
Specific Findings in Distortion Product Otoacoustic Emissions and Growth Functions with Chronic Tinnitus

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Abstract: Chronic tinnitus has a very high prevalence in industrialized countries. Latest studies found chronic tinnitus in 4% of the German population, with almost 2% suffering severely in their daily life. Because no curative therapeutic approach is available — neither pharmacological nor surgical — the main focus lies in treatments that enhance the habituation of tinnitus. Habituation occurs in almost 50% of affected patients as a normal process, leading to a complete compensation. This finding is based on the ability of the auditory perception to habituate random noise and focus on important acoustic information. According to our audiological data, 90% of tinnitus patients have deficits in inner-ear function as a generator of tinnitus, mainly in the outer hair cells. This occurrence can be verified by registration of distortion products of otoacoustic emissions. Thus, the main origin of tinnitus is peripheral, and most patients suffer from accompanying hearing loss, even though it is sometimes mild or subjectively not even noticed. In almost 50% of our patients, we find hyperfunction of outer hair cells, again recorded via distortion products of otoacoustic emissions and their growth functions. Normal efferent reduction of distortion products through contralateral acoustic stimulation does not take place in most tinnitus patients. This finding shows that central auditory functions are also disturbed in chronic tinnitus patients, leading to reduced efferent effects on the hair cells and thus impeding habituation. Tests to verify these more central pathological findings have yet to be developed. We have data on diminished ability to distinguish stimuli from random noise by bilateral sound processing: The so-called bilateral masking difference test results are pathological in almost 30% of patients suffering from chronic tinnitus. We concluded from our audiological data that chronic tinnitus is primarily a cochlear dysfunction, but habituation is impeded by accompanying or consecutive deficits of the central auditory pathway. Regarding therapeutic approaches, these central functions can be trained by hearing therapy, as we know from patients' rehabilitation.

Key Words: central auditory processing; efferent control; habituation therapy; otoacoustic emissions; tinnitus

PREVALENCE OF CHRONIC TINNITUS

The prevalence of chronic tinnitus is actually higher than older studies indicated. The latest data from Germany showed that 25% of the

population experienced tinnitus for a short period at one time of their life, 13.8% did so for a longer period, and approximately 4% suffer from tinnitus to an extent requiring special intervention. Of these, 1.5% reported that their daily life was greatly affected by the tinnitus, and some 1% believed that it interfered with their occupation. These data, published by the German Tinnitus League (DTL) [1], probably are the same for all industrialized countries. For Poland, similar data have been published [2]. The main outcome of this study shows that many people experience or suffer from tinnitus, but only a small proportion suffer to an extent requiring treatment. This is certainly owing to the normal habitu-

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ation process, which allows for people who have tinnitus to no longer experience it as disturbing.

Origins of Tinnitus

To date, no known curative medical or surgical treatment is available for addressing chronic tinnitus. We know from our own clinical data that 90% of tinnitus sounds are generated in the internal ear, mainly caused by damage of the outer hair cells (OHCs) [3]. Noise or acoustic trauma may induce decoupling of the OHCs from the tectorial or the basilar membrane. Ionic channels of the OHCs may tear off, viral toxins or other toxic agents may influence stimulus transduction in the hair cells, and stimulus transmission may be disturbed at the synaptic level. Strain may cause spasms of the precapillary blood vessels, resulting in temporary malnutrition of the cochlea. Models for types of tinnitus generation have been proposed by Zenner [4].

However, habituation to tinnitus is a central auditory process; accordingly, persistent suffering of tinnitus patients is connected to deficits within this process. The theoretical background of this auditory sensory habituation is based on understanding the complete process of hearing.

Hearing: Peripheral Hearing and the Central Auditory Pathway

The functions of sound transfer in the middle ear and the treatment of diseases in that area are well-known. Today, even the mechanisms of the inner ear are better known because of new findings of the function and structure of the OHCs [5] and the effective motor protein prestin [6]. However, a correct and sound understanding of the function of the inner ear (i.e., both the sound transfer from hair cells to the acoustic nerve and the peripheral coding of signals) is only partially realized. Already the differentiation between afferent and efferent supply of the hair cells [7] shows the existence of complicated regulating loops controlling the entire auditory pathway, with Corti's organ situated at the peripheral end. In the inner ear, sounds are mainly treated according to the discrimination of place (tonotopy) and time, whereas in higher brain centers and auditory neurons, more and more complex sound patterns are involved. There, single neurons are specialized to respond to certain characteristics. They are activated by certain pitches and blocked by others. They react to the increase or decrease of frequency or to the beginning or ending of sound impulses. Thereby, sound impulses are prepared for further treatment within the auditory cortex by the extraction of certain characteristics: Thus, only the content of information, not the en-

tire signal, is transported to the cortex (processing of information) [8].

