List of contributors

H.B. Abrams, Bay Pines VA Medical Center, Bay Pines, FL, USA

U. Ambrosetti, Department of ENT and Oftalmology, University of Milan, Milan, Italy and ENT — Audiology Unit, Ospedale Maggiore Policlinico, Mangiagalli e Regina Elena Fondazione IRCCS, Milan, Italy

M.D. Atlas, Ear Sciences Institute, University of Western Australia, Perth, Australia

A.A. de Azevedo, OTOSUL, Otorrinolaringologia Sul-Fluminense, Volta Redonda, Rio de Janeiro, Brazil

D.M. Baguley, Audiology, Addenbrooke's Hospital, Hills Road, Cambridge, CB2 2QQ, UK and Ear Sciences Centre, School of Surgery and Pathology, University of Western Australia, Perth, Australia

C.A. Bauer, Southern Illinois University School of Medicine, Division of Otolaryngology Head and Neck Surgery, Springfield, IL 62794, USA

C.A.C. Bezerra Rocha, Department of Otolaryngology of the University of São Paulo School of Medicine, Av. Padre Pereira de Andrade, 545/174-F, São Paulo, SP, Brazil 05469-000

A. Björne†, Vertigo, Tinnitus and Pain Unit, Ystad Hospital, Sturegatan 2A, SE-271 31 Ystad, Sweden

T.J. Brozoski, Southern Illinois University School of Medicine, Division of Otolaryngology Head and Neck Surgery, Springfield, IL 62794, USA

A.T. Cacace, The Neurosciences Institute and Advanced Imaging Research Center, Department of Neurology, Albany Medical College, 47 New Scotland Avenue, Albany, NY, USA

P. Cobo, Instituto de Acústica, CSIC, Madrid, Spain

C.B. Coelho, Department of Otolaryngology of the University of São Paulo Medical School, São Paulo, Brazil

A. Crocetti, Fondazione Ascolta e Vivi, Milan, Italy

T. Crönlein, Sleep Disorders and Research Center, Department of Psychiatry and Psychotherapy, University of Regensburg, Universitätsstr. 84, 93053 Regensburg, Germany

C.L. Darlington, Department of Pharmacology and Toxicology, School of Medical Sciences, University of Otago Medical School, Dunedin, New Zealand

G. De Mulder, Department of Neurosurgery, University Hospital Antwerp, Antwerp, Belgium

D. De Ridder, Department of Neurosurgery, University Hospital Antwerp, Belgium and Department of Radiology, University Hospital Louvain, Belgium

L. Del Bo, Associazione Ascolta e Vivi, Via Foppa 15, 20144 Milan, Italy

E. Diesch, Department of Clinical and Cognitive Neurosciences, University of Heidelberg, Mannheim, Germany

I. Diges, Unidad de Otorrinolaringología. Fundación Hospital Alcorcón, C/Budapest, 1. Alcorcón 28922, Madrid, Spain

K. Dohrmann, University of Konstanz, Department of Psychology, Box D 25, 78457, Konstanz, Germany

J.J. Eggermont, Departments of Physiology & Biophysics, and Psychology, University of Calgary, Calgary, AB, Canada

P. Eichhammer, Department of Psychiatry, University of Regensburg, Universitaetsstrasse 84, 93053 Regensburg, Germany

T. Elbert, University of Konstanz, Department of Psychology, Box D 25, 78457, Konstanz, Germany
P. Enrico, Department of Biomedical Sciences, University of Sassari, V.le S. Pietro 43/B, 07100 Sassari, Italy
R. Rodrigues Figueiredo, OTOSUL, Otorrinolaringologia Sul-Fluminense, Volta Redonda, Rio de Janeiro, Brazil and Faculdade de Medicina de Valença, Rio de Janeiro, Brazil
B. Fischer, Department of Otorhinolaryngology, University of Regensburg, Regensburg, Germany
H. Flor, Department of Clinical and Cognitive Neurosciences, University of Heidelberg, Central Institute of Mental Health, Mannheim, Germany
A.K. Gehringer, Department of Otolaryngology — Head and Neck Surgery and Speech Pathology and Audiology, The University of Iowa, Iowa City, IA, USA
P. Geisler, Sleep Disorders and Research Center, Department of Psychiatry and Psychotherapy, University of Regensburg, Universitätsstr. 84, 93053 Regensburg, Germany
S.A. Gogel, Department of Otolaryngology — Head and Neck Surgery and Speech Pathology and Audiology, The University of Iowa, Iowa City, IA, USA
R. Goodey, Department of Surgery, Otolaryngology Section, University of Auckland, Private Bag 92019, Auckland, New Zealand
S.E. Griest, Oregon Health & Science University, Portland, OR, USA
M.J. Guitton, Molecular Endocrinology and Oncology Research Center, Laval University Medical Center (CHUL), Quebec G1V 4G2, Canada and Faculty of Pharmacy, Laval University, Quebec G1K 7P4, Canada
B. Haarman, Department of Psychiatry, University Medical Centre Groningen, Groningen, The Netherlands
G. Hajak, Sleep Disorders and Research Center, Department of Psychiatry and Psychotherapy, University of Regensburg, Universitaetsstrasse 84, 93053 Regensburg, Germany
M. Hansen, Department of Otolaryngology: Head and Neck Surgery, The University of Iowa, Iowa City, IA, USA
T. Hartmann, University of Konstanz, Department of Psychology, Box D 25, 78457 Konstanz, Germany
K. Heijneman, Department of Otorhinolaryngology, University Medical Centre Groningen, Groningen, The Netherlands
J.A. Henry, Oregon Health & Science University, Portland, OR, USA and VA RR&D National Center for Rehabilitative Auditory Medicine, VA Medical Center, Portland, OR, USA
C. Herraiz, Unidad de Otorrinolaringología. Fundación Hospital Alcorcón, C/Budapest, 1. Alcorcón 28922, Madrid, Spain and Unidad de Acúfenos. Instituto ORL Antolí-Candela, Madrid, Spain
F.T. Husain, Brain Imaging and Modeling Section, National Institute on Deafness and Other Communication Disorders, National Institutes of Health, Bldg. 10, Rm 8S235D, MSC 1407, 9000 Rockville Pike, Bethesda, MD 20892, USA
Corresponding addresses from 1 January 2008: Department of Speech and Hearing Science, University of Illinois at Urbana-Champaign, Champaign, IL 61820, USA
M.M. Jastreboff, Department of Audiology, Speech-Language Pathology and Deaf Studies, Towson University, 8000 York Street, Towson, MD, USA
P.J. Jastreboff, Department of Otolaryngology, Emory University School of Medicine, Atlanta, GA 30322, USA
H. Ji, The University of Iowa, Department of Otolaryngology-Head and Neck Surgery, 200 Hawkins Dr., Iowa City, IA 52242, USA
J.A. Kaltenbach, Department of Otolaryngology, Head and Neck Surgery, Wayne State University School of Medicine, Detroit, MI 48201, USA

