceptual complexity, *Assoc.Res.Otolaryngol.*, 12 (1989) 191-192. (Abstract)
118. Jastreboff, P.J., Hansen, R. and Sasaki, C.T., Dose-dependent serum calcium decrease after salicylate, *Soc.Neurosci.*, 15 (1989) 210-210. (Abstract)
119. Jastreboff, P.J., Hansen, R., Sasaki, P.G. and Sasaki, C.T., Differential uptake of salicylate in serum, CSF and perilymph, *Arch.Otolaryngol.Head.Neck.Surg.*, 112 (1986) 1050-1083.
120. Jastreboff, P.J., Jastreboff, M.M., Hansen, R. and Sasaki, C.T., Salicylate-related changes in intracochlear calcium as a cause of auditory dysfunction, *Soc.Neurosci.*, 11 (1985) 244-244. (Abstract)
121. Jastreboff, P.J. and Sasaki, C.T., Salicylate-induced changes in spontaneous activity of single units in the inferior colliculus of the guinea pig, *J.Acoust.Soc.Am.*, 80 (1986) 1384-1391.
122. Jenison, G.L., Bobbin, R.P. and Thalmann, R., Potassium-induced release of endogenous amino acids in the guinea pig cochlea, *J.Neurochem.*, 44 (1985) 1845-1853.
123. Johnson, E.M., Koike, T., Chang, J.Y., Wallace, T.L., Levy, B.K. and Martin, D.P., Mechanism of trophic factor deprovation-induced neuronal death. In *Neuroscience in the Twenty-First Century: New Perspectives and Horizons. Georgetown University Bicentennila Symposium, Washington, D.C., 1989*, Fidia Research Foundation, Washington, 1989, pp. 7-9.
124. Juhn, S.K. and Rybak, L.P., Labyrinthine barriers and cochlear homeostasis, *Acta Otolaryngol.*, 91 (1981) 529-534.
125. Juhn, S.K. and Youngs, J.N., The effect on perilymph of the alteration of serum glucose or calcium concentration, *Laryngoscope*, 86 (1976) 273-279.
126. Kato, Y., Sensaki, H. and Ogura, H., Aspirin-induced hypocalcemia in the rat, *Toxicol.Appl.Pharmacol.*, 64 (1982) 64-71.
127. Kawashima, H., Kurozumi, S. and Hasimoto, Y., Aspirin inhibition of 1 alpha-hydroxyvitamin D3 or parathyroid hormone induced hypercalcemia in vivo in rats. A mechanism independent of prostaglandin biosynthesis inhibition, *Biochem.Pharmacol.*, 34 (1985) 1901-1906.
128. Kazda, S., Garthoff, B. and Luckhaus, G., Ca antagonists prevent brain damage in stroke-prone spontaneous hypertensive rats (SHR-Sp) independent of their effect on blood pressure: nimodipine vs. nitrendipine, *J.Cereb.Blood Flow Metab.*, 3 (1983) 526-527.
129. Kazda, S. and Towart, R., Nimodipine: A new calcium antagonist drug with a preferential cerebrovascular action, *Acta Neurochirurgica*, 63 (1982) 259-265.
130. Kemp, D.T., Stimulated acoustic emissions from within the human auditory system, *J.Acoust.Soc.Am.*, 64 (1978) 1386-1391.
131. Kemp, D.T., Evidence of mechanical nonlinearity and frequency selective wave amplification in the cochlea, *Arch.Otorhinolaryngol.*, 224 (1979) 37-45.
132. Kemp, D.T., Physiologically active cochlear micromechanics - one source of tinnitus. In D. Evered and G. Lawrenson (Eds.), *Tinnitus: Ciba Foundation Symposium 85*, Pitman, London, 1981, pp. 54-81.
133. Kemp, D.T., Bray, P., Alexander, L. and Brown, A.M., Acoustic emission cochleography - practical aspects, *Scand.Audiol.(Suppl.)*, 25 (1986) 71-95.
134. Kemp, D.T. and Brown, A.M., A comparison of mechanical nonlinearities in cochleae of man and gerbil from ear canal measurements. In R. Klinke and R. Hartmann (Eds.), *Hearing -- Physiological Bases and Psychophysics*, Springer Verlag, New York, 1983, pp. 82-88.

135. Kemp, S. and Plaisted, I.D., Tinnitus induced by tones, *J.Speech Hearing Res.*, 29 (1986) 65-70.
136. Kiang, N.Y.S., Liberman, M.C., Sewell, W.F. and Guinan, J.J., Single unit clues to cochlear mechanisms, *Hearing Res.*, 22 (1986) 171-182.
137. Kiang, N.Y.S., Moxon, E.C. and Levine, R.A., Auditory-nerve activity in cats with normal and abnormal cochleas. In G.E.W. Wolstenholme and J. Knight (Eds.), *Ciba Foundation Symposium on Sensorineural Hearing Loss*, Churchill, London, 1970, pp. 241-273.