This type of specialization of cells and the anatomy of the entire afferent sound path is well-known. The first binaural interaction takes place in the first neuron that ends in the dorsal and ventral nucleus cochlearis in the brainstem. As each inner ear is connected with both brain halves, one part of the neurons leads from the nucleus cochlearis to the nucleus olivaris superior of the same side, whereas the other part crosses over to the opposite side. In the further course, the same happens within the nuclei lemnisci laterales. Through further stations of the sound paths via corpus geniculatum mediale and the radiatio auditiva, the auditory cortex is reached.

The efferent path descends from the auditory cortex down to the corpus geniculatum mediale. The inferior colliculus seems to have a major function in the control of the efferent sound path and, thereby, of the function of enhancement and inhibition. This takes up the descending paths from the cortex itself and from the corpus geniculatum mediale. From there, efferent fibers run to all subordinate brain centers that, in the end, reach again the OHCs of the inner ear [9,10]. Besides providing three-dimensional hearing, a major advantage of such a complex sound path is a sophisticated hearing ability in high-noise areas or in the presence of disturbing sounds.

Diagnosis

One main target is to develop diagnostic tools to prove these functions or deficits by audiological examinations. Function controls for the different sectors of the sound paths are not commonly used in clinical practice; specific microscopical and electrophysiological research is based mainly on findings with cats and rats [11,12].

Objective diagnosis of cochlear function, mainly OHC activity, is based on recordings of otoacoustic emissions. In particular, the frequency-specific measurement of distortion product otoacoustic emissions (DPOAE) can characterize the cochlear amplification process of the OHC, originating as a consequence of nonlinear sound amplification. Calculating DPOAE growth functions can illustrate the activity of hair cells and possible compensation mechanisms after injury.

Research work on the functions and major characteristics of the psychoacoustical hearing process is based mainly on research by Zwicker [13] but, as mentioned, these elements are not very commonly known within general practices. Recently, the binaural masking level difference test, a psychoacoustic test differentiating sound detection in unilateral and bilateral broadband noise, has been evaluated for clinical use [14].

Certain objective controlling methods with humans were tested according to the idea of brain-mapping; here, especially the group working with Hoke and Hoke [15] and Pantev [16] have achieved high merits mainly because of functional nuclear magnetographic measurements. Whereas the derivation of brain cortex potentials is mainly restricted to findings of frequency-specific sound limits, research addressing specific reactions of sound processing (e.g., mismatch negativity [17], contingent negative variation [18], or other processing potentials) has not been sufficiently examined for its ability to provide diagnostic information about the central hearing function.

CLINICAL INVESTIGATIONS

Specific Audiological Findings with Tinnitus Patients

Our own clinical experience showed that many patients, especially those with high-frequency hearing loss and tinnitus, demonstrated an inverse relationship between distortion product (DP) levels and hearing threshold (i.e., displayed an increase of DP levels with increasing hearing loss). DPs could be recorded well in the frequency range that corresponded to the appearance of tinnitus. The DP slope, however, increased with increasing hearing loss and, therefore, did correlate with the hearing threshold, revealing pathological alteration. Another group of tinnitus patients showed a congruent relation between DP levels and threshold and also a congruent relation between threshold and slope or growth function.

Subjects and Method

We examined 220 patients suffering from high-frequency sensorineural hearing loss. Pure-tone audiometry showed normal thresholds (hearing loss not exceeding 10–15 dB HL) in all frequencies from 250 to 2,000 Hz. From 3 to 8 kHz, the hearing loss was 40–60 dB HL. Auditory brainstem responses were recorded, and the wave I–V interpeak interval was measured in an attempt to exclude retrocochlear pathology. Exactly one-half of patients (110) reported high-frequency, tonal tinnitus; the other 110 did not. As a rule, the patients estimated the loudness of the tinnitus somewhat above the audiometric threshold around the tinnitus frequency. The mean frequency of tinnitus was 7,000 Hz; it had existed for an average of 5.6 years.

