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Διπλωματική Εργασία

« ΥΠΕΡΑΚΟΥΣΙΑ : ΑΝΑΣΚΟΠΗΣΗ ΤΩΝ ΠΑΘΟΦΥΣΙΟΛΟΓΙΚΩΝ ΜΗΧΑΝΙΣΜΩΝ »

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CONTENTS

PREFACE

During the training years to become an Otorhinolaryngologist , audiological and otological pathologies are from the most frequent diseases that are dealed with in the Emergency Department and the Outpatient Clinic. The vast majority of patients is complaining for ear infections, hearing loss, tinnitus, dizziness/vertigo and balance issues in general, all of which are taught to a degree during the residency years to the young Doctor, and very often dealt with later by the ENT Specialist in a Hospital base or in a private clinic.

There are a only a few patients who complain for sound intolerance, and even less who experience pain from sound , and seek medical help because this hypersensitivity to ordinary sounds (that don't seem to annoy all the others), results in distress, to a degree that can affect daily activities, work, social and personal life.

Dysregulation of loudness perception can represent a serious clinical problem for both the Otologist-Audiologist and the patient. Among several definitions, hyperacusis can be defined as "intolerance to ordinary environmental sounds", although even basic terminology and definitions that are used present important variation in this research area, which mainly the last few decades attracts more research interest. Hyperacusis can take place as the only complaint, but more frequently it co-exists with tinnitus, hearing loss and other non otological symptoms. It has several potential mechanisms which are not mutually exclusive; Hyperacusis can probably be associated with both peripheral and central mechanisms, which is similar to tinnitus and hearing loss.

In this review we try to summarise what is known of hyperacusis pathophysiology, as related to specific medical conditions or as a sole presenting symptom. The understanding of the pathophysiological basis of hyperacusis, although complex, will facilitate researchers to categorise patients in distinct homogeneous groups with possible different characteristics ,and thus will help the development of novel therapies for this often devastating disorder.

ΠΕΡΙΛΗΨΗ

Εισαγωγή: Οι διαταραχές της ακουστότητας αποτελούν ένα σοβαρό κλινικό πρόβλημα τόσο για τον Ωτολόγο-Ακοολόγο όσο και για τον ασθενή. Ανάμεσα σε πολλούς ορισμούς, η Υπερακουσία ορίζεται ως "Δυσανεξία σε συνηθισμένους καθημερινούς ήχους", αν και ακόμα και η βασική ορολογία και οι ορισμοί που χρησιμοποιούνται εμφανίζουν μεγάλη ποικιλία, σε αυτό το ερευνητικό πεδίο που κυρίως τις τελευταίες δεκαετίες προσελκύει ερευνητικό ενδιαφέρον. Η υπερακουσία μπορεί να εμφανιστεί μεμονωμένα, αλλά πιο συχνά συνυπάρχει με εμβοές και άλλα μη ωτολογικά συμπτώματα. Έχει πολλούς πιθανούς παθοφυσιολογικούς μηχανισμούς που δεν αποκλείουν ο ένας τον άλλο. Συσχετίζεται και με περιφερικές και με κεντρικές διαταραχές, όπως και οι εμβοές και η βαρηκοΐα. Σε αυτήν την ανασκόπηση επιχειρούμε να καταγράψουμε τα σύγχρονα δεδομένα για την παθοφυσιολογία της υπερακουσίας, σε σχέση με συνυπάρχουσες παθήσεις ή ως μεμονώμενο σύμπτωμα.

Μέθοδος: Οι μελέτες θα επιλεγούν με βάση τα ακόλουθα κριτήρια:

Μελέτες που επικεντρώνονται στους μηχανισμούς της υπερακουσίας σε ασθενείς που έχουν μόνο υπερακουσία ή υπερακουσία ως πρωταρχικό σύμπτωμα ή ως μέρος μιας ομάδας συμπτωμάτων. Μελέτες με πειραματόζωα συμπεριλαμβάνονται στην αναζήτηση εφόσον εστιάζουν στην παθοφυσιολογία. Οι βάσεις δεδομένων που χρησιμοποιήθηκαν είναι οι Medline και GoogleScholar. Προκειμένου να συμπεριληφτούν όσες περισσότερες σχετικές μελέτες, έγινε και προσωπική μη αυτόματη αναζήτηση σχετικών εργασιών, οι οποίες είχαν τον όρο υπερακουσία και εστίαζαν σε κάποιον παθογενετικό μηχανισμό. Όλοι οι τύποι μελετών με διαθέσιμο πλήρες κείμενο συμπεριλήφτηκαν στην διαδικασία αναζήτησης. Μελέτες που δημοσιεύθηκαν τα τελευταία 10 έτη σε αγγλική γλώσσα (Medline και GoogleScholar) συμπεριελήφθησαν.

Αποτελέσματα: Συγχρονα δεδομένα σχετικά με την ορολογία, διερεύνηση και αντιμετώπιση της υπερακουσίας καταγράφονται. Πρόσφατα δεδομένα για την ανατομία και φυσιολογία του έσω ωτός και την φυσιολογία της υποκειμενικής αίσθησης ακουστότητας των ήχων θα αναλυθουν εν συντομία. Περιφερικοί και κεντρικοί παθοφυσιολογικοί μηχανισμοί που συμμετέχουν στην υπερακουσία και συγκεκριμένες αιτίες καταγράφονται και αναλύονται.

Συζήτηση: Η σύγχρονη βιβλιογραφία υποδεικνύει ότι διαφορετικές μορφές υπερακουσίας προκαλούνται από διαφορετικούς παθογενετικούς μηχανισμούς. Στους περισσότερους ασθενείς με υπερακουσία δεν μπορεί να βρεθεί συγκεκριμένη αιτία. Οι αιτίες μπορούν να χωριστούν σε τρείς κατηγορίες : α) περιφερική ακουστική διαταραχή β) κεντρική ακουστική διαταραχή γ) άλλες κατηγορίες . Οι μεταβολές των ακουστικών ερεθισμάτων εξαιτίας βαρηκοΐας (που καταγράφεται ή όχι στο τονικό ακοόγραμμα) δημιουργούν μηχανισμούς ενίσχυσης του ακουστικού κέρδους εντός των κεντρικών ακουστικών οδών, και αποτελούν σημαντικό παθοφυσιολογικό μηχανισμό της υπερακουσίας.

Συμπεράσματα: Η κατανόηση της περίπλοκης παθοφυσιολογίας της υπερακουσίας αποτελεί τη βάση για την κατηγοριοποίηση των ασθενών σε ομοιογενείς ομάδες με διακριτά κλινικά χαρακτηριστικά, και επομένως θα διευκολύνει την ανάπτυξη νέων θεραπευτικών μέσων για αυτή την ιδιαίτερη παθολογία της ακοής.

ABSTRACT

Introduction : Dysregulation of loudness perception can represent a serious clinical problem for both the Otologist-Audiologist and the patient. Among several definitions, hyperacusis can be defined as “intolerance to ordinary environmental sounds”, although even basic terminology and definitions that are used present important variation in this research area, which mainly the last few decades attracts more research interest. Hyperacusis can take place as the only complaint, but more frequently it co-exists with tinnitus and other non otological symptoms. Hyperacusis has several potential mechanisms which are not mutually exclusive; Hyperacusis can probably be associated with both peripheral and central mechanisms, which is similar to tinnitus and hearing loss. In this review we try to summarise what is known of hyperacusis pathophysiology, as related to specific medical conditions or as a sole presenting symptom.

Methods: Studies will be selected according to the following criteria:

Studies focused on the mechanisms of hyperacusis in patients complaining for hyperacusis only or hyperacusis as the primary complaint or as a symptom of a non otological syndrome. Animal studies trying to identify a potential mechanism of hyperacusis were included as well.