138. Kimura, R.S., Experimental blockage of the endolymphatic duct and its side effects on the inner ear of the guinea pig, *Ann.Otol.Rhinol.Laryngol.*, 76 (1967) 664-687.
139. Klinke, R., Neurotransmission in the inner ear, *Hearing Res.*, 22 (1986) 235-243.
140. Kronester-Frei, A., The effect of changes in endolymphatic ion concentrations on the tectorial membrane, *Hearing Res.*, 1 (1979) 81-94.
141. Kuk, F.K., Tyler, R.S., Rustad, N., Harker, L.A. and Tye-Murray, N., Alternating current at the eardrum for tinnitus reduction, *J.Speech Hearing Res.*, 32 (1989) 393-400.
142. Kulig, J. and Willott, J.F., Frequency difference limens of C57BL/6 and DBA/2 mice: relationship to auditory neuronal response properties and hearing impairment, *Hearing Res.*, 16 (1984) 169-174.
143. Landfield, P.W., `Increased calcium-current' hypothesis of brain aging, *Neurobiol. Aging*, 8 (1987) 346-347.
144. Landfield, P.W., Fleenor, D.G., Eldridge, J.C. and McEwen, B.S., Effects of aging on ^{3}H-nimodipine binding in rat brain, *Soc.Neurosci.*, 15 (1989) 542.31. (Abstract)
145. Landfield, P.W. and Morgan, G.A., Chronically elevating plasma Mg^{2+} improves hippocampal frequency potentiation and reversal learning in aged and young rats, *Brain Res.*, 322 (1984) 167-171.
146. Landfield, P.W., Pitler, T.A. and Applegate, M.D., The effects of high Mg^{2+}-to-Ca^{2+} ratios on frequency potentiation in hippocampal slices of young and aged rats, *J.Neurophysiol.*, 56 (1986) 797-811.
147. LePage, E.L., Frequency-dependent self-induced bias of the basilar membrane and its potential for controlling sensitivity and tuning in the mammalian cochlea, *J.Acoust.Soc.Am.*, 82 (1987) 139-154.
148. LePage, E.L., Functional role of the olivo-cochlear bundle: A motor unit control system in the mammalian cochlea, *Hearing Res.*, 38 (1989) 177-198.
149. Liang, C.T., Barnes, J., Takamato, S. and Sacktor, B., Effect of age on calcium uptake in isolated duodenum cells: role of 1,25-dihydroxyvitamin D3, *Endocrinology*, 124 (1989) 2830-2836.
150. Liberman, M.C., Chronic ultrastructural changes in acoustic trauma: Serial- section reconstruction of stereocilia and cuticular plates, *Hearing Res.*, 26 (1987) 65-88.
151. Liberman, M.C., Response properties of cochlear efferent neurons: Monaural vs. binaural stimulation and the effects of noise, *J.Neurophysiol.*, 60 (1988) 1779-1798.
152. Liberman, M.C., Rapid assessment of sound-evoked olivocochlear feedback: Suppression of compound action potentials by contralateral sound, *Hearing Res.*, 38 (1989) 47-56.
153. Liberman, M.C. and Brown, M.C., Physiology and anatomy of single olivocochlear neurons in the cat, *Hearing Res.*, 24 (1986) 17-36.
154. Liberman, M.C. and Dodds, L.W., Single-neuron labeling and chronic cochlear pathology. III. Stereocilia damage and alteration of threshold tuning curves, *Hearing Res.*, 16 (1984) 55-74.
155. Liberman, M.C. and Dodds, L.W., Single-neuron labeling and chronic cochlear pathology. II. Stereocilia damage and alteration of spontaneous discharge rates, *Hearing Res.*, 16 (1984) 43-53.
156. Liberman, M.C. and Dodds, L.W., Acute ultrastructural changes in acoustic trauma: Serial- section reconstruction of stereocilia and cuticular plates, *Hearing Res.*, 26 (1987) 45-64.
157. Liberman, M.C. and Kiang, N.Y.S., Acoustic trauma in cats, *Acta Otolaryngol.(Suppl.)*, 358 (1978) 1-63.
158. Liberman, M.C. and Mulroy, M.J., Acute and chronic effects of acoustic trauma: Cochlear pathology and auditory nerve pathophysiology. In R.P. Hamernik, D. Henderson and R. Salvi (Eds.), *New Perspectives on Noise-Induced Hearing Loss*, Raven Press, New York, 1982, pp. 105-136.
159. Lim, D.J., Functional structure of the organ of Corti: a review, *Hearing Res.*, 22 (1986) 117-146.
160. Lippmann, R.P., Review of neural networks for speech recognition, *Neural Comp.*, 1 (1989) 1-38.
161. Loeb, G.E., White, M.W. and Merzenich, M.M., Spatial cross-correlation. A proposed mechanism for acoustic pitch perception, *Biol.Cybern.*, 47 (1983) 149-163.