The reported causes of subjective tinnitus were as follows: noise, 24.6%; psychic strain, 32.7%; sudden hearing loss, 14.5%; and other (accident, surgery, infections), 29.2%. We performed pitch and loudness matching of the tinnitus by means of a clinical audiometer

[19]. We performed the measurements of $2f_1$ – f_2 DPs (where f represents frequency) for all patients at 51 frequencies ranging between $f_2 = 488$ and $f_2 = 8,008$ Hz, with a constant $f_2:f_1$ ratio of 1.2 using Cubedis TM/ Etymotic Research (ER-10C) instrumentation (Mimosa Acoustics, Newark, NJ). Ten stimulus levels, from $L_2 = 65$ dB SPL (sound pressure level) to $L_2 = 20$ dB SPL, were applied, whereby $L_1:L_2$ increased with decreasing primary tone levels according to the equation $L_1 = 0.4 \times L_2 + 39$ dB (for details, see Kummer et al. [20]). DPs were accepted as valid for signal-to-noise ratios exceeding 6 dB. From the numerical data obtained, we reconstructed DP-grams [$L_{dp}(f_2)$] and DP input-output (I/O) functions [$L_{dp}(L_2)$]. To quantify the DP growth, the slope (s) of the I/O functions was calculated between $L_2 = 40$ and $L_2 = 60$ dB SPL, where normal and pathological DP behavior did differ most (Fig. 1). In the lower stimulus level region, both in normal and pathological ears, the I/O functions had similar steep slopes; however, only in the 40- to 60-dB SPL stimulus level region in normally hearing ears did the I/O functions flatten considerably. In pathological ears, however, the steep slope was generally preserved. The slope was calculated if at least three data points fell in the range between $L_2 = 40$ and $L_2 = 60$ dB SPL. To avoid artificial distortion, maximum tone level was restricted to 65 dB SPL. Measurements were performed in a double-walled, soundproof room. The patients were instructed to remain quiet during the measurements. DP measurement took up to 35 minutes. Before the actual experimental is run, in each case the patient's pure-tone threshold is obtained by means of a conventional clinical audiometer.

DP data from 20 normally hearing ears, obtained in the same manner, were used as reference data [20]. The range of 1 standard deviation of the DP level and the slope of the DP I/O functions of these ears served in particular to distinguish the pathological DP pattern.

Results

Fifty-seven patients (51.8%) with tinnitus but only 8 patients (7.3%) without tinnitus showed features of hypermotility of OHCs, characterized as follows [21]: With respect to the audiogram notch, the DP did show a differential sensitivity. Specifically, at high primary tone levels, the DP level did not drop but rather increased. Around the tinnitus frequency, the DP levels were up to 10 dB higher than at the maximum hearing loss. Only with a lowering primary tone level does the DP-gram reflect the audiogram notch, which decreases by some 20 dB. Owing to this, the change in the DP growth behavior was obvious. In the region of normal hearing below 3 kHz, the DP-grams were widely spaced at lower primary tone levels but lay close together at the

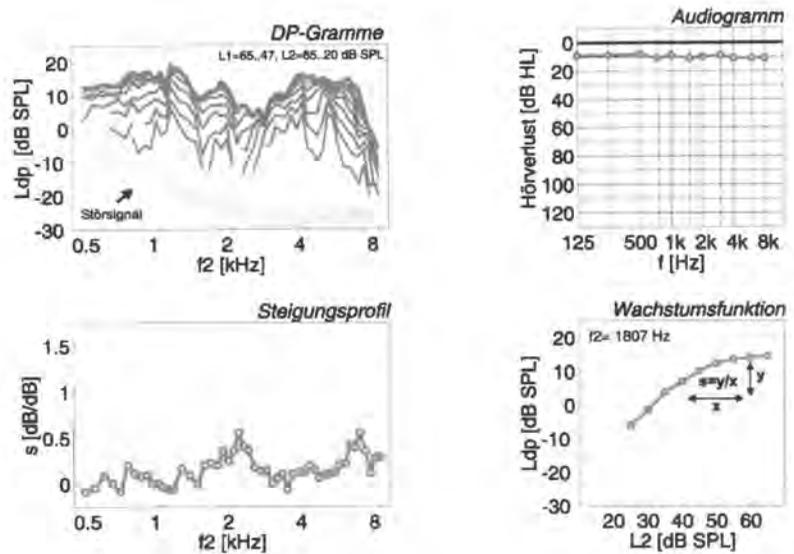


Figure 1. Normal hearing controls and normal, compressive, nonlinear DP-grams, growth function, slope (*s*), and pure-tone audiogram. Reproduced with permission from Janssen et al. [21]. (*DP* = distortion product; *SPL* = sound pressure level.)