Medline and Google Scholar will be searched for eligible studies. In addition, to include as many relevant studies as possible, manual searches of any relevant article which had hyperacusis and a possible mechanism/cause in the title was performed.

All type of studies with full-text availability will be included in the research process. There will be restriction concerning the year of publication, including publications of the last 10 years (for Medline and Google Scholar) . Only studies published in English will be included.

Outcomes: Updated data regarding the terminology, assessment, and management of hyperacusis will be presented . Recent knowledge for the anatomy and physiology of the inner ear and the process of loudness neural encoding will be briefly reviewed. Peripheral and central mechanisms leading to the generation of hyperacusis and specific causes of hyperacusis related to pathophysiology is analysed.

Discussion: Current evidence suggests that different forms of hyperacusis may be mediated by distinct mechanisms. In most patients with hyperacusis, no specific medical cause can be diagnosed. In patients with hyperacusis as part of a symptoms set, possible causes of hyperacusis can be divided into three different groups: a) peripheral auditory system disorders b) central nervous system disorders c) other groups of causes. Changes to auditory input due to hearing loss (including hidden hearing loss) can lead to mechanisms of enhancement of central gain which is described as an important mechanism for loudness hyperacusis.

Conclusion: The understanding of pathophysiological basis of hyperacusis, although complex, will facilitate researchers to categorise patients in distinct homogeneous groups with different characteristics ,and thus will help the development of novel therapies for this often devastating disorder.

Key words: Hyperacusis, Mechanisms, Pathophysiology

ABBREVIATIONS

5-HT	5-hydroxytryptamine (Serotonine)	Σεροτονίνη
AF	Afferent Fibers	Κεντρομόλες ίνες
AN	Auditory Nerve	Ακουστικό Νεύρο
ANF	auditory nerve fiber	Ακουστική νευρική ίνα
ANFI	type I Auditory Nerve Fibers	Ακουστική νευρική ίνα τύπου Ι
APs	action potentials	Δυναμικά ενέργειας
ARTs	Auditory Reflex Thresholds	Ουδός έκλυσης ακουστικού αντανακλαστικού
ASD	Autism Spectrum Disorders	Φάσμα Αυτιστικών Διαταραχών
CBT	Cognitive Behavioural Therapy	Γνωσιακή Συμπεριφορική Θεραπεία
CNS	Central Nervous System	Κεντρικό Νευρικό Σύστημα
DR	Dynamic Range	Δυναμικό εύρος
DST	Decreased Sound Tolerance	Μειωμένη ανοχή σε ήχους
HL	Hearing Level	Επίπεδο ακοής
HQ	Hyperacusis Questionnaire	Ερωτηματολόγιο Υπερακουσίας
HT	Hearing Threshold	Ουδός ακοής
IHCs	Inner Hair Cells	Έσω τριχωτά κύτταρα
iPhC	Inner Phalangeal Cells	Έσω φαλαγγικά κύτταρα
LDLs	Loudness Discomfort Levels	Ουδός δυσανεξίας στον ήχο
LOC	Lateral Olivo-Cochlear	Έξω ελαιο-κοχλιακή δέσμη
MASH	Multiple-Activity Scale for Hyperacusis	Κλίμακα πολλαπλών Δραστηριοτήτων για την Υπερακουσία
MGB	Medial Geniculate Body	Έσω γονατώδες σώμα
MOC	Medial Olivo-Cochlear	Έσω ελαιο-κοχλιακή δέσμη
OHCs	Outer Hair Cells	Έξω τριχωτά κύτταρα
SFR	Spontaneous Firing Rate	εύρος αυτόματων εκφορτίσεων
SR	spontaneous rate	εύρος αυτόματων
TRT	Tinnitus Retraining Therapy	Θεραπεία επανεκπαίδευσης για τις Εμβοές
ULLs	Uncomfortable Loudness Levels	Ουδός δυσανεξίας στον ήχο

INTRODUCTION

Title

"Hyperacusis : review of pathophysiological mechanisms"

Citation

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Keywords

Hyperacusis, Mechanisms, Pathophysiology

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Background – Rationale

Disorders of loudness perception can represent a serious clinical problem for both the Otologist-Audiologist and the patient. Hyperacusis has been defined as 'unusual intolerance to ordinary environmental sounds' (1) although even basic terminology and definitions still varie in this under-researched area.
Like hearing loss and tinnitus, hyperacusis probably can be associated with both peripheral and central factors (2). Hyperacusis has several potential mechanisms which are not mutually exclusive; as with tinnitus, the patient population is likely to be heterogeneous (3).

In this review we try to summarise what is known of hyperacusis mechanisms and pathophysiology, as related to specific medical conditions or as a sole presenting symptom.

METHODS

Eligibility criteria

Studies will be selected according to the following criteria:

Participants:
Studies focused on the mechanisms of hyperacusis in adults and children complaining only for hyperacusis or hyperacusis as the primary complaint or as a symptom of a non otological syndrome. Animal experiments trying to identify a potential mechanism of hyperacusis were included as well.

All type of studies with full-text availability will be included in the research process. There will be restriction concerning the year of publication, including publications of the last 10 years (for Medline and Google Scholar) . Only studies published in English will be included.

Information Sources

Medline and Google Scholar will be searched for eligible studies. In addition, to seek further eligible documents for inclusion, manual searches of the reference lists of any relevant review articles which had hyperacusis and a possible mechanism/cause in the title was performed. The final manual search was conducted in November 2019.

Search strategy

Pubmed

Pubmed syntax
Search terms for hyperacusis (free text and MesH terms)
1#hyperacusis
2#"hyperacusis" [MeSH]
3# 1 OR 2
4#"mechanisms"
5#"pathophysiology"
6#"genesis"
7#"basis"
8#4 OR 5 OR 6 OR 7

9#"tinnitus"
10#"recruitment"
11#"phonophobia"
12# "misophonia"
13#9 OR 10 OR 11 OR 12
So we have the following syntax :

3# AND #8 NOT #13

(("Hyperacusis"[Mesh]OR "hyperacusis") AND (mechanisms[Title/Abstract] OR pathophysiology[Title/Abstract] OR basis[Title/Abstract] OR genesis[Title/Abstract])) NOT (tinnitus[Title] OR recruitment[Title] OR phonophobia[Title] OR misophonia[Title]) AND "last 10 years"[PDat]

Google scholar

Google scholar syntax:

allintitle: hyperacusis mechanisms OR pathophysiology OR basis OR genesis OR aetiopathology -tinnitus -recruitment -phonophobia -misophonia

Results - Outcomes

Search records were screened by the author, first screening by title and abstract and then by full text.

From the total number of studies yielded from PubMed and Google Scholar (35 and 11 respectively), initially 5 were eliminated (2 duplicates and 3 different publication reports of the same book). Another 7 were excluded because the title and abstract indicated that the article did not fit our eligibility criteria. Most commonly these studies excluded because they did not focus on hyperacusis or did not report a specific mechanism of hyperacusis.

14 records were excluded at the full-text screening stage. Commonly, this was because the record did not report specifically on the pathophysiology of hyperacusis.

Manual searches (without date of publication exclusion criteria) in reference lists of the included records identified a further 31 articles which were subjected to full-text screening and included in the final reference list.

DEFINITIONS

Numerous descriptions of hyperacusis have been used, but there are no universally accepted definitions (2).

Hyperacusis has been defined as ‘unusual tolerance to ordinary environmental sounds’ (1) which seems to be a widely accepted definition of the condition.