162. Long, G.R. and Tubis, A., Modification of spontaneous and evoked otoacoustic emissions and associated psychoacoustic microstructure by aspirin consumption, *J.Acoust.Soc.Am.*, 84 (1988) 1343-1353.
163. Lonsbury-Martin, B.L., Martin, G.K., Probst, R. and Coats, A.C., Acoustic distortion products in rabbit ear canal. I. Basic features and physiological vulnerability, *Hearing Res.*, 28 (1987) 173-189.
164. Lyttkens, L., Pharmacological treatment of tinnitus with special reference to the role of melanin, *Scand.Audiol.(Suppl.)*, 26 (1986) 27-31.
165. Lyttkens, L., Lindberg, P., Scott, B. and Melin, L., Treatment of tinnitus by external electrical stimulation, *Scand.Audiol.*, 15 (1986) 157-164.
166. Marks, N.J., Karl, H. and Onisiphorou, C., A controlled trial of hypnotherapy in tinnitus, *Clin.Otolaryngol.*, 10 (1985) 43-46.

167. Martin, G.K., Lonsbury-Martin, B.L., Probst, R. and Coats, A.C., Spontaneous otoacoustic emissions in a nonhuman primate. I. Basic features and relations to other emissions, *Hearing Res.*, 33 (1988) 49-68.
168. Martin, G.K., Lonsbury-Martin, B.L., Probst, R., Scheinin, S.A. and Coats, A.C., Acoustic distortion products in rabbit ear canal. II. Sites of origin revealed by suppression contours and pure- tone exposures, *Hearing Res.*, 28 (1987) 191-208.
169. McFadden, D., Tinnitus: Facts, theories, and treatments, National Academy Press, Washington, D.C., 1982, 1-150 pp.
170. McFadden, D. and Plattsmier, H.S., Aspirin abolishes spontaneous oto-acoustic emissions, *J.Acoust.Soc.Am.*, 76 (1984) 443-448.
171. Mendel, D., A basis for the pharmacology of hearing, *J.Laryngol.Otol.*, 94 (1980) 1363-1376.
172. Meyer zum Gottesberge, A.M., The role of melanocytes in the pathophysiology of experimental hydrops. In J.B. Nadol (Ed.), *Meniere's Disease. Second International Symposium on Meniere's Disease, Cambridge, MA, 1988*, Kugler and Ghedini Publications, Amsterdam, 1988, pp. 343-350.
173. Meyer zum Gottesberge, A.M., Physiology and pathophysiology of inner ear melanin, *Pigment Cell Res.*, 1 (1988) 238-249.
174. Meyer zum Gottesberge-Orsulakova, A-M. and Kaufman, R., Is an imbalanced calcium-homeostatis responsible for the experimentally induced endolymphatic hydrops, *Acta Otolaryngol.(Stockh.)*, 102 (1986) 93-98.
175. Meyerhoff, W.L., The thyroid and audition, *Laryngoscope*, 86 (1976) 483-489.
176. Miller, R.J., Multiple calcium channels and neuronal function, *Science*, 235 (1987) 46-52.
177. Moller, A.R., Pathophysiology of tinnitus, *Ann.Otol.Rhinol.Laryngol.*, 93 (1984) 39-44.
178. Moller, A.R., Can injury to the auditory nerve cause tinnitus?. In H. Feldmann (Ed.), *Proceeding III International Tinnitus Seminar, Muenster 1987*, Harsch Verlag, Karlsruhe, 1987, pp. 58-63.
179. Moller, M.B., Vascular compression of the eight nerve as cause of tinnitus. In H. Feldmann (Ed.), *Proceedings III International Tinnitus Seminar, Muenster 1987*, Harsch Verlag, Karlsruhe, 1987, pp. 340-347.
180. Moller, M.B. and Moller, A.R., Audiometric abnormalities in hemifacial spasm, *Audiol.*, 24 (1985) 396-405.
181. Moller, M.B., Moller, A.R., Jannetta, P.J. and Sekhar, L., Diagnosis and surgical treatment of disabling positional vertigo, *J.Neurosurg.*, 64 (1986) 21-28.
182. Mongan, E., Kelly, P., Nies, K., Porter, W.W. and Paulus, H.E., Tinnitus as an indication of therapeutic serum salicylate levels, *JAMA*, 226 (1973) 141-145.
183. Montgomery, P.R., Berger, L.G., Mitenko, P.A. and Sitar, D.S., Salicylate metabolism: Effects of age and sex in adults, *Clin.Pharmacol.Ther.*, 39 (1986) 571-576.
184. Mooseker, M.S., Graves, T.A., Wharton, K.A., Falco, N. and Howe, C.L., Regulation of microvillus structure: Calcium-dependent solation and cross-linking of actin filaments in the microvilli of intestinal epithelial cells, *J.Cell Biol.*, 87 (1980) 809-822.