T. Kleinjung, Department of Otorhinolaryngology, University of Regensburg, Regensburg, Germany
S. Koehler, Department of Biomedical Engineering, University of Michigan, 1301 E Ann St., Ann Arbor, MI 48109, USA
S. Kovacs, Department of Radiology, University Hospital Louvain, Louvain, Belgium
J.M. Lainez, Department of Neurology, University of Valencia, Valencia, Spain
M.J.A. Láinez, Department of Neurology, Hospital Clínico Universitario, University of Valencia (Spain), Avenida Blasco Ibáñez, 17, 46010, Valencia, Spain
M. Landgrebe, Department of Psychiatry, University of Regensburg, Universitaetsstrasse 84, 93053 Regensburg, Germany
B. Langguth, Department of Psychiatry, University of Regensburg, Universitaetsstrasse 84, 93053 Regensburg, Germany
J. Lautermann, Department of Otorhinolaryngology, University of Duisburg-Essen, Hufelandstraße 55, 45122 Essen, Germany
G. Lehnerdt, Department of Otorhinolaryngology, University of Duisburg-Essen, Hufelandstraße 55, 45122 Essen, Germany
R.A. Levine, Eaton-Peabody Laboratory, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114-3096, USA
A. Londero, Service ORL et chirurgie cervicofaciale, hôpital européen Georges-Pompidou, Paris, France
E. van der Loo, Department of Neurosurgery, University Hospital Antwerp, Antwerp, Belgium
W.H. Martin, Oregon Health & Science University, Portland, OR, USA
M. Mazzoli, U.O.C. ORL-OTOCHIRURGIA, Padova, Italy
R. McArdle, Bay Pines VA Medical Center, Bay Pines, FL, USA
M.B. Meikle, Oregon Health & Science University, Portland, OR, USA and Department of Otolaryngology, Oregon Hearing Research Center, Portland, OR, USA
J.R. Melcher, Eaton-Peabody Laboratory, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114-3096, USA
T. Menovsky, Department of Neurosurgery, University Hospital Antwerp, Antwerp, Belgium
M. Mereu, Department of Biomedical Sciences, University of Sassari, V.le S. Pietro 43/B, 07100 Sassari, Italy
J. Morrrison-Low, Section of Audiology, School of Population Health, Faculty of Medical and Health Sciences, The University of Auckland, New Zealand.
A.R. Møller, School of Behavioral and Brain Sciences, University of Texas at Dallas, GR41, P.O. Box 830688, Richardson, TX 75083-0688, USA
M.B. Møller, School of Behavioral and Brain Sciences, University of Texas at Dallas, GR41, PO Box 830688, Richardson, TX 75083-0688, USA
E.C. Nam, Eaton-Peabody Laboratory, Massachusetts Eye and Ear Infirmary, 243 Charles Street, Boston, MA 02114-3096, USA and Department of Otolaryngology, Kangwon National University College of Medicine, Chunchon, Korea
C.W. Newman, The Cleveland Clinic Foundation, Cleveland, OH, USA
W. Noble, The University of Iowa, Department of Otolaryngology-Head and Neck Surgery, 200 Hawkins Dr., Iowa City, IA, USA and University of New England, School of Psychology, Armidale, Australia
J. Oleson, Department of Biostatistics, The University of Iowa, Iowa City, IA, USA
Y. Oron, Department of Otolaryngology, Wolfson Medical Center, Holon, Israel
J.F. Piccirillo, Clinical Outcomes Research Office, Department of Otolaryngology — Head and Neck Surgery, Washington University School of Medicine, St. Louis, MO, USA

A. Piera, Department of Neurology, Hospital Clínico Universitario, University of Valencia (Spain), Avenida Blasco Ibáñez, 17, 46010, Valencia, Spain

J.-L. Puel, Inserm U583 and University Montpellier 1, INM-Hôpital Saint Eloi, 80 rue Augustin Fliche, 34295 Montpellier cedex 5, France

J.P. Rauschecker, Department of Physiology and Biophysics, Georgetown University Medical Center, Washington, USA

L.E. Roberts, Department of Psychology, Neuroscience and Behavior, McMaster University, 1280 Main Street West, Hamilton, ON, L8S 4K1, Canada

S. Robinson, University of California at San Diego, Veterans Administration Healthcare System, 3350 La Jolla Village Dr., Mail Code 116A, San Diego, CA 92161, USA

T.G. Sanchez, Department of Otolaryngology of the University of São Paulo Medical School, São Paulo, Brazil

P.G. Sand, Department of Psychiatry, University of Regensburg, Regensburg, Germany

S.A. Sandridge, The Cleveland Clinic Foundation, Cleveland, OH, USA

W. Schlee, University of Konstanz, Department of Psychology, Box D 25, 78457 Konstanz, Germany

G.D. Searchfield, Section of Audiology, School of Population Health, Faculty of Medical and Health Sciences, The University of Auckland, New Zealand

S. Shore, Kresge Hearing Research Institute, Department of Otolaryngology, University of Michigan, 1301 E Ann St., Ann Arbor, MI 48109, USA

S.M. Silver, Otolaryngology Service, Stratton VA Medical Center, Albany, NY, USA

D. Sirca, Department of Biomedical Sciences, University of Sassari, V.le S. Pietro 43/B, 07100 Sassari, Italy

P.F. Smith, Department of Pharmacology and Toxicology, School of Medical Sciences, University of Otago Medical School, Dunedin, New Zealand

T. Steffens, Department of Otorhinolaryngology, University of Regensburg, Regensburg, Germany

B.J. Stewart, Oregon Health & Science University, Portland, OR, USA

M. Struve, Department of Clinical and Cognitive Neurosciences, University of Heidelberg, Central Institute of Mental Health, Mannheim, Germany

A. Toledano, Unidad de Otorrinolaringología. Fundación Hospital Alcorcón, C/Budapest, 1. Alcorcón 28922, Madrid, Spain

S. Sunaert, Department of Radiology, University Hospital Louvain, Louvain, Belgium

S. Trellakis, Department of Otorhinolaryngology, University of Duisburg-Essen, Hufelandstraße 55, 45122 Essen, Germany

J.G. Turner, Department of Surgery/Otolaryngology Head and Neck Surgery, Southern Illinois University School of Medicine, Springfield, IL 62794-9629, USA and Department of Psychology, Illinois College, Jacksonville, IL 62650, USA

R.S. Tyler, Department of Otolaryngology Head and Neck Surgery, and Speech Pathology and Audiology, University of Iowa, Iowa City, IA, USA

P. Van Dijk, Department of Otorhinolaryngology, University Medical Center Groningen, Groningen, The Netherlands

P. Van De Heyning, Department of Otolaryngology, University Hospital Antwerp, Antwerp, Belgium

R. Vergara, Fundacion Ciencia & Tecnologia, Bogotá, Colombia

N. Weisz, INSERM U821, Brain Dynamics and Cognition, Lyon, France

K. Wise, Section of Audiology, School of Population Health, Faculty of Medical and Health Sciences, The University of Auckland, New Zealand

J. Zhou, Department of Molecular and Integrative Physiology, University of Michigan, 1301 E Ann St., Ann Arbor, MI 48109, USA

Foreword

A major part of this book is the result of the work of a group of people from different disciplines who agreed to work together in better understanding the pathophysiology of tinnitus and in searching a cure for it.

Often - not only in science – progress and discovery have initiated from the efforts of a small group of people with little means but with creativity and enthusiasm.

In the 50's small "Cinecittà" in Rome surprised the Moguls of Hollywood and produced artists like Rossellini, De Sica and Fellini. A small movie studio but a big school nearby, where students could interact with artists and writers and directors with just one aim: do nice movies.

In other words a group of people working with the right model, the right dynamics and for the right reasons.

As giant pharmaceutical companies take less risks and focus more and more on manufacturing and marketing, small but efficient groups continue to have an important role in the structuring and creation of new solutions for old pathologies.

As founder and sponsor of the Tinnitus Research Initiative (TRI), as well as other organisations, I have come to realize that if one succeeds in gathering a group of motivated people who think and act correctly in a collaborative way and for the right reasons, you get back much more than you have given, whether it is in time, experience or money.

I believe that the organizers of TRI have gathered such a group.

The practical result of their work will not be visible for a few more years, but I think and wish they will succeed.

As a tinnitus sufferer, thank you!

Principality of Monaco, July 2007
Matteo de Nora

Preface

Tinnitus: Pathophysiology and Treatment

There are two main types of tinnitus, objective and subjective tinnitus. Objective tinnitus is caused by sounds generated in the body and transmitted to the ear. Subjective tinnitus is caused by abnormal neural activity. Objective tinnitus is rare but subjective tinnitus is a frequent disorder that occurs with different severity. There are many forms of subjective tinnitus; it can be just noticeable, an annoyance or it can reduce the quality of life by impairing the ability of intellectual work, making it difficult to sleep, and tinnitus can lead to suicide. There are no objective tests that can measure subjective tinnitus, and the only person who can assess the tinnitus is the person who has the tinnitus. This is one of the aspects of subjective tinnitus that is similar to central neuropathic pain.