Some have defined hyperacusis as a heightened awareness of sounds. Hyperacusis has also been described as a disturbed loudness function. Sounds that are perceived as moderately loud by people with normal hearing and without hyperacusis are perceived as very loud by someone with hyperacusis. Others have referred to an abnormally strong response to moderate sound, a pathological auditory hypersensitivity , as a discomfort for sounds that would be acceptable to most normally hearing people, an increased auditory sensitivity, a noise sensitivity, an audiosensitivity , a soft sound sensitivity, or a select sound sensitivity.

Hyperacusis has been referred to as a sound intolerance problem (17).

To summarise, definitions and descriptions of hyperacusis have included heightened awareness, hypersensitivity, loudness discomfort, hyperresponsiveness, intolerance, phonophobia, irritability, misophonia, annoyance, fear, and pain.

Tyler et al (2) suggests that a distinction of the different forms of hyperacusis should focus on loudness, annoyance, fear, and pain . People with hyperacusis can experience these different reactions singly or in combination. The loudness percept could be considered as a basic primary psychoacoustical response, and the annoyance and fear could be considered as self-report emotional reactions. Pain hyperacusis might be one or the other, or both (2).

Jastreboff and Jastreboff (10) divided disorders of sound tolerance in four subgroups: recruitment, hyperacusis, phonophobia and misophonia (4).

Phonophobia (fear of sound) and misophonia (dislike of sound) (3), both carry a suggestion that the intolerance may be specific to certain sounds with emotional associations. In neurology, phonophobia tends to be used specifically for the loudness intolerance reported by some patients with migraine (3).
Loudness recruitment describes an experience commonly associated with cochlear hearing loss and specifically with dysfunction of the outer hair cells of the organ of Corti: as the level of a sound rises, the perceived loudness increases faster than normal. This phenomenon may be distinguished from hyperacusis if the individual perceives sound of large intensity as uncommonly loud (recruitment) or sound of low or moderate intensity as uncomfortably loud (hyperacusis). The two conditions are not mutually exclusive, and patients with sensorineural hearing loss can have both recruitment and hyperacusis.

PREVALENCE

Lack of robust epidemiological data is a major shortcoming of the published work on hyperacusis.
Fabijanska et al. (5) undertook a postal questionnaire of tinnitus in Poland which included an unspecified question on hyperacusis. Of the 10 349 respondents, 15.2% reported hyperacusis (12.5% of males, 17.6% of females).
More recently Andersson and co-workers (6) investigated the prevalence of hyperacusis in the adult Swedish population.
Two methods were used—an internet study and a postal population study. Of 1167 individuals who clicked upon the web banner 595 responded, a response rate of 52%. The point prevalence of hyperacusis in this group was 9%. The postal group comprised 987 individuals of whom 589 responded (response rate 60%) and the point prevalence was 8%. Participants were not asked if they had ever sought a medical opinion regarding their hyperacusis.
Another large scale questionnaire-based study revealed a prevalence of 2.2% for physician diagnosed hyperacousis and 10.5% for self-reported hyperacousis in Swedish population (7).

Regarding the prevalence of hyperacusis in children, Coelho et al. (2007) assessed hyperacusis in a randomly selected group of 506 children from Brazil (5–12 years of age), and they reported a 3.2% prevalence by questionnaire (annoyance hyperacusis) and a 1.2% prevalence by lowered ULL (loudness hyperacusis) (8) . In a study of 7096 11-year old children in the UK, 3.7% answered affirmatively to the question “do you ever experience oversensitivity or distress to particular sounds?” (9).

A coincidence of tinnitus complaint and hyperacusis has been widely noted. Among patients attending tinnitus clinics with a primary complaint of tinnitus the prevalence of hyperacusis is about 40%(10); and in patients with a primary complaint of hyperacusis the prevalence of tinnitus has been reported as 86%(11).

However, Andersson et al. (12) found that only 21% (Internet sample) and 9% (postal sample) of people reporting hyperacusis also reported tinnitus.
The apparent link has led to speculation about common mechanisms. The variation in the prevalence of tinnitus with hyperacusis across studies is influenced by different definitions and criteria for diagnosing hyperacusis and tinnitus. It should also be noted that much of the literature on tinnitus and hyperacusis comes from tinnitus clinics and might not be representative of the general population.

DIAGNOSTIC PROCEDURES, MEASURING HYPERACUSIS

Measuring Uncomfortable Loudness Levels (ULLs) and Dynamic Range (DR) for both ears and over a range of frequencies is an important diagnostic first step (13).
There is general agreement in the literature that ULL estimates of decreased sound tolerance provide a valid clinical measure of the threshold of discomfort for sound (4). A method for ULLs (or Loudness Discomfort Levels, LDLs) is proposed by the British Audiological Association.
Sherlock and Formby (14) noted that ULLs for listeners with normal hearing varied greatly, with some being as low as 80 dB HL. Anari and colleagues (11) suggested that ULLs of 70 dB HL or less be used as a criterion for diagnosing loudness hyperacusis.
Different criteria regarding the range of DR and ULLs have been used among researchers . In the literature, it has been suggested that LDLs below 100 dB HL might indicate hyperacusis , or LDLs below 90 dB HL at least at two frequencies (15).

Anari et al. (11) studied 100 patients with hyperacusis. Most patients had normal or near-normal HTs. LDLs were measured at 0.5, 1, 2, 3, and 4 kHz, and were similar across frequencies, averaging between 75 and 80 dB HL, thus showing a decrease compared to normal values, which are in the order of 100–105 dB HL (14).
A similar decrease of LDLs in subjects with hyperacusis has been reported by Formby et al. (14) for LDLs measured at 1, 2, 4, and 8 kHz. So far, LDLs at frequencies below 0.5 kHz have not been reported, and no study has investigated the full range of audiometric frequencies.

In another study (16), audiometric data from 381 patients with a primary complaint of hyperacusis have been analysed. On average, the LDLs are almost flat across frequencies from 125 to 8 kHz, and decreased by about 16–18 dB compared to a reference group .

Therefore, it is suggested that LDL measurements can only be one aspect to diagnose hyperacusis, in addition to other symptoms like annoyance, discomfort, and fear of sound (6).

There are several interval and category scales used to measure loudness (13).
Tyler et al. suggested a clinical procedure for measuring loudness hyperacusis. Patients were asked to assign a number from 0 to 100 to represent the loudness of tones, with 100 described as representing the loudest tone that they could imagine. Lower level sounds were presented first (so as not to frighten the patient), and the highest sound level used was that which produced a loudness rating of 80. Such loudness growth

functions provide additional confidence in the diagnosis of loudness hyperacusis or may be used in place of the potentially more unpleasant determination of ULLs (13).

QUESTIONNAIRES

Only a few questionnaires have been developed to quantify-assess decreased sound tolerance. The evidence to support their validity is limited (4). Some commonly used questionnaires are :

The *Hyperacusis Questionnaire (HQ)* was developed in France by Khalfa et al. (17).

There is reasonable body of evidence on the development and reliability of the HQ as a diagnostic tool, but the validity and reliability of the HQ as an outcome measure are yet to be fully examined (8).

The Multiple-Activity Scale for Hyperacusis (MASH) was developed in France by Dauman and Bouscau-Faure in 2005 (18).

The German Questionnaire on Hypersensitivity to Sound (GUF) developed in 2002 (19) but is not frequently used among researchers.

TREATMENT OPTIONS

Recently a scoping review was published, that focused on management strategies used for hyperacusis, the definitions of hyperacusis, tools used for assessment and evaluation, and future research priorities (8).

The research result was that more than half of the research currently reported was based on individual case studies and therefore cannot be generalised. In addition to this, management strategies were typically evaluated in patients reporting hyperacusis as a secondary complaint or

as part of a symptom set, and as such the outcomes reported only provided an indication of effectiveness for hyperacusis.