185. Morison, W.L., What is the function of melanin, *Arch.Dermatol.*, 121 (1985) 1160-1163.
186. Mott, J.B., Norton, S.J., Neely, S.T. and Warr, W.B., Changes in spontaneous otoacoustic emissions produced by acoustic stimulation of the contralateral ear, *Hearing Res.*, 38 (1989) 229-242.
187. Mroz, E.A. and Sewell, W.F., Pharmacological alterations of the activity of afferent fibers innervating hair cells, *Hearing Res.*, 38 (1989) 141-162.
188. Ninoyu, O. and Meyer zum Gottesberge-Orsulakova, A-M., Changes in Ca^{++} activity and DC potential in experimentally induced endolymphatic hydrops, *Arch.Otorhinolaryngol.*, 243 (1988) 106-107.
189. Norton, S.J., Mott, J.B. and Champlin, C.A., Behavior of spontaneous otoacoustic emissions following intense ipsilateral acoustic stimulation, *Hearing Res.*, 38 (1989) 243-258.
190. Offner, F.F., Dallos, P. and Cheatham, M.A., Positive endocochlear potential: Mechanism of production by marginal cells of stria vascularis, *Hearing Res.*, 29 (1987) 117-124.
191. Orman, S. and Flock, A., Active control of sensory hair mechanics implied by susceptibility to media that induce contraction in muscle, *Hearing Res.*, 11 (1983) 261-266.
192. Penner, M.J., Two-tone forward masking patterns and tinnitus, *J.Speech Hearing Res.*, 23 (1980) 779-786.
193. Penner, M.J., The annoyance of tinnitus and the noise required to mask it, *J.Speech Hearing Res.*, 26 (1983) 73-76.
194. Penner, M.J., Equal-loudness contours using subjective tinnitus as the standard, *J.Speech Hearing Res.*, 27 (1984) 274-279.
195. Penner, M.J., Tinnitus as a source of internal noise, *J.Speech Hearing Res.*, 29 (1986) 400-406.
196. Penner, M.J., Magnitude estimation and the "paradoxical: loudness of tinnitus, *J.Speech Hearing Res.*, 29 (1986) 407-412.
197. Penner, M.J., Masking of tinnitus and central masking, *J.Speech Hearing Res.*, 30 (1987) 147-152.
198. Penner, M.J., The effect of continuous monaural noise on loudness matches to tinnitus, *J.Speech Hearing Res.*, 31 (1988) 98-102.

199. Penner, M.J., Judgments and measurements of the loudness of tinnitus before and after masking, *J.Speech Hearing Res.*, 31 (1988) 582-587.
200. Penner, M.J., Audible and annoying spontaneous otoacoustic emissions. A case study, *Arch.Otolaryngol.Head.Neck.Surg.*, 114 (1988) 150-153.
201. Penner, M.J., Empirical tests demonstrating two coexisting sources of tinnitus: a case study, *J.Speech Hearing Res.*, 32 (1989) 458-462.
202. Penner, M.J., Aspirin abolishes tinnitus caused by spontaneous otoacoustic emissions. A case study, *Arch.Otolaryngol.Head.Neck.Surg.*, 115 (1989) 871-875.
203. Penner, M.J. and Bilger, R.C., Adaptation and the masking of tinnitus, *J.Speech Hearing Res.*, 32 (1989) 339-346.
204. Penner, M.J., Brauth, S. and Hood, L., The temporal course of the masking of tinnitus as a basis for inferring its origin, *J.Speech Hearing Res.*, 24 (1981) 257-261.
205. Penner, M.J. and Burns, E.M., The dissociation of SOAEs and tinnitus, *J.Speech Hearing Res.*, 30 (1987) 396-403.
206. Peterson, C., Ratan, R.R., Shelanski, M.L. and Goldman, J.E., Altered response of fibroblasts from aged and Alzheimer donors to drugs that elevate cytosolic free calcium, *Neurobiol. Aging*, 9 (1988) 261-266.
207. Pickles, J.O., Sensorineural hearing loss. In *An Introduction to the Physiology of Hearing*, Academic Press, London, 1988, pp. 297-320.
208. Pribram, K.H., Languages of the Brain - experimental Paradoxes and Principles in Neurophysiology, Prentice Hall, Englewood Cliffs, NJ, 1971, 1-432 pp.
209. Pribram, K.H., Holography and brain function. In G. Adelman (Ed.), *Encyclopedia of Neuroscience*, Birkhauser, Boston, 1987, pp. 499-500.
210. Probst, R., Coats, A.C., Martin, G.K. and Lonsbury-Martin, B.L., Spontaneous, click-, and toneburst-evoked otoacoustic emissions from normal ears, *Hearing Res.*, 21 (1986) 261-275.
211. Probst, R., Lonsbury-Martin, B.L., Martin, G.K. and Coats, A.C., Otoacoustic emissins in ears with hearing loss, *Am.J.Otolaryngol.*, 8 (1987) 73-81.