In general, studies show that the incidence of subjective tinnitus increases with age from approximately 5% at young age (20–30 years) to approximately 12% for individuals above the age of 50 years but available data regarding the prevalence of tinnitus varies between studies. Bothersome tinnitus is infrequent at young age becoming increasingly frequent with age, reaching 12–14% for people at age 65 and older. There are many risk factors for tinnitus such as hearing loss, including age-related hearing loss (presbycusis) and tinnitus may follow after exposure to noise, administration of ototoxic antibiotics and cytostatics, infectious diseases and trauma to the auditory nerve are also risk factors.

It is generally agreed that subjective tinnitus is not a disease but a symptom and the many forms of tinnitus probably have different pathophysiology. For a long time it was believed that tinnitus arose from the ear and that the anatomical location of the physiological abnormalities that caused the tinnitus was the ear. However it was later understood that most forms of tinnitus was caused by abnormalities in the central nervous system and these abnormalities were often caused by expression of neural plasticity. Realizing the complexity of tinnitus has highlighted the importance of interdisciplinary research. The fact that most forms of tinnitus are disorders of the nervous system put emphasis on neuroscience in studies of tinnitus.

The first chapters in this book discuss the pathophysiology of subjective tinnitus. The anatomical locations of the physiological abnormality that cause the abnormal neural activity that give the sensation of sounds when no sound reaches the ear are discussed. The similarity between tinnitus and pain and various hypotheses for tinnitus are the subjects of other chapters. Evaluation of the results of animal studies is the topic of other chapters. Subjective tinnitus is often accompanied by abnormal perception of sounds and many have a lowered tolerance to sounds (hyperacusis). People who have tinnitus may experience an interaction with other sensory modalities (cross-modal interaction), such as with the somatosensory system. These matters are discussed in detail in the book.

Treatments that are available are medical and behavioral, and some use electrical stimulation of the skin, the ear or structures of the central nervous system. However, presently used treatments are often unable to relieve the tinnitus in a satisfactory way. This book discusses many different kinds of treatment and their efficacy and the different chapters describe new means and approaches to treatment of subjective tinnitus.

Most of the contributors to this volume participated in a conference held in Regensburg, Germany, 2006 that was sponsored by a newly formed private organization "The Tinnitus Research Initiative" the goal of which is to improve treatments for tinnitus through advances in the understanding of the pathophysiology of tinnitus. The organization promotes a collaborative interdisciplinary approach to research on tinnitus.

Berthold Langguth
Göran Hajak
Tobias Kleinjung
Anthony Cacace
Aage Møller
Dallas, May 2007

B. Langguth, G. Hajak, T. Kleinjung, A. Cacace & A.R. Møller (Eds.)
Progress in Brain Research, Vol. 166
ISSN 0079-6123

CHAPTER 1

Tinnitus: presence and future

Aage R. Møller*

School of Behavioral and Brain Sciences, University of Texas at Dallas, GR41, P.O. Box 830688, Richardson, TX 75083-0688, USA

Abstract: Tinnitus has many forms; it can be caused by sounds generated in the body (objective tinnitus) that reaches the ear through conduction in body tissue, but much more common is the tinnitus that occurs without any physical sound reaching the ear. Such tinnitus (subjective tinnitus) is a phantom sensation, where abnormal neural activity is generated in the ear, the auditory nerve, or the central nervous system. There are many forms of subjective tinnitus and it can occur with different severity. Subjective tinnitus often occurs in connection with hearing loss such as may occur after exposure to loud sounds (noise), or after administration of drugs such as certain antibiotics, but often no cause can be found. Tinnitus often occurs together with presbycusis and it can occur in deafness. Tinnitus is a part of the symptoms of Ménière's disease and individuals with vestibular Schwannoma almost always have tinnitus. Some individuals who have severe tinnitus hear sounds as distorted and some have hyperacusis (reduced tolerance to sounds) or phonophobia (fear of sounds). Tinnitus can be referred to one ear, or both ears, or to a location inside the head. The anatomical location of the physiological abnormality of chronic subjective tinnitus, however, is rarely in the ear but more often in the auditory nervous system. There are indications that the pathophysiology of unilateral and bilateral tinnitus is different. There is considerable evidence that expression of neural plasticity plays a central role in the development of the abnormalities that cause many forms of chronic subjective tinnitus. Expression of neural plasticity can change the balance between excitation and inhibition in the nervous system, promote hyperactivity, and it can cause reorganization of specific parts of the nervous system or redirection of information to parts of the nervous system not normally involved in processing of sounds (non-classical or extralemniscal pathways). Since there are many kinds of subjective tinnitus, search for a (single) cure for tinnitus is futile. Testing of new treatments is hampered by the fact that it is not possible to distinguish between different forms of tinnitus for which different treatments may be effective.

Keywords: tinnitus; neural plasticity; phantom sounds; hyperacusis; tinnitus treatment

Introduction

Tinnitus and auditory hallucinations are perception of sounds that occur in the absence of external sounds. Tinnitus can be divided into two broad groups, objective and subjective tinnitus. Objective tinnitus is caused by sound generated in the body reaching the ear through conduction in body tissues (Møller, 2003a) (Chapter 22). The source can be turbulent flow of blood in an artery where there is a constriction, or it can be caused by muscle contractions. Unlike subjective tinnitus, an observer, using a stethoscope, can often hear

*Corresponding author. Tel.: +1 972 883 2313;
Fax: +1 9728832310; E-mail: amoller@utdallas.edu

DOI: 10.1016/S0079-6123(07)66001-4

objective tinnitus. Subjective tinnitus is meaningless sounds that are not associated with a physical sound and only the person who has the tinnitus can hear it. Subjective tinnitus is far more prevalent than objective tinnitus; this chapter will concern subjective tinnitus. Auditory hallucinations are meaningful sounds such as music and voices. Hallucinations are rare but occur in various forms of psychiatric disorders such as schizophrenia. This chapter will not discuss hallucinations.

Tinnitus can have different effects on an individual. It can be just minor nuisance or it can cause suffering by disturbing sleep, causing anxiety, and affective symptoms such as depression or phonophobia.

Subjective chronic tinnitus belongs to a group of phantom sensations (Jastreboff, 1990) similar to central neuropathic pain (see Chapter 4). Phantom sensations are not disorders but symptoms of various kinds of abnormalities in which expression of neural plasticity is involved. Paresthesia of the somatosensory system are similar "phantom sensations" as tinnitus. Phantom sensations rarely occur in other sensory systems but have been reported in vision (phosphene) and olfaction (phantosmia, or olfactory hallucinations) (Møller, 2003b). Little is known about phantom taste sensations except from certain medications that can cause odd sensations such as a metallic taste.

Severe tinnitus are often accompanied by abnormal perception of sound including an abnormal low tolerance for sounds (hyperacusis)[1] (Baguley, 2003) or distortion of sounds. Hyperacusis is common in traumatic head injuries, where it often occurs together with tinnitus and hypersensitivity to light. Sequella of meningitis, especially where appropriate treatment was delayed, may include similar symptoms of severe tinnitus and hyperacusis, often accompanied by severe hearing loss or deafness.

[1]Different definitions of hyperacusis are in use and the term is sometimes used to describe abnormal perception of loudness. However, abnormal perception of loudness is a different anomaly known as "recruitment of loudness", an audiologic term that is used to describe a condition that is common in people with cochlear hearing loss and which means that the loudness of a sound increases more rapidly than normal (Møller, 2006a).

Recently the term *misophonia* (Jastreboff and Jastreboff, 2006) has been suggested to describe dislike of sound. Phonophobia and misophonia are forms of intolerance that may regard specific sounds with emotional associations whereas hyperacusis is normally unrelated to the type of sound. Affective disorders such as depression and phonophobia may also accompany severe tinnitus and thereby tinnitus can result in suicide.