There is a lack of sufficient evidence to identify effective management strategies. These findings highlight an urgent need for controlled trials to evaluate the effectiveness of management strategies for patients experiencing hyperacusis.

Management strategies that are applied to patients with hyperacusis include:

Cognitive Behavioural Therapy (CBT), Tinnitus Retraining Therapy (TRT) , counselling,

sound generating devices, pharmacological therapy, and surgery.

Cognitive Behavioural Therapy.

CBT principles are aiming to educate, target overt emotional reactions to sounds though graded exposure to sounds, reduce stress though relaxation, and provide patients with the tools to manage more difficult situations and restart activities (behavioural activation).

Briefly, the treatment includes education, applied relaxation, graded exposure to sounds, and cognitive therapy for distressing thoughts and beliefs regarding sounds (13).

Tinnitus Retraining Therapy (**TRT**)

A classic TRT protocol to elevate hyperacusis with/without tinnitus is taking place. This includes educational training in which the Jastreboff neurophysiological model is described to explain treatment and demystify the patients' experience. Guidance is given about avoidance behaviour (e.g., use of earplugs, avoiding environment sounds, or avoiding quiet) and the application of desensitising sound and sound enrichment is discussed. The depth of counselling and sound components depends on the treatment category (0–4: presence of tinnitus, hearing loss, hyperacusis, or noise exposure) assigned; for categories 1-2, sound generators are recommended; for categories 3-4 aimed at hyperacusis, bilateral open-fitting sound generators are fitted with instructions to gradually increase the sound daily to be tolerable without difficulties.

Counselling (13).

A collaborative approach to counseling will do the following:

1. Encourage the patient to express his or her reluctance or fear of being exposed to sound by describing specific situations in which problems occur.
2. Identify behaviors and emotions attributed to others who are making the noise (e.g., lack of consideration) that might contribute to the patient's annoyance.
3. Discuss repressed behaviors that might be associated with the annoyance or fear produced by sounds
4. Identify noisy circumstances over which the patient has some control—this has the potential to assure him or her that he or she is able to tolerate some sounds (18).

Sound Generating Devices .

Four general sound-therapy strategies for hyperacusis are reviewed by Pienkowski et al (13).

Continuous low-level broadband noise. Hazell, Sheldrake, and Graham (35) suggested presenting the patient with a continuous low-level broadband noise. Success with this strategy for some people with loudness hyperacusis has been reported: There were substantial increases in LDLs. Several other studies have noted that such sound therapy can be effective for treating loudness hyperacusis for some but not all patients, and that it may take a long time before positive results appear.

Successive approximations to high-level broadband noise. Another approach is to choose a time of day for specific sound (pink noise, defined as "very similar to the white noise, but with the amplitude decreasing with frequency at a constant rate 3dB per octave) exposure and to gradually increase the level and/or duration over several days, weeks, and perhaps months. No outcome is reported (13).

Successive approximations to troublesome sounds. Another strategy involves recording specific sounds or noises that are troublesome for patients (36). The patient then listens to the sounds at a time when he or she can relax (perhaps in a quiet room in the evening). The level and duration of these sounds are gradually (over weeks) increased until the patient is comfortable listening to the sounds at his or her typically encountered levels. Eventually, when they feel ready, the patients can expose themselves to the actual sounds. It is sometimes helpful if this is first done with some support (perhaps with family members) and sometimes with control over the duration and level of the real sounds.

Gradual increase of maximum output of hearing aid.

The amplification provided by hearing aids might be the last thing someone with hyperacusis wants, particularly for moderate to high input levels. Decreasing the gain for moderate

to high levels, and lowering the maximum output level, should help. However, this is likely to negatively influence speech perception.

Pharmacological Therapy (8).

The use of medication to treat hyperacusis has not been investigated in clinical trials, but interest is high. The published work is limited to clinical case reports.

Alprazolam (a short-acting anxiolytic), Carbamazepine (an anticonvulsant and mood-stabilizing drug) , selective serotonin receptor inhibitors (Fuvloxamine and Fluoxetine), Citalopram (another selective serotonin receptor inhibitor) are reported to have some success.

The discovery of an auditory pain pathway provides a target for pharmacologic treatment of pain hyperacusis. Liu et al (33) report that the damage response of the type II fibres could be completely blocked through the bath application of retigabine, suggesting that a "painkiller for the ear" might be a possibility.

Hearing protection is desirable for everyone when they are exposed to very intense sounds, which can of course cause hearing loss and tinnitus and can worsen hyperacusis. However, when hyperacusis patients are using protection for everyday sounds with moderate levels, the results can be counterproductive. Patients should be informed that the use of hearing protection can reinforce the association between the sounds and distress and, hence, maintain the underlying fears and concerns (13). Active hearing protection devices can attenuate higher level sounds while not attenuating low-to-conversational level sounds; these could potentially be utilised in people with hyperacusis.

AETIOLOGIES

Like hearing loss and tinnitus, hyperacusis probably can be associated with both peripheral and central factors (2).

In the great majority of cases, no underlying medical condition can be found. The conditions in which hyperacusis has been reported as a symptom have been reviewed by Katzenell and Segal (20), some of which can be treated.

A list of clinical conditions associated with hyperacusis will follow. If there is a specific pathophysiological mechanism related to the hyperacusis, a brief description will be provided.

Clinical conditions associated with hyperacusis (13).

Otologic: Bell's palsy, Ramsay Hunt syndrome, Ménière's disease, perilymph fistula, superior semicircular canal dehiscence, acoustic trauma (38,48), barotrauma, noise-induced hearing loss, stapedectomy, tympanoplasty, stapes hypermobility (37), lateral semicircular canal dysplasia (39).

Neurologic: Autism, carotid aneurysm, middle cerebral aneurysm, migrainous cerebral infarction, head injury (41, 42), Chiari's malformation, sympathetic reflex dystrophy, multiple sclerosis, migraine, epilepsy, myasthenia gravis, cerebrospinal hypertonia, primary thalamo deficiency, attention-deficit disorder, anxiety and depression disorders (40), post-traumatic stress disorder, complication of spinal anesthesia

Endocrine: Addison's disease, pan-hypopituitarism, hyperthyroidism

Infection: Neurosyphilis, Lyme disease, typhoid fever

Medication: Benzodiazepine and antidepressant withdrawal, acute phenytoin intoxication

Deficiency: Magnesium and pyridoxine

Genetic or congenital: Williams syndrome, idiopathic hypercalcemy (Fanconi and Williams–Beuren syndrome), Cri du Chat syndrome, Tay–Sachs disease, Cogan syndrome, GM1 gangliosidosis, spina bifida

Other: Temporomandibular disorders, fibromyalgia

It should be noted, however, that of peripheral conditions identified, several involve **facial nerve dysfunction**. Hyperacusis in relation with stapedial reflex dysfunction has been reported in Bell's palsy, Ramsay Hunt syndrome, myasthenia gravis, and after stapedectomy. Abnormalities of the stapedial reflexes have been reported in patients with hyperthyroidism, with raised thresholds and decreased amplitudes, but with no mention for hyperacusis. Since the facial nerve innervates the stapedial reflex, which is a mechanism for reducing the perceived intensity of impulse sound, these conditions may reduce the efficacy of that reflex and hence increase the perceived intensity of sound (20).

If the stapedial reflex is impaired (e.g., because of neuro-muscular dysfunction or injury during stapedectomy), then intense low-frequency sounds may appear louder than normal (2). There are several studies that contradict this supposition.