212. Puel, J.-L., Bledsoe, S.C.Jr., Bobbin, R.P., Ceasar, G. and Fallon, M., Comparative actions of salicylate on the amphibian lateral line and guinea pig cochlea, *Comp.Biochem.Physiol.*, 93 (1989) 73-80.
213. Puel, J.-L., Bobbin, R.P. and Fallon, M., The active process is affected first by intense sound exposure, *Hearing Res.*, 37 (1988) 53-64.
214. Puel, J.-L., Bobbin, R.P. and Fallon, M., 2-amino-4-phosphonobutyric acid receptors are not involved in synaptic transmission from hair cells to auditory neurons, *Hearing Res.*, 37 (1988) 83-88.
215. Puel, J.-L., Bobbin, R.P. and Fallon, M., Salicylate, mefenamate, meclogenamate, and quinine on cochlear potentials, *Arch.Otolaryngol.Head.Neck.Surg.*, 102 (1990) 66-73.
216. Rabie, A., Ferraz, C., Clavel, M.-C. and Legrand, C., Gelsolin immunoreactivity and development of the tectorial membrane in the cochlea of normal and hypothyroid rats, *Cell Tissue Res.*, 254 (1988) 241-245.
217. Rebillard, G., Abbou, S. and Lenoir, M., Oto-acoustic emissions. II. Spontaneous oto-emissions: results in normal subjects or patients with tinnitus, *Ann.Otolaryngol.Chir.Cervicofac.*, 104 (1987) 363-368.
218. Risey, J., Briner, W., Guth, P.S. and Norris, C.H., The superiority of the Goodwin procedure over the traditional procedure in measuring the loudness level of tinnitus, *Ear & Hearing*, 10 (1989) 318-322.
219. Robertson, D. and Johnstone, B.M., Effects of divalent cations on spontaneous and evoked activity of single mammalian auditory neurones, *Pflugers Arch.*, 380 (1979) 7-12.
220. Russell, I.J. and Sellick, P.M., Tuning properties of cochlear hair cells, *Nature*, 267 (1977) 858-860.
221. Russell, I.J. and Sellick, P.M., Intracellular studies of hair cells in the mammalian cochlea, *J.Physiol.*, 284 (1978) 261-290.
222. Saito, H., Yokoyama, A., Takeno, S., Sakai, T., Ueno, K., Masumura, H. and Kitagawa, H., Fetal toxicity and hypocalcemia induced by acetylsalicylic acid analogues, *Res.Commun.Chem.Path.Pharmacol.*, 38 (1982) 209-220.
223. Salomon, G., Hearing problems and the elderly, *Dan.Med.Bull.*, 33 (1986) 1-22.
224. Salt, A.N. and Thalmann, R., Rate of longitudinal flow of cochlear endolymph. In J.B.Jr. Nadol (Ed.), *Meniere's Disease*, Kugler & Ghedini Pub., Amsterdam, Berkeley, Milano, 1989, pp. 69-73.
225. Salvi, R., Perry, J., Hamernik, R.P. and Henderson, D., Relationship between cochlear pathologies and auditory nerve and behavioral responses following acoustic trauma. In R.P. Hamernik, D. Henderson and R. Salvi (Eds.), *New Perspectives on Noise-induced Hearing Loss*, Raven Press, New York, 1982, pp. 165-188.
226. Salvi, R.J. and Ahroon, W.A., Tinnitus and neural activity, *J.Speech Hearing Res.*, 26 (1983) 629-632.
227. Sand, O., Ozawa, S. and Hagiwara, S., Electrical and mechanical stimulation of hair cells in the mudpuppy, *J.Comp.Physiol.*, A 102 (1975) 13-26.
228. Santos-Sacchi, J. and Dilger, J.P., Whole cell currents and mechanical responses of isolated outer hair cells, *Hearing Res.*, 35 (1988) 143-150.
229. Sasaki, C.T., Babitz, L. and Kauer, J.S., Tinnitus: Development of a neurophysiologic correlate, *Laryngoscope*, 91 (1981) 2018-2024.

230. Sasaki, C.T., Kauer, J.S. and Babitz, L., Differential [14C]2-deoxyglucose uptake after deafferentation of the mammalian auditory pathway - a model for examining tinnitus, *Brain Res.*, 194 (1980) 511-516.
231. Sataloff, J., Sataloff, R.T. and Lueneburg, W., Tinnitus and vertigo in healthy senior citizens without a history of noise exposure, *Am.J.Otol.*, 8 (1987) 87-89.
232. Saunders, J.C., Canlon, B. and Flock, A., Growth of threshold shift in hair-cell stereocilia following overstimulation, *Hearing Res.*, 23 (1986) 245-255.
233. Saunders, J.C., Canlon, B. and Flock, A., Changes in stereocilia micromechanics following overstimulation in metabolically blocked hair cells, *Hearing Res.*, 24 (1986) 217-225.