higher levels, indicating compressive growth. In the notch region and around the tinnitus, the DP-grams were widely spaced and actually equidistant, revealing linear growth. The difference between the highest and lowest DP levels equaled 30 dB. In the region of normal hearing, the *I/O* functions were alike, having a steep slope (up to 1 dB/dB) in the lower primary tone level region and a flat run (as low as 0.1 dB/dB) in the upper level, characteristic for normal hearing. This can be seen in a comparison of the individual data and its range of plus or minus the standard deviation of the DP level of the normally hearing control group at the corresponding frequencies.

The DP growth predominantly changed at primary tone levels above $L2 = 40$ dB SPL. Below $L2 = 40$ dB SPL, the respective *I/O* functions ran almost parallel, the slopes of both being near 1 dB/dB. In the tinnitus region, the DP did behave differently. Above $L2 = 40$ dB SPL, the DP level were higher, the difference amounting to almost 10 dB. At lower primary tone levels, the DP level was either equal or lower. Taking into account the amount of hearing loss around the tinnitus, these high DP levels are fairly surprising and could result in incorrect conclusions about cochlear integrity. However, the steep *I/O* function unambiguously indicates the pathological state.

To quantify the DP growth, the slope was calculated between $L2 = 40$ and $L2 = 60$ dB SPL, where a flat course occurred in the normal hearing state and a steep course in the pathological state. Calculation of the slope between 40 and 60 dB SPL was chosen because, in that range, normal and pathological DP growth did differ most. Corresponding to the threshold run, the slope increased rapidly on the low-frequency side of

the notch but gradually decreased on the high-frequency side. The DP level yields an ambiguous pattern at different primary tone levels. Thus, the slope reflected the threshold better than did the DP level. Also, high slopes were found between 2 and 3 kHz, possibly revealing a disturbance that was not reflected in the behavioral audiogram (Fig. 2).

Between 1 and 3 kHz, where the hearing threshold L_1 was within normal limits, the DP levels were unusually low. The DP-grams at high primary tone levels, however, lay close together, indicating normal compressive growth behavior. Above 3 kHz, where the threshold continuously increased up to 45 dB, the DP level rose by more than 10 dB, demonstrating a run that was actually inverse to that of the hearing threshold. This means that an increase of the DP level occurred with increasing hearing loss. Even at lower primary tone levels, the DP level did not decrease with increasing hearing loss. Only the growth behavior of the DP did correlate to the hearing loss: The distance of the DP-grams increased, demonstrating a linear (i.e., pathological) growth behavior. The slope, which was within the normal range in the frequencies up to 3 kHz, rose considerably above that range where the hearing threshold started to increase and reached values of 1 dB/dB.

However, 92.7% of the nontinnitus patients but only 48.2% of the patients with high-frequency hearing loss and tinnitus showed congruent relations between both hearing threshold and DP-grams and congruent relation between hearing threshold and growth functions (as exemplified in Figure 3). The patient whose record is depicted in this figure suffered from high-frequency steep-sloping hearing loss of up to 70 dB HL at 8 kHz; tinnitus was measured with a loudness of 75 dB and