Several animal models of tinnitus have been created either by noise exposure or by administration of salicylate (aspirin). The use of animal models depends on the ability to detect when the animals perceive tinnitus and several different methods for that have been described (Jastreboff et al., 1988; Jastreboff, 1989; Bauer et al., 1999) (see Chapter 13).

It is unfortunate that the same name, tinnitus, is used for so many different disorders. This hampers both understanding of the pathophysiology of tinnitus and the treatment because it implies that it is possible to find *the* cause of tinnitus and *the* treatment for tinnitus. Central neuropathic pain is similar (see Chapter 4). Disorders of the vestibular system was earlier in the same category, but the introduction of specific names such as, for example, benign positional paroxysmal nystagmus (BPPN) and disabling positional vertigo (DPV) has greatly improved treatment and understanding of the causes of various symptoms from the vestibular system.

Characteristics of subjective tinnitus

Subjective tinnitus has many different forms and its severity and character varies widely. It can be localized (referred) to one side or both sides and it can be felt as coming from the center of the head. Some investigators divide tinnitus in three groups according to the way it is perceived: mild tinnitus, moderate tinnitus, and severe (disabling) tinnitus (Reed, 1960).

Mild forms of tinnitus rarely cause any problems; moderate tinnitus can interfere with intellectual work and sleep and often cause suffering. Severe tinnitus can have major effect on a person's entire life, making sleep difficult and intellectual work impossible.

Quantitative assessment of the intensity of tinnitus is hampered by the fact that tinnitus when matched to real sounds appear to have very low intensity even in individuals who report that their tinnitus is very loud. Fowler in 1943 reported that though patients described their tinnitus as very loud, yet the tinnitus could usually be matched at only 5–10 dB sensation level (SL) (Vernon, 1976) and that tinnitus is difficult to mask (Fowler, 1942; Reed, 1960; Vernon, 1976). This is an obstacle in an attempt to quantitatively evaluate tinnitus and in monitoring the results of treatment. Some investigators use a visual analog scale (VAS) to estimate the intensity of tinnitus. VAS is in extensive use in pain research and now often used for comparing tinnitus before and after treatment. The use of a VAS seems to produce results that agree better with tinnitus patients' own evaluation similar to what is experienced with attempts to quantify pain (Chapter 4). Some forms of tinnitus cause suffering while other forms do not. Tinnitus that involves suffering has also been called "bothersome tinnitus" (Chapter 44) or "problem tinnitus" by some investigators (Gerken et al., 2001). There are indications that suffering from tinnitus involves parts of the central nervous system (CNS) that are outside the auditory nervous system (Chapters 3 and 40).

Prevalence of subjective tinnitus

It is difficult to get a clear picture of the prevalence of tinnitus. The fact that tinnitus has many forms and that it has widely different severity has caused different studies of the prevalence of tinnitus to yield widely different results (Ahmad and Seidman, 2004; Hoffmann and Reed, 2004; Henry et al., 2005). Different studies have arrived at different values of prevalence (Hoffmann and Reed, 2004). For people of all ages the prevalence of tinnitus varied from 4.4% to 15.1%. All studies reviewed agreed that the prevalence is higher above the age of 50. In this age group the different studies reported prevalence between 7.6% and 20.1%. Most elderly people have some forms of tinnitus particularly when visiting in a quiet environment but it is disturbing for only some individuals and only a few individuals suffer from the tinnitus.

The fact that the severity of tinnitus and pain can only be assessed by the patient and cannot be measured objectively is a source of uncertainty in epidemiologic studies. Most of the variations in the reported prevalence of tinnitus between different investigators are likely caused because investigators had different criteria for what they regarded as tinnitus, and also the inclusion criteria in some studies may have been biased. Individuals who have tinnitus but no noticeable problems do not seek medical assistance except for those individuals who are concerned that their tinnitus may be a sign of a severe disease such as a brain tumor. Most people over the age of 50 occasionally experience tinnitus but many do not find their tinnitus to be a significant problem. Some people who do find their tinnitus debilitating may have given up their attempts to find help from the medical profession.

Hyperacusis

Hyperacusis often is present together with tinnitus. Different definitions of the term hyperacusis are in general use (Jastreboff and Jastreboff, 2004). Some investigators have used the term hyperacusis synonymously to the term hyperesthesia, which for the somatosensory system is defined as "abnormal acuteness of sensitivity to touch, pain, and other sensory stimuli" (Stedman's Concise Medical Dictionary, 26th ed., Baltimore: Williams and Wilkins, 1997). Others have described hyperacusis as an abnormal, lowered tolerance to (any) sound (Baguley, 2003). We will use the definition proposed by Baguley in this chapter.

Hyperacusis often occurs together with tinnitus but may also occur alone. Hyperacusis occurs in most individuals with Williams-Beuren's syndrome (WBS) (Gothelf et al., 2006) (infantile hypercalcaemia), a genetic disorder that is characterized by multiple congenital anomalies including cardiovascular disorders, mental retardation, postnatal growth retardation, and facial anomalies. Hyperacusis also often occurs as a sequel to meningitis and traumatic head injuries and together

with Ramsay-Hunt syndrome and Lyme disease. Discomfort from loud sounds and even fear of sounds (phonophobia) occurs in autism.

Cause of tinnitus

Several layers of complexity are involved in the pathophysiology and the cause of tinnitus and it is rarely known what causes an individual's tinnitus (idiopathic tinnitus). Hearing loss such as from noise exposure or from presbycusis is often followed by tinnitus but not always. Administration of ototoxic substances such as certain antibiotics, diuretics (furosemide), salicylate, and quinine can result in tinnitus. Disorders that affect the CNS such as meningitis, encephalitis, and strokes are often accompanied by tinnitus (and hyperacusis). Traumatic brain injury of various kinds is often accompanied by tinnitus and abnormal perception of sounds and visual stimuli. Herpes infections such as the Ramsey-Hunt syndrome and different forms of injury to the auditory nerve such as surgically induced injuries are often followed by tinnitus.

Other forms of injury to the auditory nerve are often accompanied by tinnitus (Møller, 2006a) and close contact between the auditory nerve and a blood vessel may also cause tinnitus (Chapters 38 and 39).

Tinnitus often begins without any external or internal events can be identified. One possible reason may be the gradual deterioration of neural function that occur with age, characterized by decrease in number of functioning nerve fibers, which is a part of the age-related (normal) decrease in the reserves of the nervous system. Another age-related change includes increase in the variation in conduction velocity as has been shown to occur in the auditory nerve (Spoendlin and Schrott, 1989). Tinnitus may begin when these gradual changes have reached a certain critical level and this form of tinnitus is thus related to the occurrence of a specific event. This makes it difficult to identify the source of many forms of tinnitus.

Tinnitus is one of the three symptoms that characterize Ménière's disease. Individuals who have a vestibular Schwannoma almost always have tinnitus. Tinnitus may accompany bodily disorders that affect the head such as temporomandibular joint (TMJ) disorders (Morgan, 1992) and certain forms of head and neck muscle spasm (Bjorne, 1993; Levine et al., 2003) (see Chapters 17 and 19). Such forms of tinnitus are known as somatic tinnitus (Chapter 10), and when the muscle disorders are resolved, the tinnitus usually also decreases or disappear.

Change in the function of the central nervous system

The changes in the function of the auditory nervous system that can cause tinnitus include altered balance between inhibition and excitation, reorganization of neuronal networks, changes in tonotopic maps, and rerouting of information. Altered balance between inhibition and excitation may cause hyperactivity.

The cochlea normally provides not only excitatory input to the cochlear nuclei but also inhibitory input is abundant. When the cochlea is impaired both excitatory and inhibitory input to the cochlear nucleus is reduced (Caspary et al., 2005), but often inhibitory input is reduced more than excitatory input resulting in a shift in the balance between inhibition and excitation.