234. Saunders, J.C. and Flock, A., Changes in the cochlear hair-cell stereocilia stiffness following overstimulation, *Assoc.Res.Otolaryngol.*, 8 (1985) 51-51. (Abstract)
235. Saunders, J.C. and Flock, A., Recovery of threshold shift in hair-cell stereocilia following exposure to intense stimulation, *Hearing Res.*, 23 (1986) 233-243.
236. Schuknecht, H., The pathophysiology of Meniere's disease. In K.H. Vosteen, H. Schuknecht, C.R. Pfaltz, J. Wersall, R.S. Kimura, C. Morgenstern and S.K. Juhn (Eds.), *Meniere's disease*, Thieme, Stuttgart, 1981, pp. 10-15.
237. Schuurman, T., Klein, H., Beneke, M. and Traber, J., Nimodipine and motor deficits in the aged rat, *Neurosci.Res.Comm.*, 1 (1987) 9-15.
238. Schuurman, T. and Traber, J., Old rats as an animal model for senile dementia: Behavioural effects of nimodipine. In Bergener and Reisberg (Eds.), *Diagnosis and Treatment of Senile Dementia*, Springer-Verlag, Berline, Heidelberg, 1989, pp. 295-307.
239. Scriabine, A., Schuurman, T. and Traber, J., Pharmacological basis for the use of nimodipine in central nervous system disorders, *FASEB J.*, 3 (1989) 1799-1806.
240. Sejnowski, T.J., Koch, C. and Churchland, P.S., Computational neuroscience, *Science*, 241 (1988) 1299-1306.
241. Sellick, P.M., Patuzzi, R. and Johnstone, B.M., Comparison between the tuning properties of inner hair cells and basilar membrane motion, *Hearing Res.*, 10 (1983) 93-100.
242. Sewell, W.F. and Mroz, E.A., Neuroactive substances in inner ear extracts, *J.Neurosci.*, 7 (1987) 2465-2475.
243. Shambaugh, G.E., Jr., Zinc: the neglected nutrient, *Am.J.Otol.*, 10 (1989) 156-160.
244. Shehata, W.E., Brownell, W.E., Cousillas, H. and Imredy, J.P., Salicylate alters membrane conductance of outer hair cells and diminishes rapid electromotile responses, *Assoc.Res.Otolaryngol.*, 13 (1990) (Abstract)
245. Shepherd, G.M,, Vision. In *Neurobiology*, Oxford University Press, New York, 1983, pp. 305-329.
246. Shofner, W.P. and Young, E.D., Excitatory/inhibitory response types in the cochlear nucleus: Relationships to discharge patterns and responses to electrical stimulation of the auditory nerve, *J.Neurophysiol.*, 54 (1985) 917-939.
247. Siegel, J.H. and Kim, D.O., Efferent neural control of cochlear mechanics? Olivocochlear bundle stimulation affects cochlear biomechanical nonlinearity, *Hearing Res.*, 6 (1982) 171-182.
248. Silverstein, H., Haberkamp, T. and Smouha, E., The state of tinnitus after inner ear surgery, *Otolaryngol.Head Neck Surg.*, 95 (1986) 438-441.
249. Smith, D.I., Lawrence, M. and Hawkins, J.E., Effects of noise and quinine on the vessels of the stria vascularis: An image analysis study, *Am.J.Otolaryngol.*, 6 (1985) 280-289.
250. Steen, P.A., Gisvold, S.E., Milde, J.H., Newberg, L.A., Scheithauer, B.W., Lanier, W.L. and Mitchenfelder, J.D., Nimodipine improves outcome when given after complete cerebral ischemia in primates, *Anesthesiology*, 52 (1985) 406-411.
251. Steen, P.A., Newberg, L.A., Milde, J.H. and Michenfelder, J.D., Nimodipine improves cerebral blood flow and neurological recovery after complete cerebral ischemia in the dog, *J.Cereb.Blood Flow Metab.*, 3 (1983) 38-43.
252. Sterkers, O., Bernard, C., Ferrary, E., Sziklai, I., Tran Ba, H.uy P. and Amiel, C., Possible role of Ca ions in the vestibular system, *Acta Otolaryngol.Suppl.(Stockh.)*, 460 (1988) 28-32.
253. Stypulkowski, P.H., Physiological mechanisms of salicylate ototoxicity (Ph.D. thesis), University of Connecticut, Storr, 1989, 1-176 pp.
254. Thedinger, B.S., Karlsen, E. and Schack, S.H., Treatment of tinnitus with electrical stimulation: an evaluation of the Audimax Theraband, *Laryngoscope*, 97 (1987) 33-37.
255. Theopold, H-M., A new therapy concept for inner ear illness, *Laryng.Rhinol.Otol.*, 64 (1985) 609-613.
256. Tilney, L.G., Egelman, E.H., Derosier, D.J. and Saunders, J.C., Actin filaments, stereocilia, and hair cells of the bird cochlea II. Packing of actin filaments in the stereocilia and in the cuticular plate and what happens to the organization when the stereocila are bent, *J.Cell Biol.*, 96 (1983) 822-834.