Stapes Hypermobility (37).This study describes 21 patients, 7 of whom stapes hypermobility is believed to be a mechanical cause of their hyperacusis symptoms. Treatment results are better when there is excess tissue placed around the stapes. This study provides evidence that round and oval window reinforcement using

either tragal perichondrium or temporalis fascia may reduce sound sensitivity in patients suffering from hyperacusis.

Lyme disease is a systemic infection with the tick-borne spirochaeta Borrelia burgdorferi which targets specific body organs including the peripheral and central nervous systems. Some caution must be exercised in interpreting reports of hyperacusis because facial palsy can be a feature, hence stapedial reflex dysfunction as described above. There are, however, reports of hyperacusis in Lyme disease without facial nerve dysfunction.

Williams syndrome is a multisystem neurodevelopmental genetic disorder characterized by several facial abnormalities (e.g., short upturned nose with long philtrum and wide mouth), developmental delay learning disabilities, cardiovascular abnormalities, hearing loss, and hyperacusis, with an incidence of 1 in 20 000 live births. As many as 90% of individuals with this syndrome report hyperacusis. Moreover, in Williams syndrome the excessive auditory gain may be explained partly by the high incidence of otitis media with effusion and the associated conductive hearing loss. In addition, the majority of children with William's syndrome have absent stapedial reflexes.

The high prevalence of hyperacusis in Williams syndrome led Marriage and Barnes (32) to consider the mechanism in that condition and the extent to which it might be generalized to other individuals. Their suggestion that 5-HT might be implicated was based partly on the clinical observation that hyperacusis tends to occur in other conditions where 5-HT function is thought to be disturbed—namely, migraine, depression and post-traumatic stress disorder (3).
5-HT does appear to have a role in modulating auditory gain and the determination of significance of sound. However, there is no evidence that 5-HT disturbance contributes to hyperacusis of non-syndromic types. Moreover, even in Williams syndrome the excessive auditory gain may be explained partly by the high incidence of otitis media with effusion and the associated conductive hearing loss.

Autism Spectrum Disorders ASD (4)
Sensory hypersensitivity has long been recognised in ASD. Autism can affect both social and communicative development, and it has been linked to hyperacusis in several studies . Auditory hypersensitivity has been linked to reduced inhibitory processing.
In one study, a significant correlation between hyperacusis and physiological measurements of the MOC reflex in children with ASD has been reported (46).

Other conditions in which hyperacusis has been reported are **middle cerebral aneurysm (4)**.
The authors linked hyperacusis with irritation of auditory cortex by the nearby aneurysm.
A case of middle cerebral aneurysm presenting with brief, intermittent episodes of bilateral hyperacusis has been published (2). Audiologic and otologic examinations were completely normal. The middle cerebral artery supplies the lateral cerebrum, which includes the auditory cortex. The authors postulated that turbulent arterial blood-flow and pressure influence serotonin regulation of the auditory cortex. Serotonin, specifically

5-HT, is an inhibitory regulator of central sensory processing, and a pathological disruption to this system could result in central hyperacusis (21). Treatment of the aneurysm resulted in a reduction in hyperacusis symptoms.

A case series of hyperacusis in **multiple sclerosis** has been reported, though the association is unusual. The link between hyperacusis and multiple sclerosis is unclear, but Weber et al. (2002) speculated on demyelination in the pons and in the central auditory pathways.

Fibromyalgia : In summary, hyperacusis in cases of fibromyalgia seems to be associated with a general hypersensitivity (2). There are some reports that link hyperacusis in patients with chronic pain with hyper sensitisation of central pain circuits, even in the absence of an actual peripheral pain trigger (45).

Migraine (2)

Fear hyperacusis (phonophobia) is the most frequent hearing symptom associated with migraine: 81%–90% of sufferers experience hyperacusis during the migraine attack. In addition, migraine sufferers are more likely to have hyperacusis between attacks than people without migraine. The sound levels that result in hyperacusis are reportedly lower during migraine attacks and occur without changes of hearing thresholds in most cases. Importantly, people with migraine combined with allodynia have lower LDLs than people with migraine alone.

Superior Semicircular Dehiscence Syndrome (2)

Superior semicircular dehiscence syndrome is thought to be caused by a thinning of the bony covering of the superior semicircular canal. Air-conduction audiometric thresholds are normal, but bone-conduction thresholds are usually lower than normal. This greater sensitivity to bone-conducted sound is a direct result of the dehiscent superior semicircular bone acting as a third window into the inner ear. This has also been called conductive hyperacusis. Symptoms of superior semicircular dehiscence syndrome are autophonia, vertigo, ear fullness, and hyperacusis. Some sufferers can hear internal sounds, for example, those produced by eye movements when reading. In addition to hypersensitivity to internal sounds, a case series has been published describing increased sensitivity to external sounds (4).

Noise Exposure (2)

Occupational noise exposure is often associated with increased risk of hyperacusis, often together with tinnitus. Many patients with hyperacusis and tinnitus report that background noise makes their tinnitus worse. Although it is likely that noise exposure is the most common cause of hyperacusis, the data are limited. It has also been reported in several studies that hyperacusis is associated with recreational noise exposure, for example, to loud music. It should also be noted that some people might have an adult-onset, genetically based hearing loss. Susceptibility to noise-induced hearing loss, tinnitus, and/or hyperacusis could be influenced by genetic factors.

Increased spontaneous activity in the cochlear nucleus after noise trauma has been correlated with hyperacusis. Although the exact biological mechanisms remains unclear, a possible alteration in

neurotransmission or local inflammation has been tested, and indicated implication of such mechanisms in the genesis of somatic tinnitus and hyperacusis (47).

Recent evidence suggests that the effects of noise extend beyond the duration of the noise exposure. Kujawa and Liberman (24) showed in mice that a single noise exposure causing temporary (but not permanent) threshold shifts can destroy inner hair cell synapses, leading to a slow degeneration of the denervated auditory nerve fibers. Such degeneration could give rise to tinnitus and perhaps hyperacusis as well as to impaired speech perception in noise and eventual permanent threshold shifts.

There are some recent results from experiments in rats, suggesting that hearing loss at an early age is a significant risk factor for hyperacusis (44).

Unexpected Intense Impulsive Noise (acoustic shock)

An unexpected intense sound exposure, via a headset or telephone, sometimes referred to as an acoustic shock, can result in hyperacusis, as a part of other associated symptoms like tinnitus, discomfort or pain around the ear, altered hearing, even dizziness. It is reported that if an associated hearing loss is present, it is in the middle or low range of frequencies rather than the classic high frequency acoustic trauma. It is suggested that an unexpected intense impulse can trigger **tonic tensor tympani syndrome,** which is described as an involuntary, anxiety-based condition in which the reflex threshold for tensor tympani muscle activity is reduced, causing a frequent spasm.

Music Exposure

Several studies have reported hyperacusis among musicians.

NEURAL ENCODING OF LOUDNESS

The loudness of a sound is a subjective attribute corresponding to the impression of its magnitude (22).

Briefly, as sound intensity increases above the threshold of a (Type I) auditory nerve fiber (ANF), its spike rate rises from some spontaneous value and saturates at some maximal value, which is maintained at higher intensities. The 10 or so auditory nerve fibers normally innervating a single IHC have graded thresholds, so the number of activated nerve fibers grows with increasing sound intensity. Because the less sensitive (high-threshold) fibers tend to saturate at higher intensities than the more sensitive (low-threshold) fibers, changes in sound intensity produce changes in firing rate in some fibers across the full hearing intensity range (normally >100 dB) despite the more limited dynamic ranges (typically <40 dB) of the individual fibers.