Tinnitus is often associated with injuries to the cochlear sensory cells or to auditory nerve fibers. Such injuries cause reduced input to central auditory structures, and in general, inhibitory synapses are affected more than excitatory synapses (Kim et al., 2004) thus creating the basis for hypersensitivity (Gerken et al., 1984) and hyperactivity (Chapter 2).

Deprivation of input to the cochlear nuclei such as has been studied in experimental animals by unilateral removal of one cochlea has been shown to cause a down-regulation of bilateral glycine receptors in the dorsal cochlear nucleus (DCN), the ventral cochlear nucleus (VCN), and the lateral superior olive, and glycinergic activity in the medial superior olive nucleus was strengthened (Suneja et al., 1998; Eggermont, 2005) (Chapter 2). Inhibition is strong in the DCN where fusiform cells receive focused glycinergic inhibiting inputs. Age-related loss of markers for glycinergic

neurotransmission in the DCN occur (Caspary et al., 2005). Loss or reduction of inhibition from the cochlea can also cause increased excitability in other nuclei of the ascending auditory pathways.

The abnormalities in the function of the nervous system that cause many forms of tinnitus are most often a result of expression of neural plasticity that may be brought about by abnormal input from the ear or through abnormal function of the auditory nerve, or by unknown causes (Møller, 2006b) (Chapter 3).

Deprivation of input may cause expression of neural plasticity that can change the relation between inhibition and excitation and protein synthesis (Sie and Rubel, 1992) and cause reorganization of the nervous system (Møller, 2006b), which may cause tinnitus (see Chapter 3). Deprivation of input may also alter temporal integration as shown in animals after deprivation of input (Gerken et al., 1991) and after exposure to loud noise (Szczepaniak and Møller, 1996b). In a similar way, temporal integration of somatosensory stimuli may be altered in individuals with signs of chronic central neuropathic pain (Møller and Pinkerton, 1997) (Chapter 4) (Møller, 2006b).

Anatomical location of the abnormality that cause the sensation of tinnitus

It is of fundamental importance to identify the anatomical location of the physiological abnormality that generates the neural activity that is perceived as tinnitus. Tinnitus is often referred to one ear or both or as coming from the inside of the head. This has resulted in focus on the ear as the location of the physiological abnormality that causes the tinnitus. There is evidence that injuries of cochlear hair cells can be involved in causing tinnitus, at least as a first stage of the development of chronic tinnitus, and there are indications that the auditory nerve may be the primary or secondary cause of some forms of tinnitus (Møller, 1984). However, it has become evident that most forms of severe tinnitus is generated in the CNS and many studies have found evidence that the abnormalities are caused by expression of neural plasticity. This means that the anatomical location of the physiologic abnormalities have incorrectly been assumed to be the ear.

Some studies have involved the possible role of the olivocochlear bundle. The fact that tinnitus can occur after the auditory nerve has been severed is strong evidence that tinnitus can occur without involvement of the ear and that the anatomical site of the physiological abnormalities that causes the sensation of tinnitus is the CNS. It also means that most forms of tinnitus are not generated at the location where the symptoms are felt (the ear) thus similar to, for example, phantom pain. It was therefore a major step forward when it became understood that the neural activity that caused most forms of tinnitus was generated in the nervous system with or without the involvement of the ear. In studies of the role of the CNS in tinnitus the focus has mainly been on three different structures: the DCN, the inferior colliculus, (IC), and the primary and secondary auditory cortices. Indications that the DCN (Chapter 9), IC (Chapter 2), and the cerebral cortex (Chapters 8, 11, and 36) are involved in tinnitus have been presented by many investigators. Little attention has been given to the thalamus.

The neural activity that produces the sensation of tinnitus (see Chapter 3) differs between the different forms of tinnitus and it may be generated in neural structures that are not normally activated by sounds that reach the ear, which can occur because of rerouting of information (see Chapter 3).

Several studies in humans (Ma et al., 2006; Melcher et al., 2000) and in studies in animals (Szczepaniak and Møller, 1996b) indicate that the IC may be implicated in tinnitus in several ways (Chapters 2 and 3). Hyperactivity in the central nucleus of the IC (ICC) is a possible cause of tinnitus. Activation of the external nucleus of the IC (ICX) and the dorsal cortex (DC) of the IC that are parts of the non-classical pathways (earlier known as the non-specific or the extralemniscal pathways (Aitkin, 1986)) may be involved in tinnitus and cause rerouting of information to the non-classical pathways (Chapter 3).

Studies have indicated that the cerebral cortex in humans is implicated in some forms of tinnitus (Mühlnickel et al., 1998). The involvement of the auditory cortex has also been supported by studies

in which electrical or magnetic stimulation of the cerebral cortex have been able to affect tinnitus (Chapters 34, 35, and 36). Some studies using imaging techniques have found evidence of an abnormal activation of the auditory cortices and of the amygdala (Lockwood et al., 1998).

Little attention has been devoted to the thalamic auditory nucleus, the medial geniculate body (MGB), although inference from studies of pain indicates that the MGB may play an important role in some forms of tinnitus. Some of the results of stimulation of the auditory cerebral cortex may in fact have been caused by an effect on the MGB through the descending cortico-thalamic pathways.

The neurons in the DCN receive similar input from the auditory nerve as neurons in the two other parts of the cochlear nucleus, and the DCN has been extensively studied for its role in tinnitus (Chapter 9) (Kaltenbach, 2000; Kaltenbach and Afman, 2000; Kaltenbach et al., 2004) (see Chapter 9) (Levine, 1999). Many features of DCN hyperactivity that may be caused by lack of input are similar to those of tinnitus. Modulation of tinnitus by change of gaze (Cacace et al., 1994; Coad et al., 2001) and jaw movements (Pinchoff et al., 1998) may also be mediated by the DCN. The fact that the DCN receives input from the upper spinal cord (C_2) (Young et al., 1995; Kanold and Young, 2001), which normally has to do with movement of the pinna, may be important for its role in tinnitus. These connections may explain why electrical stimulation of the skin around the outer ear can modulate tinnitus in some individuals (Schulman et al., 1985) and why manipulations of muscles in the mouth (Bjorne, 1993) (Chapter 19) or the neck (Levine, 1999) (Chapter 17) can affect tinnitus. TMJ disorders are often accompanied by tinnitus (Morgan, 1992). Stimulation of C_2 affects neurons in the DCN, and muscle stretch was more effective than skin stimulation indicating that proprioception is important. That explains why stretching of muscles is more efficient in modulating tinnitus than brushing the skin, which means that proprioceptors have a larger influence on the DCN than skin receptors. Proprioceptive input to the DCN from neck muscles would mean that head position has influence on DCN neurons (Kanold and Young, 2001).

Severing the fiber tract that constitutes the output of the DCN, the dorsal stria (stria of Monaco) in animal experiments had little effect on hearing indicating that the DCN normally does not seem to play an important role in hearing (Masterton et al., 1994). This does not mean, however, that the DCN is not involved in generating tinnitus. Normally the DCN seems to be involved in localization behavior rather than processing of sound stimuli (May, 2000). It is generally assumed that the DCN integrate sound localization information with head position.

It has been shown that there are connections between the trigeminal ganglion and the VCN (Shore et al., 2000) and stimulation of the trigeminal ganglion affect responses from single cells in the VCN (Shore et al., 2003) as well as in the DCN (Shore, 2005) (Chapter 10).

The pathophysiology of disorders that have bilateral symptoms are often different from those that have unilateral symptoms and there are many signs that the pathophysiology of unilateral tinnitus is distinctly different from that of bilateral tinnitus. The difference in the pathophysiology of unilateral and bilateral tinnitus can explain why microvascular decompression (MVD) is less efficient in treatment of bilateral tinnitus compared with unilateral tinnitus (Vasama et al., 1998) (Chapters 38 and 39).