257. Tilney, L.G. and Saunders, J.C., Actin filaments, stereocilia, and hair cells of the bird cochlea I. Length, number, width, and distribution of stereocilia of each hair cell are related to the position of the hair cell on the cochlea, *J.Cell Biol.*, 96 (1983) 807-821.

258. Tilney, L.G., Tilney, M.S. and Cotanche, A., New observation on the stereocilia of hair cells of the chick cochlea, *Hearing Res.*, 37 (1988) 71-82.
259. Tilney, M.S., Tilney, L.G. and Derosier, D.J., The distribution of hair cell bundle lengths and orientations suggests an unexpected pattern of hair cell stimulation in the chick cochlea, *Hearing Res.*, 25 (1987) 141-151.
260. Tonndorf, J., Acute cochlear disorders: The combination of hearing loss, recruitment, poor speech discrimination, and tinnitus, *Ann.Otol.*, 89 (1980) 353-358.
261. Tonndorf, J., Stereociliary dysfunction, a cause of sensory hearing loss, recruitment, poor speech discrimination and tinnitus, *Acta Otolaryngol.*, 91 (1981) 469-479.
262. Tonndorf, J., The analogy between tinnitus and pain: a suggestion for a physiological basis of chronic tinnitus, *Hearing Res.*, 28 (1987) 271-275.
263. Tyler, R.S. and Conrad-Armes, D., Spontaneous acoustic cochlear emissions and sensorineural tinnitus, *Brit.J.Audiol.*, 16 (1982) 193-194.
264. Tyler, R.S. and Conrad-Armes, D., The determination of tinnitus loudness considering the effects of recruitment, *J.Speech Hearing Res.*, 26 (1983) 59-72.
265. Tyler, R.S. and Conrad-Armes, D., Masking of tinnitus compared to masking of pure tones, *J.Speech Hearing Res.*, 27 (1984) 106-111.
266. Tyler, R.S. and Stouffer, J.L., A review of tinnitus loudness, *Hearing J.*, 42 (1989) 52-57.
267. Ueno, K., Shimoto, Y., Yokoyama, A., Kitagawa, H., Takeno, S., Sakai, T. and Saito, H., Alleviation of acetylsalicylic acid-induced fetal toxicity, *Res.Comm.Chem.Path.Pharmacol.*, 39 (1983) 179-188.
268. Ulfendahl, M., Motility in auditory sensory cells, *Acta Physiol.Scand.*, 130 (1987) 521-527.
269. Valli, P. and Zucca, G., The origin of slow potentials in semicircular canals of the frog, *Acta Otolaryngol.(Stockh.)*, 81 (1976) 395-405.
270. van der Zee, C.E., Schuurman, T., Traber, J. and Gispen, W.H., Oral administration of nimodipine accelerates functional recovery following peripheral nerve damage in the rat, *Neurosci.Lett.*, 83 (1987) 143-148.
271. Vermeij, P. and Hulshof, J.H., Dose finding of tocainide in the treatment of tinnitus, *Int.J.Clin.Pharmacol.Ther.Toxicol.*, 24 (1986) 207-212.
272. Vernon, J., Assessment of the tinnitus patient. In J.W.P. Hazell (Ed.), *Tinnitus*, Churchill Livingstone, Edinburgh, 1987, pp. 71-95.
273. Vernon, J. and Meikle, M.B., Tinnitus masking: unresolved problems. In D. Evered and G. Lawrenson (Eds.), *CIBA Foundation Symposium 85, Tinniuts*, Pitman, London, 1981, pp. 239-256.
274. von Wedel, H., Strahlmann, U. and Zorowka, P., Effectiveness of various non-medicinal therapeutic measures in tinnitus. A long-term study, *Laryngorhinootologie*, 68 (1989) 259-266.
275. Waibel, A., Modular construction of time-delay neural networks for speech recognition, *Neural Comp.*, 1 (1989) 39-46.
276. Warren, E.H., III. and Liberman, M.C., Effects of contralateral sound on auditory-nerve responses. I. Contributions of cochlear efferents, *Hearing Res.*, 37 (1989) 89-104.
277. Wiederhold, M.L., Physiology of the olivocochlear system. In R.A. Altschuler, R.P. Bobbin and D.W. Hoffman (Eds.), *Neurobiology of Hearing: The Cochlea*, Raven Press, New York, 1986, pp. 349-370.
278. Wiederhold, M.L. and Kiang, N.Y.S., Effects of electric stimulation of the crossed olivocochlear bundle on single auditory-nerve fibers in the cat, *J.Acoust.Soc.Am.*, 48 (1970) 950-965.
279. Wier, C.C., Pasanen, E.G. and McFadden, D., Partial dissociation of spontaneous otoacoustic emissions and distortion products during aspirin use in humans, *J.Acoust.Soc.Am.*, 84 (1988) 230-237.