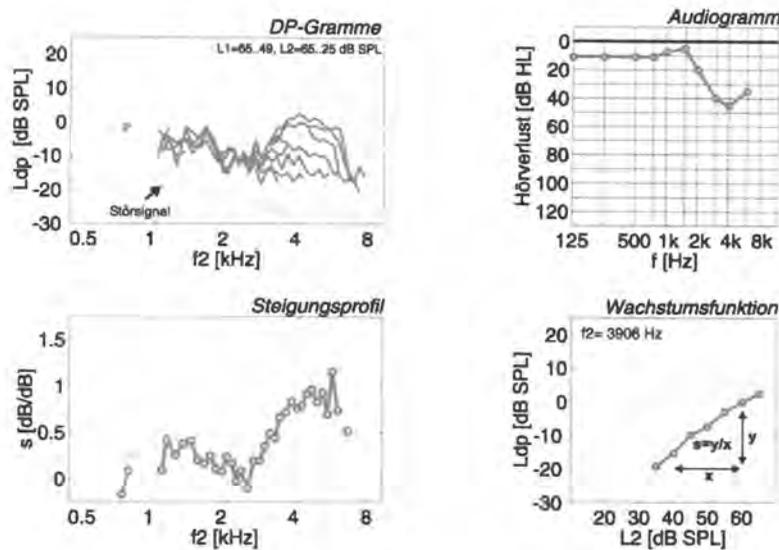


Figure 2. Patient with sudden hearing loss and tinnitus measured at 6 kHz: DP-gram, growth function, slope (*s*), and pure-tone audiogram. Reproduced with permission from Janssen et al. [21]. (*DP* = distortion product; *SPL* = sound pressure level.)

8,000 Hz. Here, the DP level decrease between 2 and 4 kHz corresponded to the increasing hearing loss, resembling most of the nontinnitus ears. Most distinctly, the DP level decreased at lower primary levels, as indicated by the spread of the DP-grams, changing the DP growth functions to a linear process. The slope, which was within or slightly above the normal range below 1.5 kHz, rose considerably with increasing hearing loss up to approximately 1 dB/dB.

Specific Audiological Findings with Hyperacusis Tinnitus Patients

Similar findings led us to examine these functions with hyperacusis patients with normal subjective hearing on

pure-tone audiogram. We examined 72 patients with a mean age of 35.9 years (range, 17–59 years; 53% male, 47% female). Tinnitus was mainly bilateral, with a mean frequency of 6,000 Hz; 66.2% of subjects described their tinnitus as tonal. We measured hyperacusis by pathological loudness scaling and decreased loudness discomfort levels (< 70 dB HL). Pure-tone audiograms and DP-grams were measured as explained earlier.

Hearing thresholds were normal in all patients, with a maximum hearing loss of > 15 dB HL. According to DP growth functions, 49 patients (68%) showed normal to high DP levels and increased slopes of I/O functions; 18 patients (25%) had normal DP emissions and growth functions; and 5 patients (7%) had decreased DP levels and increased slopes of growth function.

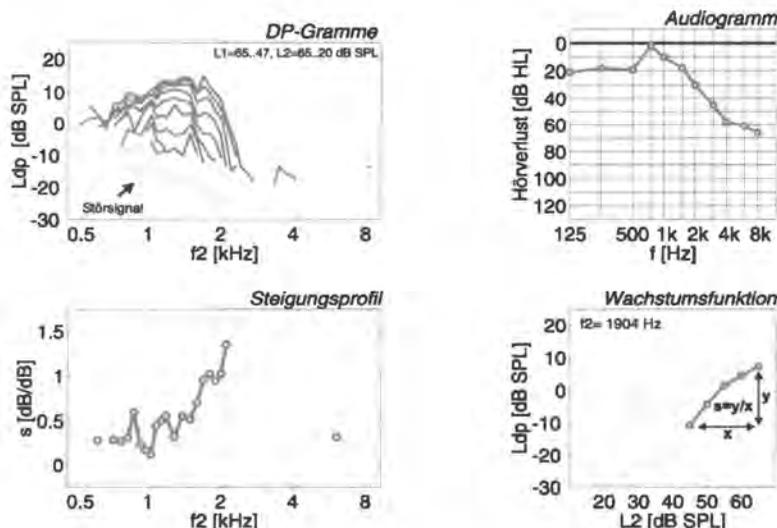


Figure 3. Patient with progressive cochlear hearing loss and tinnitus at 8 kHz: DP-gram, growth function, slope (*s*), and pure-tone audiogram. Reproduced with permission from Janssen et al. [21]. (*DP* = distortion product; *SPL* = sound pressure level.)

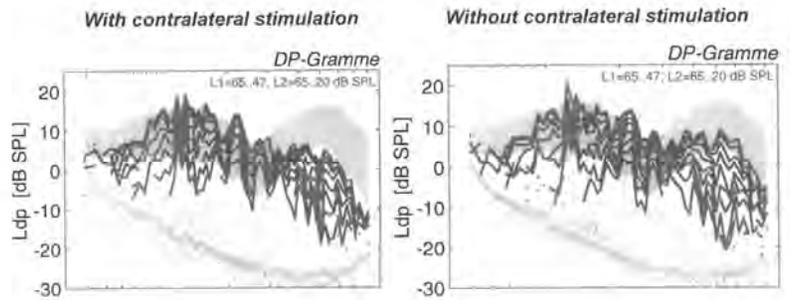


Figure 4. In normal-hearing individual, distortion product otoacoustic emission amplitudes decreased after contralateral stimulation with a 60-dB broadband noise. (*DP* = distortion product; *SPL* = sound pressure level.)