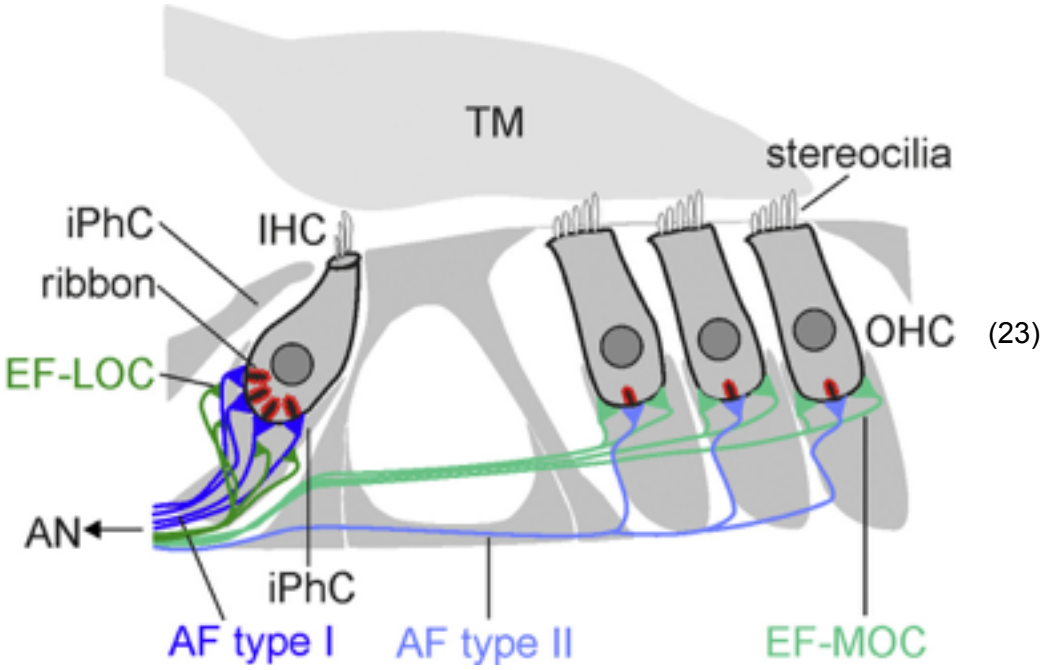
Furthermore, as sound intensity increases, the initially sharply tuned basilar membrane vibration profile evoked by narrowband sounds broadens toward the cochlear base, which also increases the total number of auditory nerve fibers activated at higher intensities.

Finally, for sounds with frequencies up to a few kHz (a limit imposed by the capacitance of the IHC membrane), spikes are phase-locked to individual cycles of the waveform on the basilar membrane. Improvements in phase-locking with sound level may also provide a “neural code” for loudness.

A major complication for neural models of sound intensity representation is that the primary goal of the auditory system is to recognise a meaningful sound regardless of its intensity or signal-to-noise ratio. Thus,

by the level of auditory cortex, complex sounds may be represented in a largely intensity-independent, “object-oriented” fashion, particularly during attentive listening, although the basis for such representations may begin to emerge in the cochlear nucleus (13).

Loudness perception is dynamic. Modulating the background noise levels during the presentation of a sound can change the perceived loudness of that sound. This is thought to be accomplished by gain modulation in the auditory system. Indeed, central auditory neurons can adapt their sensitivity to auditory input based on the sound level statistics, allowing them to maintain a relatively stable range of activity thereby preserving neural coding efficiency. Consistent with this model, psychoacoustic studies have determined that loudness perception is more closely correlated with the level of sound-evoked activity in the CNS than with the absolute sound level. Thus, central gain modulation is likely to be intimately linked to loudness perception, suggesting that central gain enhancement may manifest as hypersensitivity to loudness, i.e., hyperacusis (43).



(23)

MECHANISMS OF HYPERACUSIS

Hyperacusis has several potential mechanisms which are not mutually exclusive. Since the normal mechanism of loudness perception is related to the total number of auditory nerve fibers activated at different degrees of intensities, hyperacusis could result from either a mechanism that increases the cochlear output (meaning the total activity of type I Auditory Nerve Fibers, ANFI), or from malinterpretation of the cochlear signal in the Central Nervous System (CNS) to the direction of enhancment. The latter could result from a mechanism of amplification or disinhibition of the signal in the first stages of its transfer to the auditory centres, or from changes inside the loudness perception circuits themselves.
The perception of loudness possibly depends partly on the degree of neural synchrony in the auditory brain, independent of the firing rate. Just as tinnitus could result from abnormally synchronized spontaneous activity, perhaps even in the absence of changes in average spontaneous rates, hyperacusis could result from an abnormally high synchrony of sound-evoked activity (13).

PERIPHERAL Mechanisms

There is no data to support that noise- or age-related cochlear damage , could result in a direct pathological increase of the activity of ANF type I population. Stereocilia damage , loss of synaptic ribbons, degeneration of ANFI, loss of IHCs or OHCs, atrophy of the stria vascularis , which are all the main results of noise- or age-cochlear damage, increase the ANFs response threshold and thus produce an opposite result in the total amount of ANFs activity.

Efferent system dysfunction.
Both the middle and inner ear receive efferent innervation, and one of its functions is to regulate the responses of the inner ear to loud sounds (acoustic reflex). Regarding the ARTs of hyperacousis patients, they have been reported to be in normal range, and it is thus unlikely that malfunction of acoustic reflex contributes to hyperacusis (4).

Efferent feedback has a protective effect on the inner ear (24) , and it has been shown that efferent innervation of the ear may undergo plastic remodelling after noise trauma or with ageing (4).

An auditory efferent system is common to all mammals, and in humans consists of both a lateral and a medial system.
In the lateral system, whose function remains unclear, the pathways originate around the lateral superior olive and terminate on the primary afferent dendrite beneath the inner hair cell.
The LOC feedback utilises a variety of inhibitory neurotransmitters, suggesting a possible inhibitory function, although unclear till today (4).

In the medial system the pathways begin medially with the superior olivary complex and terminate on the base of outer hair cells, and functions of the system appear to include modulation (decrease) of auditory gain and the behavioural response to sound (manifest in anatomical links with the reticular formation).
Medial auditory dysfunction might contribute to both hyperacusis and tinnitus; thus, disturbance of the ability to modulate central gain might result in persistent sensitivity despite exposure to noise of moderate to high intensity. There is evidence against any such role, however, in that patients who have undergone vestibular nerve section (usually for symptoms of vertigo refractory to other treatments) do not complain of increased tinnitus or of loudness intolerance and psychoacoustic testing of such patients reveals no decrement in auditory performance (3). Failure of the medial olivocochlear efferent system and the resulting loss of control over the gain of cochlear amplification could result in hyperacusis without any hearing loss, as suggested by studies of people with brain injury (2).

Complete removal of both MOC and LOC feedback has been investigated in a rat model (Zheng et al 1999) - sectioning of the olivocochlear bundle- and did produce results compatible with loudness hyperacusis.

Peripheral processes as a trigger for CENTRAL changes that lead to Hyperacusis

Auditory system adapts to the input changes it receives from the periphery.
Cochlear damage could lead to **neuroplastic** changes in the CNS that could play a significant role in the development of hyperacusis (25).

Homeostatic plasticity is the process by which the central nervous system attempts to stabilise neural firing rates within a prescribed long-term range (when averaged over hours or days) by adjusting the intrinsic excitability of neurons and/or the number and strength of their excitatory and inhibitory synaptic inputs (13). Such plasticity can be triggered by changes in the prevailing patterns of sensory stimuli. In the auditory system, reduced sound input (e.g., following hearing loss) can lead to an increase in central auditory excitability, whereas increased sound input (e.g., following persistent exposure to moderate-level noise) can lead to a decrease in central auditory excitability (13).