Rerouting of information

Rerouting of information may cause structures of the CNS that are normally not involved in processing auditory information to become activated by sound stimulation. An example of such rerouting is an abnormal involvement of the non-classical (non-specific or extralemniscal) pathways. The fact that the perception of tinnitus by some individuals with severe tinnitus is affected by stimulation of the somatosensory system (Møller et al., 1992; Cacace et al., 1994) is a sign of involvement of the nonclassical auditory pathways. Neurons in the nonclassical auditory pathways respond to more than one sensory modality while neurons in the

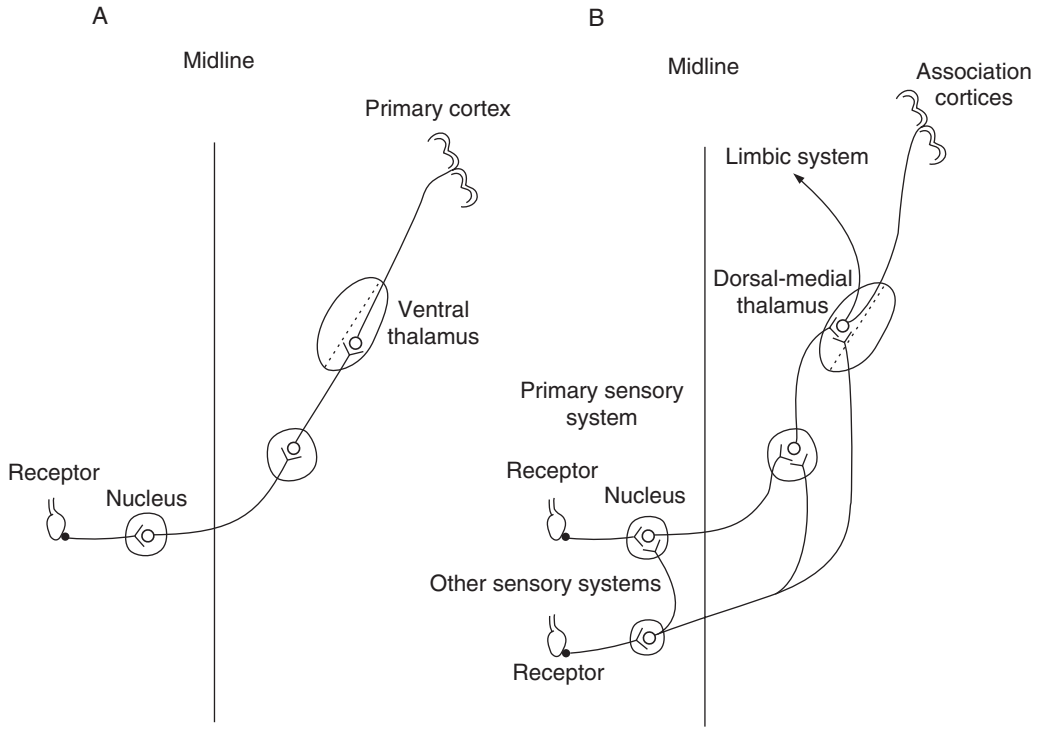

Fig. 1. Schematic drawing of the general outline of the ascending pathways of a sensory system emphasizing the difference and the similarities between the classical (A) and the non-classical pathways (B). (Note that the two receptors in B are from two different sensory systems, for instance auditory and somatosensory.) (Adapted with permission by Elsevier, from Møller, 2003b.)

classical pathways up to and including the primary auditory cortex only respond to auditory stimuli. This means that if only the classical pathways are activated, perception of auditory stimuli cannot be modulated by stimulation of other sensory system. If input from other senses can modulate perception of sound, it is taken as an indication of involvement of the nonclassical auditory system. This fact has been used as a test of the involvement of the nonclassical auditory pathways (Møller et al., 1992; Møller and Rollins, 2002) (Fig. 1).

The anatomical location where the results of somatic stimulation interact with auditory information is the ICX and DC of the IC (Aitkin et al., 1978). These nuclei are parts of the nonclassical auditory pathways, whereas the ICC is part of the classical ascending auditory pathways (Aitkin, 1986; Møller, 2003b). Animal experiments have shown that electrical somatosensory stimulation of the upper body is more efficient than stimulation of the lower body (Aitkin, 1986).

Risk factors for tinnitus

Known risk factors for tinnitus are age, exposure to noise, administration of certain drugs, Ménière's disease, vestibular schwannoma, head trauma, injuries to the auditory nerve, and cardiovascular disorders.

It is well known that tinnitus becomes more prevalent with age. While tinnitus is often associated with noise exposure, administration of ototoxic antibiotics, or hearing loss due to various causes such as age (presbycusis), these same conditions also often occur without tinnitus and tinnitus occurs in individuals who have none of these conditions. Although individuals with tinnitus often have hearing loss, some individuals with normal hearing have tinnitus. Silence can often cause tinnitus in individuals who do not experience tinnitus in a normal environment (Chapter 42). In fact many people, especially elderly, will experience tinnitus in silence such as in a sound insulated

audiologic test room with low ambient noise level and most people will experience tinnitus when in a silent room (anechoic chamber) (Tucker et al., 2005). This means that deprivation of input can cause acute tinnitus. Reduced inhibitory influence from the ear is assumed to cause this kind of tinnitus. Individuals with TMJ disorders often have tinnitus (Morgan, 1992), and TMJ is thus another risk factor for tinnitus. Tinnitus in connection with TMJ problems disappears when the TMJ disorder has been treated successfully (Morgan, 1992). This kind of tinnitus is assumed to be caused by abnormal stimulation of the somatosensory systems (trigeminal system) and it may have to do with stimulation of nerve fibers of the C_2 root of the spinal cord, stimulation of which has been shown to influence cells in the DCN (Young et al., 1995, see p. 8). Problems with neck muscles (Levine, 1999) (Chapter 17) and muscles of the mouth (Chapter 19) are also often accompanied by tinnitus thus indicating that such problems are risk factors for tinnitus.

Treatment of tinnitus

Progress in so many areas of care of the sick has depended on studies of epidemiology, basic research (pathophysiology), clinical research, and experience of different kinds of treatment. Progress in treatment of tinnitus may come from basic science that provides increased knowledge about the changes in the ear and the nervous system that underlies tinnitus. Areas of basic science that may contribute to understanding of the pathophysiology of tinnitus include hearing science, neuroscience, biochemistry, molecular biology, epidemiology, and genetics. Exploring similarities between some forms of tinnitus and some forms of neuropathic (physiological) pain may provide suggestions about treatments of some forms of tinnitus. Inability to distinguish between different forms of tinnitus and lack of adequate objective diagnostic methods are obstacles in the management of the tinnitus patient (see Chapter 22). It is an obstacle in treatment of tinnitus that patients do not have a clear direction regarding which specialty of the medical profession to consult. At the present state of understanding of the pathology of tinnitus, treatment of the various forms of tinnitus would benefit from involvement of several clinical specialties such as neurology, psychiatry, psychology, audiology, and otolaryngology.

Progress in treatment may also come from serendipitous observations, and from clinical experience of treatment of patients with other disorders when these patients also have tinnitus. Many effective treatments of a wide range of disorders have been discovered in that way. However, as Louis Pasteur said ‘‘Chance favors only the prepared mind.’’ Therefore only the prepared clinician can take advantage of such incidences. To facilitate serendipitous discoveries that can benefit treatment of tinnitus, physicians within all specialties of medicine should have basic knowledge about tinnitus and medical schools should be encouraged in teaching the basics about tinnitus. Even though there are many forms of pain, there are treatments (analgesics) that can reduce or eliminate most forms of pain. There is no known comparable medication that can benefit patients with different forms of tinnitus.

The fact that tinnitus has many forms and that there are no diagnostic methods that can separate individuals with different forms of tinnitus are major obstacles in testing possible treatments for tinnitus.