Effects of Contralateral Stimulation on DPOAE Recordings

Studies by Plinkert et al. [22], Chery-Croze et al. [23], and Liberman et al. [24] proved that acoustic stimulation controls hair cell activity (i.e., OHCs) via the olivocochlear bundle. With contralateral stimulation, the tuning curves of the cochlea and the acoustic nerve flatten. Regarding the DPOAE recordings, contralateral sound decreases the emissions; thus, the amplitudes are reduced. Accordingly, if tinnitus is influenced by malfunction or is even due to deregulation of efferent auditory control, it should be interesting to examine the effects of lateral inhibition (via contralateral sound) with tinnitus patients.

Between the years 2001 and 2002, we examined 127 patients with tinnitus and an almost normal hearing threshold. Their mean age was 42.5 years; the male-female ratio was 45.2–54.8%. Acting as controls were 41 normally hearing nontinnitus individuals (average age, 33.5 years). DPOAEs were recorded according to the described paradigm in a session with and without a contralateral sound stimulus of 60 dB HL.

In individuals in the control group ($n = 41$), the average amplitude reduction was 1.76 dB, with a standard deviation of 1.14 dB. In tinnitus patients, this reduction was much smaller: The average reduction was only 0.91 dB ($SD = 1.59$ dB). This proved to be significant in a statistical evaluation (t -test: $p = .002$; Figs. 4 and 5). Differentiating these effects further led us to analyze certain frequency partitions: With tinnitus patients,

the amplitude reduction was significantly larger in the high frequencies (4–8 kHz; Fig. 6), whereas in the normally hearing controls, the largest reduction occurred in the low frequencies (0.5–2.0 kHz; Fig. 7); amplitudes in general were reduced significantly more.

All these findings give evidence that in a great number of tinnitus and hyperacusis patients, the efferent regulation of the OHCs fails or is even turned off completely.

DISCUSSION

Our audiological data show specific findings in many tinnitus and hyperacusis patients, although they are not similar in all such patients. In general it is assumed, that OHC activity is the source of DPs [22,25]. Decreased DP levels and increased growth functions seem to be proof of diminished sensitivity and tuning of the cochlear amplifier. Increased DP emissions and increased slope of I/O functions, however, seem to reflect a specific impairment in OHC micromechanics, wherein a reinforced distortion generates—and might be responsible for—some type of tinnitus. Presumably, this matches only for so-called motor tinnitus, the type of tinnitus confined to destruction or decoupling of the OHCs [4].

Similar to these findings with tinnitus patients [26,27], our data show the same effect with 68% of normally hearing hyperacusis patients. However, in tinnitus patients without hyperacusis, this inverse reaction

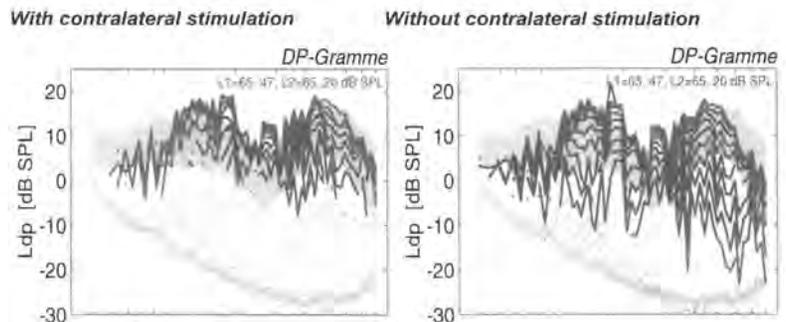


Figure 5. Distortion product otoacoustic emission in patient with tinnitus of 4 kHz. Note similar amplitudes with and without contralateral acoustic stimulation. (*DP* = distortion product; *SPL* = sound pressure level.)