280. Willott, J.F., Changes in frequency representation in the auditory system of mice with age-related hearing impairment, *Brain Res.*, 309 (1984) 159-162.
281. Willott, J.F., Effects of aging, hearing loss, and anatomical location on thresholds of inferior colliculus neurons in C57BL/6 and CBA mice, *J.Neurophysiol.*, 56 (1986) 391-408.
282. Willott, J.F., Demuth, R.M. and Lu, S.-M., Excitability of auditory neurons in the dorsal and ventral cochlear nuclei of DBA/2 and C57BL/6 mice, *Exp.Neurol.*, 83 (1984) 495-506.
283. Willott, J.F., Jackson, L.M. and Hunter, K.P., Morphometric study of the anteroventral cochlear nucleus of two mouse models of presbycusis, *J.Comp.Neurol.*, 260 (1987) 472-480.
284. Willott, J.F. and Lu, S-M., Noise-induced hearing loss can alter neural coding and increase excitability in the central nervous system, *Science*, 216 (1982) 1331-1332.
285. Wilson, J.P., The combination tone $2f_1$-f_2, in psychophysics and ear-canal recording. In G. van den Brink and F.A. Bilsen (Eds.), *Psychophysical, physiological, and behavioral studies in hearing*, Delft University Press, Delft, 1980, pp. 43-52.
286. Wilson, J.P., Evidence for a cochlear origin for acoustic re-emissions, threshold fine-structure and tonal tinnitus, *Hearing Res.*, 2 (1980) 233-252.
287. Wilson, J.P., Model for cochlear echoes and tinnitus based on an observed electrical correlate, *Hearing Res.*, 2 (1980) 527-532.

288. Wilson, J.P., Theory of tinnitus generation. In J.W.P. Hazell (Ed.), *Tinnitus*, Churchill Livingstone, Edinburgh, 1987, pp. 20-45.
289. Winslow, R.L. and Sachs, M.B., Single-tone intensity discrimination based on auditory- nerve rate responses in backgrounds of quiet, noise, and with stimulation of the crossed olivocochlear bundle, *Hearing Res.*, 35 (1988) 165-190.
290. Wright, A., Dimensions of the cochlear stereocilia in man and the guinea pig, *Hearing Res.*, 13 (1984) 89-98.
291. Yamazaki, T., Ogawa, K., Imoto, T., Hayashi, N. and Kozaki, H., Senile deafness and metabolic bone disease, *Am.J.Otol.*, 9 (1988) 376-382.
292. Zemlan FP, ;.Hirschowitz J ; Sautter F ; Garver DL., Relationship of psychotic symptom clusters in schizophrenia to neuroleptic treatment and growth hormone response to apomorphine, *Psychiatry Res.*, 18 (1986) 239-55.
293. Zenner, H.P., K+-induced motility and depolarization of cochlear hair cells Direct evidence for a new pathophysiological mechanism in Meniere's disease, *Arch.Otorhinolaryngol.*, 243 (1986) 108-111.
294. Zenner, H.P., Motile responses in outer hair cells, *Hearing Res.*, 22 (1986) 83-90.
295. Zenner, H.P., Motility of outer hair cells as an active, actin-mediated process, *Acta Otolaryngol.(Stockh.)*, 105 (1988) 39-44.
296. Zenner, H.P., Zimmermann, R. and Gitter, A.H., Active movements of the cuticular plate induce sensory hair motion in mammalian outer hair cells, *Hearing Res.*, 34 (1988) 233-239.
297. Zenner, H.P., Zimmermann, U. and Schmitt, U., Reversible contraction of isolated mammalian cochlear hair cells, *Hearing Res.*, 18 (1985) 127-133.
298. Zurek, P.M., Spontaneous narrowband acoustic signals emitted by human ears, *J.Acoust.Soc.Am.*, 69 (1981) 514-523.
299. Zurek, P.M., Clark, W.W. and Kim, D.O., The behavior of acoustic distortion products in the ear canals of chinchillas with normal or damaged ears, *J.Acoust.Soc.Am.*, 72 (1982) 774-780.
300. Zwicker, E., Objective otoacoustic emissions and their uncorrelation to tinnitus. In H. Feldmann (Ed.), *Proceedings III International Tinnitus Seminar, Muenster 1987*, Harsch Verlag, Karlsruhe, 1987, pp. 75-81.
301. Zwislocki, J.J., Theory of cochlear mechanics, *Hearing Res.*, 2 (1980) 171-182.
302. Zwislocki, J.J., Sharp vibration maximum in the cochlea without wave reflection, *Hearing Res.*, 9 (1983) 103-111.
303. Zwislocki, J.J., Cochlear function - An analysis, *Acta Otolaryngol.*, 100 (1985) 201-209.
304. Zwislocki, J.J., Analysis of cochlear mechanics, *Hearing Res.*, 22 (1986) 155-169.