Now, different forms of treatment are in clinical use such as tinnitus retraining therapy (TRT) (Chapter 40) and other forms of therapies that use counseling together with sound stimulation (Chapters 41, 42, and 44). Use of surgical treatment such as MVD (Chapters 38 and 39), stimulation of the cochlea through cochlear implants (Chapter 33), and stimulation of the auditory cortex (Chapters 34, 35, and 36) are beginning to be used in some specialized clinics.

Many substances have been tried for treatment of tinnitus (Chapters 23, 24, 25, 27, and 30). Some are based on evidence that reduced inhibitory influence is involved in some forms of tinnitus and it is known that the number of gamma aminobutyric acid (GABA)-immunoreactive neurons in the auditory nuclei decreases with age (Caspary et al., 1990, 1999) (Chapter 2). Efforts to restore or enhance the function of these receptors have been made using administration of substances such as

benzodiazepines that interact with (enhance) $GABA_A$ receptors. Substances that increase the level of GABA in the CNS (Vigabatrin, Brozoski et al., 2007; Gabapentin, Chapter 27) have been tried in humans and in animal experiments.

It has also been hypothesized that $GABA_B$ receptors were involved in some forms of tinnitus and the $GABA_B$ agonist, baclofen, has been tried in humans and in animal models of tinnitus. While animal studies have been encouraging (Szczepaniak and Møller, 1996a), attempts to use baclofen in treatment of tinnitus showed a non-significant difference from placebo (Westerberg et al., 1996). However, baclofen provided improvements in 9.7% after 3 weeks treatment compared with 3.4% for placebo. Again, 2.5 times as many had benefited from baclofen as placebo; while this difference was not significant, the results of the trial may indicate that the population that was studied might have had several different kinds of tinnitus (see p. 4). The beneficial effect on one of these kinds of tinnitus may have reached a level of significance if studied alone.

Serotonergic activity is affected by administration of salicylate that can cause tinnitus (Chapter 2), and that may explain why selective serotonin re-uptake inhibitors (SSRIs) that manipulate the serotonin can, however, also increase tinnitus (Chapter 24). The *N*-methyl-D-aspartic acid (NMDA) (glutamate) receptor is most likely also involved in tinnitus, as it is in many forms of central neuropathic pain. However, attempts to use NMDA receptor inhibitors (such as the MK801 experimental drug) in treatment of pain have not been successful (Møller, 2006b). While it has been shown that aspirin activate cochlear NMDA receptors and that application of an NMDA receptor antagonist at the round window abolishes tinnitus (Chapter 12), administration of an NMDA antagonist, flupirtine, a drug that is similar to Memantine, had little effect on tinnitus in animal experiments (Salembier et al., 2006). Memantine, used to treat neuropathic pain and Alzheimer's disease, acts both on the glutamate and the cholinergic systems. The drug suppresses glutamatergic transmission in hair cells and it is known from animal studies that salicylate acts on the glutamate system in hair cells (Lobarinas et al., 2006). More exotic substances such as Acamprosat, a drug used for treatment of alcohol dependence and which is an antagonist to glutamate and an agonist to GABA receptors, have been tried in treatment of tinnitus with some success (Chapter 25). The fact that motor systems are involved in some forms of tinnitus has inspired the tests of substances that affect the motor systems, such as botulinum toxin (Chapter 31).

The effect of lidocaine on tinnitus has been studied by many investigators (Chapter 28) but the fact that it has to be administrated intravenously makes it unsuitable for general practical use in treatment of tinnitus. Lidocaine, a local anesthetic with complex action on the CNS, is primarily a sodium channel blocker (see Chapter 28). Attempts to find drugs with similar beneficial effect on tinnitus and which can be administrated orally have not been successful. Tocainide was developed with that in mind but its effect was questionable and it has severe side effects (Emmett and Shea, 1980; Lenarz, 1986). The benefit of using dietary supplements such as vitamins and minerals in treatment of tinnitus is controversial (see Chapters 26 and 29).

Electrical stimulation of the cochlea (Cazals et al., 1978; Rubinstein et al., 2003) is one such attempt that has been tried with some success. In people with hearing loss, electrical stimulation of the cochlea can suppress tinnitus (McKerrow et al., 1991; Miyamoto and Bichey, 2003; Rubinstein et al., 2003) (Chapter 33), and even in patients with near normal hearing and tinnitus (Sininger et al., 1987).

Sound stimulation and psychological treatment (counseling) such as the TRT (Jastreboff and Jastreboff, 2000) (Chapter 40), tinnitus habituation therapy (Hallam et al., 1984), tinnitus activities treatment (Chapter 41) (Tyler and Baker, 1983) have been shown to be beneficial to individuals with some forms of tinnitus.

More recently, electrical stimulation of the cerebral cortex (Plewnia et al., 2003, 2007; De Ridder et al., 2005; Kleinjung et al., 2005) (see Chapters 34, 35, and 36) has shown ability to alleviate some forms of tinnitus. These are thus similar treatments to what has been in use for treatment of central neuropathic pain such as transderm electric

nerve stimulation (TENS), dorsal column stimulation, thalamic stimulation, premotor cortex stimulation, etc. (Melzack and Wall, 1999). Thalamic stimulation has not been described for treatment of tinnitus but it is possible that electrical (and magnetic) stimulation of the cerebral auditory cortex acts on the thalamus through the cortico-thalamic tract.

Attempts to influence neurons in the DCN by electrical stimulation of the skin behind the ear has shown beneficial effect on tinnitus (Schulman et al., 1985). This implies activation of nerve fibers of the C_2 root, stimulation of which is known to affect the activity in the DCN (Young et al., 1995; Kanold and Young, 2001).

However, also electrical stimulation on other location on the body such as the median nerve (Møller et al., 1992) has been shown to modulate tinnitus in some individuals. This may be achieved through different mechanism. The ICX and DC of the IC receive input from the dorsal column nuclei (Aitkin, 1986), and there is evidence that the ICX and DC are involved in the nonclassical auditory pathways and thereby such stimulation may influence activity in the nonclassical auditory pathways (Møller et al., 1992).

The MVD operation on the auditory nerve intracranially is an effective treatment for some patients with tinnitus (Chapter 38) (Møller et al., 1993). MVD is also an effective treatment for some pain disorders of cranial nerves V and IX, and of nervous intermedius (Møller, 1998). The success rate of this form of treatment for tinnitus depends on the time the individual has had symptoms and the success has been shown to be much higher in women than in men (55 vs. 29%) (Møller et al., 1993).

Clinical trials for treatment of tinnitus

Rigorous studies of the efficacy of medications for tinnitus are few (Dobie, 1999) (Chapter 48), and many are case reports and anecdotes. Double blind tests for determining the efficacy often indicate that a drug has a low degree of efficacy over placebo (Robinson et al., 2005) (Chapter 24).

The heterogeneity of tinnitus complicates clinical trials of new treatments and it may make the results to be misleading because the tinnitus of the different participants in such trials are likely to have different pathophysiology and therefore not amendable to the same treatment. Currently established test criteria (double blind) for new treatments are therefore not suitable for tinnitus because it is not possible to distinguish between tinnitus with different pathophysiology, and the participants in trials inevitably would have different forms of tinnitus. Treatments may have been discarded because of that, which is unfortunate if the treatment is beneficial to patients, which must be the goal of treatment, and not to satisfy some scientific criteria. If the treatment that is tested is 80% effective in one form of tinnitus that has a 20% representation in the study, the study will show an efficacy of 16%, which is not impressive and most likely will lead to discarding of the treatment as ineffective. That means that the samples of individuals who have a large likelihood of benefit have often been diluted by individuals with other forms of tinnitus (that produce similar symptoms) and thereby distort the results of trials of treatments.

Interpretations of trials of the efficacy of a drug in treatment of diseases that have one single cause, such as, for example, pneumonia caused by bacterial infections, are straightforward and the effect of treatment can be validated without being influenced by any noticeable placebo effect. Trials of the efficacy of treatment for complex and poorly defined disorders such as tinnitus and central neuropathic pain are difficult to design and the results of such trials are difficult to interpret and often such trials give controversial results when repeated by other investigators.