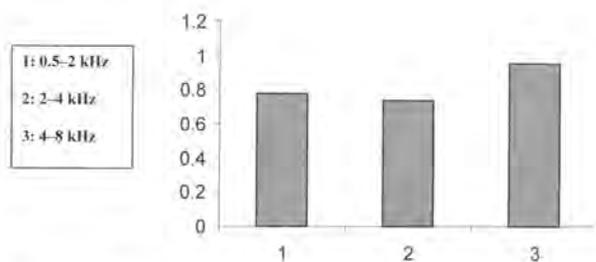


Figure 6. Distortion product otoacoustic emission amplitude reduction in certain frequencies in tinnitus patients.

or hypermotility of OHCs is restricted to the tinnitus frequency; in hyperacusis patients, it seems to reflect a wider range of frequencies.

These results suggest that in many hyperacusis patients and in tinnitus patients, some alteration of auditory processing already occurs on the cochlear level. Most probably, hyperacusis as an oversensitivity to all sounds is due to an inefficient input control of sounds or even overamplification of incoming sound [28]. This dysfunction is mainly the result of disturbances in the cortical network of auditory processing that leads either to ineffective or diminished efferent control of the auditory pathway [9] or to an efferent overactivity on all levels, including that of the OHCs.

Our results in comparing otoacoustic emissions with and without contralateral stimulation emphasize this hypothesis: that 38% of patients with tinnitus showed these signs of deficient efferent inhibition (e.g., lack of amplitude reduction and linear growth functions). Thus, audiological analysis, especially recording of DPOAEs, provides objective signs of different auditory processing in at least 40–50% of tinnitus patients. Therein, the cortical reflection of incoming sound or electric activity leads, via smaller or ineffective efferent inhibition, to hyperactivity in the OHCs, where it then can be recorded.

Definitely these findings must be studied further. Instruments and specific tests for central auditory func-

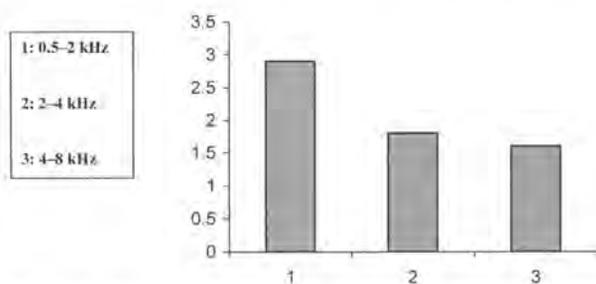


Figure 7. Distortion product otoacoustic emission amplitude reduction in certain frequencies (controls).

tion also must be developed to give evidence to these deficits of efferent control: They must be easily applicable so as to be used on a wider clinical scale.

CONCLUSIONS

Until today, tinnitus perception could not be influenced by any medicine without completely destroying the sense of hearing or incurring the risk of severe side effects. Optimization of cochlear blood flow and oxygen supply may be efficient in acute types of OHC damage, especially after acoustic trauma or sudden sensorineural hearing loss. Antiarrhythmic agents such as lidocaine can stop tinnitus in perhaps 50% of cases but only temporally for the time of infusion [29]. Side effects, conversely, are very serious and forbid longer application of this medicine.

Some approaches involve implanting special catheters, placing them at the area close to the round window and trying to apply medicine with a special dosage pump as a local therapy for the inner ear. First results, however, are not very promising [30]. The agents thus far tested (e.g., vasoactive substances, steroids, lidocaine, or Caroverine) did not have any effect on the persistence of tinnitus if applied locally [31].

Surgical approaches (except, of course, surgery that treats such middle-ear diseases as otosclerosis and thus preserves or restores hearing as the main goal) are restricted to cutting the acoustic nerve, with its known complications. However, even in these cases, more than 50% retain their tinnitus owing to central excitation of a primarily peripherally generated sound [32].

Therefore, as curative treatments are far from being applicable, the focus of tinnitus therapy is trained on habituation processes [33]. This process works the innate ability of the auditory system to alter the perception of random noise if its meaning is not connected to such emotions as fear or anger. This ability of the auditory perception can be developed and trained even in older people by using the filter capacities of the efferent system, with its effects on all parts of the auditory pathway, including the OHCs.

With our clinical data, we could prove that in a large number of tinnitus patients, these deficits of central auditory processing and efferent inhibition can be recorded. Our results further indicate that in many tinnitus and hyperacusis patients, abnormal hypermotility of OHCs may occur even if hearing is completely normal. Thus, training of these central auditory abilities and functions [34] is a promising approach to facilitate tinnitus and hyperacusis habituation [14]. The recorded audiological data play an important role in our understanding of tinnitus generation in at least some patients. They are also very helpful for the counseling of patients

and for preventing further frustrating and expensive therapeutic failures.

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