Zeng et al postulated in 2013 that hyperacusis could be a result of abnormal increase in neuronal gain in central auditory system, through a non linear gain mechanism (26). Diehl and Schaette in 2015 investigated the same model (27).
Gu et al performed in 2010 a neuroimaging (fMRI) study , and reported increased sound evoked neuronal responses in midbrain, thalamus, cortex of patients with Decreased Sound Tolerance (DST)(28).
Conductive hearing loss has been investigated as well, with the use of earplugs , and proved to have reversible results to the perceived loudness. Plasticity of loudness works in both directions, as shown by the use of noise generators for days, which produced opposite alterations to the loudness perception (29).
It remains unclear if plasticity of loudness is frequency specific , or it occurs as a generalised increase of sensitivity that affects all frequencies (4).

Hyperacusis and Hearing Loss

The relationship between hyperacusis and hearing loss is unclear, and complex, but it is believed that hearing loss (and hidden hearing loss) is an initiating condition.

Noise Induced Hearing Loss has been, in a previous view, typically defined by a permanent loss of hearing thresholds (23).

While hearing loss induced by noise- exposure or ototoxic drugs reduces the neural activity transmitted from the cochlea to the central auditory system, spontaneous and sound-evoked responses at higher auditory structures, such as the auditory cortex (AC), medial geniculate body (MGB), and inferior colliculus (IC), are paradoxically increased.

In IC, increase only of sound-evoked SR has been reported , without increase of spontaneous SR, after noise induced cochlear synaptopathy (49).

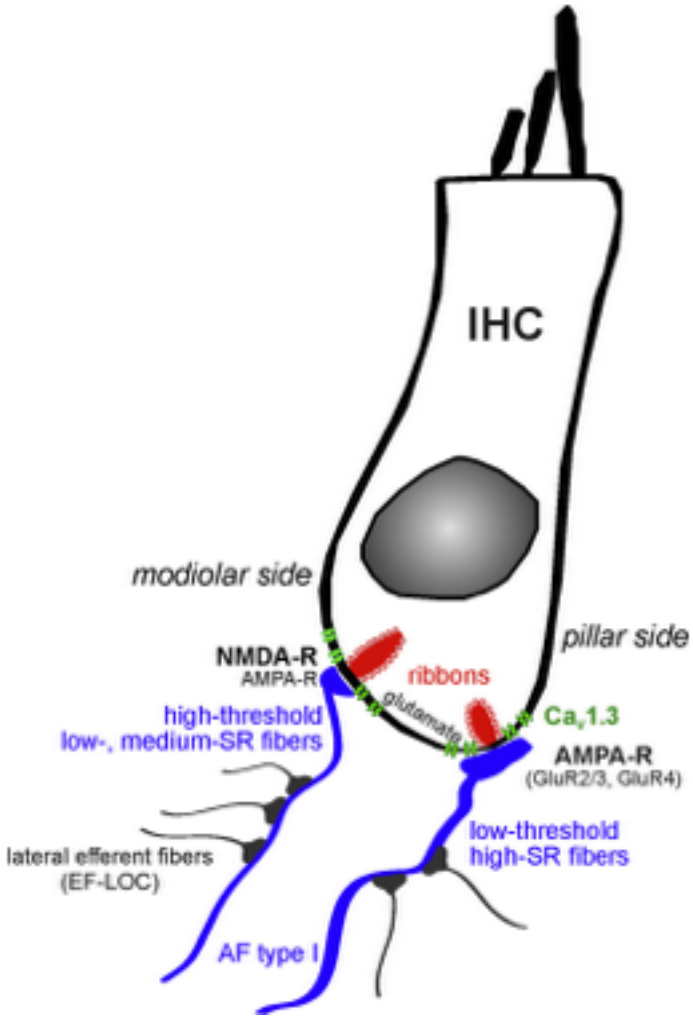
This observed increase in neural activity is at the core of the Central Gain Model, which proposes that tinnitus and hyperacusis result from a compensatory increase in gain or neural amplification in the central auditory system to compensate for a loss of sensory input from the cochlea (43).

While there is strong support for the central gain model, less is known about how these neuronal gain changes are implemented at the cellular and molecular level. One possible mechanism is homeostatic plasticity which, in essence, is a form of cellular gain control that allows neurons to increase/decrease their overall activity level in response to changes in synaptic input (25,50).

Hidden Hearing Loss can lead to changes in the central auditory pathways that are expressed as hyperacusis-like behaviour in animals and humans. Mechanisms of homeostatic and/or Hebbian plasticity are believed to underlie these effects which reflect increased central gain in auditory pathways (4).

Normal thresholds rely on the proper function of outer hair cells (OHCs). Per inner ear, there are approximately 11,000 OHCs, which are, in the human cochlea, typically arranged in 3 rows. OHCs function is to nonlinearly amplify basilar membrane vibration in response to soft sounds near the place of characteristic frequency within the cochlea. OHCs are therefore crucial for the high sensitivity of the hearing organ, its frequency selectivity, and understanding speech in noise. We can conclude that loss of hearing thresholds after noise exposure is mostly linked to OHC loss.

The IHCs are the primary sensory hair cells of the cochlea that transmit sound information over an intensity range spanning 12 orders of magnitude (120 dB) and 3 orders of magnitude of frequency (20 Hz to 20 kHz). This powerful capacity of IHC synapses is achieved through their numerous specialised afferent contacts. Each IHC is innervated by 8 (human) unbranched spiral ganglion neurons, which represent about 90– 95% of all afferent fibers (AF) in the auditory nerve (AN) (Fig. 1, AN; Figs. 1 AF type I). Each IHC contains electron-dense presynaptic subcellular structures, so-called ribbons (Figs. 1, red) that tether >100 synaptic vesicles. This specialized presynaptic machinery thereby maintains a large releasable pool of



neurotransmitter, allowing afferent auditory neurons to code the temporal characteristics of sound with high reliability and temporal precision.

The afferent fibers that innervate IHCs are classified based on their response threshold and spontaneous discharge rate (or spontaneous rate, SR). Approximately 17,000 high-SR fibers (60% of the total number) have an SR above 18 action potentials (APs) per second. These neurons are sensitive to low sound pressure levels, with thresholds between 0 and 20 dB SPL, and are situated on the pillar side of the IHCs. These fibers are believed to determine the Hearing Threshold (HT) in the clinical audiogram.

In contrast, approximately 4500 low- SR and medium-SR fibers (40%) with an SR between <0.5 and 18 AP/s have elevated thresholds, between 20 and 40 dB and are situated on the modiolar side of the IHCs.

The different thresholds and different patterns of spontaneous or sound evoked firing rates offers a mechanism of sound intensity coding.

Each afferent neuron connects to an estimated seven presynaptic OHCs. It has been suggested that if these reach the action potential threshold at all, the threshold is only reached if the entire pool of presynaptic OHCs are maximally depolarized, such as during the loudest sounds.

IHC damage would doubtless dramatically compromise cochlear transduction and lower the firing rates of auditory nerve fibers.

The 3500 IHCs (Figs. 1 and 2, IHC) in the cochlea rarely die from NIHL, however. According to Lobarinas 2016, if at least 20% of IHCs remain intact no elevation of hearing threshold is present in the audiogram

Instead, the innervated dendrites of the auditory nerve fibers undergo neurodegeneration. This process has been revealed to be tightly correlated with an altered number of transmitter release sites in IHC nerve terminals.

Homeostatic plasticity could increase gain by -increasing presynaptic transmitter release, -modifying receptors in the post synaptic membrane of the affected neutrons, or -modifying the intrinsic response of the neuron to its inputs, or- all three mechanisms (4).

In addition to its expression in many levels of auditory pathway, gain enhancement occurs at different time scales and in structures outside the classic auditory pathway (4).

Secondary to degeneration of the afferent dendrites of auditory fibers, spiral ganglion cells undergo neurodegeneration as shown after glutamate-induced excitotoxic trauma in vitro, after intense tone exposure, or after long-term mild trauma. Indeed, the long-standing dogma that cochlear nerve degeneration is a consequence of IHC death after acoustic trauma was only recently overturned, as degeneration can occur when IHCs are present. It has been proposed that the glial supporting cells that surround IHCs, the inner phalangeal cells (Fig. 1, iPhC), are crucial for auditory nerve survival (Zilberstein et al., 2012). Consistent with this, after acoustic trauma, these phalangeal cells also are important to stabilize exocytosis and the number of transmitter release sites in IHCs in the intact cochlea, as well as to destabilize stable pre-and postsynaptic IHC/afferent contacts .

Noise trauma sufficient to damage the cochlear transduction mechanism or auditory synapses, reduces the spontaneous and driven activity in the auditory nerve. In response to reduced input, neurons in central auditory structures become hyperactive (increase in SFRs or in sound-evoked responses), reflecting changes in central gain, which could lead to tinnitus or hypercusis respectively.
Loss of input from deafferentation could lead to a generalised decrease in inhibition in cortical pathways. Current evidence suggests that slow-wave activity generated be deafferentation of MGB neutrons, disinhibits processing over wide cortical areas, potentially contributing to hyperacousie and broadening its frequency profile (4).

Novel findings (23) suggest that an over-adaptive compensating central gain that spreads from the brainstem toward ascending pathways may be associated with hyperacusis, but not with tinnitus.
Studies in animals and humans may directly or indirectly support the notion that tinnitus is related to a failure of the central auditory pathway to adapt to a critical loss of afferent peripheral fibers. For hyperacusis and tinnitus Knipper et al. (23) hypothesise compensating and non-compensating central changes, respectively. Cortical reorganization is not a prerequisite for the generation of tinnitus or hyperacusis, just like a loss of threshold sensitivity is not a necessary condition for either etiology. Functional cortical reorganization is possibly a concomitant phenomenon and a risk factor for tinnitus and hyperacusis, rather than part of its origin (23).
The central gain model of hyperacusis (30) proposes that loss of auditory input can result in maladaptive neuronal gain increases in the central auditory system, leading to the over-amplification of sound-evoked activity and excessive loudness perception.
The central auditory system employs a variety of adaptive gain control mechanisms to maintain hearing sensitivity in response to changes in auditory input. According to the central gain model of hyperacusis, when these gain control mechanisms are dysregulated, hearing loss can cause a maladaptive over-amplification of sound-evoked activity along the central auditory pathway, leading to normal sounds being perceived as excessively loud.
It is becoming increasingly clear that central auditory plasticity is a critical component to the perceptual consequences of cochlear hearing impairment. Recent studies have demonstrated that compensatory central gain enhancement can restore sound detection thresholds in the face of even profound cochlear denervation (31). This likely contributes to the phenomenon of ‘‘hidden hearing loss”, where individuals present with

clinically normal hearing but nonetheless exhibit more subtle auditory perceptual disturbances as a result of significant damage to the inner hair cell/auditory nerve synapse (i.e., synaptopathy) (24). In addition to hidden hearing loss, excessive gain enhancement has long been speculated to be a potential mechanism underlying tinnitus and hyperacusis, two of the most common auditory perceptual disruptions associated with hearing loss. The study of Auerbach et al. (30) offers substantial evidence in support of the central gain model of hyperacusis, demonstrating that sound-evoked hyperactivity is directly correlated with increased loudness growth within individual animals.

Central gain enhancement has been observed in many auditory areas in response to a variety of acoustic or ototoxic insults and a myriad of potential mechanisms have been implicated in these changes. The question remains, however, as to how these changes may contribute to tinnitus and/or hyperacusis. According to the Central Gain Model, the central auditory system recalibrates its mean firing rate activity to a new“set-point” after a lack of sensory input, thereby generating an amplification of neural noise, which would be perceived as tinnitus. Importantly, this neuronal recali- bration would also result in an amplification of incoming sensory signals, which may underlie loudness intolerance and hyperacusis that also often accompanies hearing loss. Thus, an attractive aspect of the Central Gain model is that it could account for both tinnitus and hyperacusis (43).

PAIN FROM SOUND

One of the most distressing aspects of hyperacusis is the experience of pain from sound at levels that do not cause any pain sensation in non-hyperacusic persons (4).

The pain threshold for normal hearing listeners is stated to be between 120 and 140 dB SPL.

In 2015, two studies were published that provided evidence for a role of the type II auditory nerve fibers (ANFS), first as detectors of tissue damage in the ear (33), and second as a pathway to convey a damage signal to the brain (34). Based on these reports, the type II fibers would be prime candidates for a role as pain fibers of the ear.

Type II fibers are less numerous, as only 5 to 10 % of the AN fiber population are type II. These fibers are thin and unmyelinated, and they contact the outer hair cells (OHCs) of the cochlea. Each type II fiber contacts approximately 7 OHCs. Type II ANFs receive glutamatergic synaptic excitation from OHCs.

These studies thus demonstrated that damaging sound levels activated the type II fiber pathway, and that this pathway conveyed a signal about the OHCs damage to the cochlear nucleus, the first central processing stage of the auditory system. How this signal is processed further, and which other brain regions in the ascending auditory pathway are involved in this process, remains to be determined.

The mechanism responsible for the activation of this pathway at much lower sound intensities, as would be required to generate the symptoms observed in patients with pain hyperacusis, remains to be determined. One possible scenario could involve cross-talk between ANFs, which might happen, for example, when the myelin sheath around type I ANFs is damaged, as has been observed after acoustic trauma.

COCNCLUSIONS

Hyperacusis can have a very important impact on daily life activities, working, socialising and the overall quality of life of the patient. Hyperacusis is only lately attracting researchers interest, and generally underestimated. In Greece particularly, this happens probably either because people do not seek medical help for this condition, either because clinicians and audiologists don't ask for its presence, or because even when a patient complains for hypersensitivity to ordinary sounds the clinician is "not listening to him".

The pain felt and described by hyperacusis patients led to the recent finding of certain fibers (the type II auditory nerve fibers) acting as nocioceptive fibers in the inner ear. These fibers may prove to be a target for paharmalocological therapy, intratympanic or systematic, with various analgesic medication.

Acoustic shock is recognised as a possible cause of hyperacusis. It is believed that the unexpected exposure to a sound can have similar importance as the intensity level, for the development of hyperacusis.

Hyperacusis is considered to a degree as a disorder of central gain function, and since auditory gain can change through neuronal plasticity procedures, there is probably space for hyperacusis treatment.

The use of hearing protection is recommended in limited activities only and generally not encouraged.

Briefly, treatment options include education of the patient for the hyperacusis pathophysiology, applied relaxation, graded exposure to sounds, and cognitive therapy for distressing thoughts and beliefs regarding sounds Recalibration of loudness perception is the main target of various sound therapies. Since the auditory system and auditory processing are active during night time, it is advised to take advantage of night/sleep time for the recalibration process.

Many questions for hyperacusis still remain to be answered. The prevalence in adult and children population, risk factors and medical causes, the natural history of the symptom, how to inhibit nocioceptive fibers with medication, what are the exact pathophysiological mechanisms, what is the nature of correlation of tinnitus and hyperacusis on the same patient, what is the clinical usefulness of different questionnaires in assessing hyperacusis impact to the patient and to evaluate the effectiveness of various treatments, what is the most effective type of treatment (alone or in combination)? All these have been identified by Baguley D and Hoare DJ (51) as the major research targets in the future.

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