The considerable placebo effect of many of the treatments that have been tried for tinnitus may be regarded to be an obstacle in evaluating results of trials of efficacy of treatment but it supports the experience that counseling is an effective component of treatment of many forms of tinnitus (see Chapters 40 and 41).

If a patient with tinnitus feels benefit from a specific treatment despite the treatment has not received the scientific certificate of effectiveness or other patients with tinnitus do not experience the same benefit, should the treatment not be

continued on that patient? Whether the cause of the beneficial effect is called placebo effect or an unusual incidence is irrelevant to the patient, but an authoritative denial of the beneficial effect from the patient's physician can make the patient terminate the treatment.

Involvement of the sympathetic nervous system

Sympathetic nerve fibers may liberate noradrenaline that terminate near hair cells in the cochlea (Densert, 1974) and these may sensitize hair cells upon increased activity of the sympathetic nervous system (see Chapter 4). The sympathetic nervous system may also be involved in noise induced hearing loss (temporary threshold shift (Hildesheimer et al., 1991)) that often is associated with tinnitus. Tinnitus is related to stress as indicated by a study that found that cortisol reactivity to psychosocial stress is blunted in tinnitus sufferers (Hebert and Lupien, 2007). It was shown a long time ago that sympathectomy can relieve tinnitus in patients with Ménière's disease (Passe, 1951).

Future

For many years tinnitus was regarded as an auditory disorder and because it was often referred to the ear, the ear became the focus of studies of the pathophysiology of tinnitus and for the search of treatment. Recent studies and experience have shown that tinnitus is far more complex and that the anatomical location of the physiological abnormalities that cause the tinnitus is instead the CNS for most forms of subjective tinnitus. Implicating the CNS in the generation of the abnormal nervous activities that cause tinnitus was a major step forward and this progress was achieved by researchers who were "thinking outside the box." There is no doubt that more of that kind of thinking is what can bring important progress in the future regarding understanding of the pathophysiology of tinnitus and regarding development of effective treatments.

More efficient organization of research will facilitate research and search for better treatment. Because of its complexity and diversity individual patients with tinnitus would benefit from a multidisciplinary approach regarding their treatment. Treatment and research on tinnitus therefore would benefit from a multidisciplinary approach involving neurologists, psychiatrists, and psychologists in addition to audiologists and otolaryngologists. The clinicians of these different disciplines should be educated about the neurophysiologic basis for tinnitus and the basic scientists should be educated about clinical aspects of tinnitus. It is also important that clinicians in other fields have an understanding of tinnitus so that they can be prepared for unforeseen events that may suggest useful treatment methods.

Researchers who work on tinnitus would benefit from being acquainted with progress in other fields of medicine. Many forms of tinnitus have similarities with different forms of neuropathic pain especially chronic central neuropathic pain (Chapter 4) (Møller, 2006b). Tinnitus is often associated with different forms of affective symptoms and it would be interesting to know if that is associated with activation of specific CNS structures. For example, it is known that inescapable and escapable pain use different parts of the periaqueductal gray (PAG) (Keay et al., 2001; Lumb, 2002). It would be interesting to know if there is a similar anatomical separation of different forms of affective disorders that occur together with tinnitus.

Conclusion

The pathophysiology of the different forms of tinnitus is far more complex than earlier assumed, and each one of the many different forms of tinnitus may have different pathophysiology and consequently requires different kinds of treatment to obtain the best benefits. The fact that tinnitus is not a single disease and that there are no methods available that can differentiate between tinnitus of different causes is an obstacle for diagnosing tinnitus and for treatment. It is also an obstacle in testing the efficacy of treatments because it is not possible to assemble a group of participants who have the same form of tinnitus for studies of the efficacy of treatments. It was an important step

forward when it became documented that the anatomical location of the physiological abnormality that cause the tinnitus was not always the ear but the CNS. Understanding that expression of neural plasticity is the cause of many forms of tinnitus or at least play an important role in creation of the neural activity that plays an important role in causing tinnitus was equally important.

Abbreviations

BPPN	benign positional paroxysmal nystagmus
CNS	central nervous system
DC	dorsal cortex (of the IC)
DCN	dorsal cochlear nucleus
DPV	disabling positional vertigo
GABA	gamma aminobutyric acid
HFS	hemifacial spasm
IC	inferior colliculus
ICC	central nucleus (of the IC)
ICX	external nucleus (of the IC)
MGB	medial geniculate body
NMDA	*N*-methyl-D-aspartic acid
MVD	microvascular decompression
SL	sensation level
TENS	transderm electric nerve stimulation
TMJ	temporomandibular joint (disorder)
TRT	tinnitus retraining therapy
VAS	visual analog scale
VCN	ventral cochlear nucleus
WBS	Williams-Beuren's syndrome

References

Ahmad, N. and Seidman, M. (2004) Tinnitus in the older adult: epidemiology, pathophysiology and treatment options. Drugs Aging, 21: 297–305.

Aitkin, L.M. (1986) The Auditory Midbrain: Structure and Function in the Central Auditory Pathway. Humana Press, Clifton, NJ.

Aitkin, L.M., Dickhaus, H., Schult, W. and Zimmermann, M. (1978) External nucleus of inferior colliculus: auditory and spinal somatosensory afferents and their interactions. J. Neurophysiol., 41: 837–847.

Baguley, D.M. (2003) Hyperacusis. J. R. Soc. Med., 96: 582–585.

Bauer, C.A., Brozoski, T.J., Rojas, R., Boley, J. and Wyder, M. (1999) Behavioral model of chronic tinnitus in rats. Otolaryngol. Head Neck Surg., 121: 457–462.

Bjorne, A. (1993) Tinnitus aurum as an effect of increased tension in the lateral pterygoid muscle (letter). Otolaryngol. Head Neck Surg., 109: 5558.

Brozoski, T.J., Spires, J.D. and Baure, C.A. (2007) Vigabatin: a GABA transaminase inhibitor, reversibly eliminates tinnitus in an animal model. JARO, 8: 105–118.

Cacace, A.T., Lovely, T.J., McFarland, D.J., Parnes, S.M. and Winter, D.F. (1994) Anomalous cross-modal plasticity following posterior fossa surgery: some speculations on gaze-evoked tinnitus. Hear. Res., 81: 22–32.

Caspary, D.M., Holder, T.M., Hughes, L.F., Milbrandt, J.C., McKernan, R.M. and Naritoku, D.K. (1999) Age-related changes in $GABA_A$ Receptor subunit composition and function in rat auditory system. Neuroscience, 93: 307–312.

Caspary, D.M., Raza, A., Lawhorn, Armour, B.A., Pippin, J. and Arneric, S.P. (1990) Immunocytochemical and neurochemical evidence for age-related loss of GABA in the inferior colliculus: implications for neural presbycusis. J. Neurosci., 10: 2363–2372.

Caspary, D.M., Schatteman, T.A. and Hughes, L.F. (2005) Age-related changes in the inhibitory response properties of dorsal cochlear nucleus output neurons: role of inhibitory inputs. J. Neurosci., 25: 10952–10959.

Cazals, Y., Negrevergne, M. and Aran, J.M. (1978) Electrical stimulation of the cochlea in man: hearing induction and tinnitus suppression. J. Am. Audiol. Soc., 3: 209–213.

Coad, M.L., Lockwood, A.H., Salvi, R.J. and Burkhard, R. (2001) Characteristics of patients with gaze-evoked tinnitus. Otol. Neurotol., 22: 650–654.

De Ridder, D., De Mulder, G., Walsh, V., Muggleton, N., Sunaert, S., Verlooy, J., Van de Heyning, P. and Møller, A.R. (2005) Transcranial magnetic stimulation for tinnitus — a clinical and pathophysiological approach: influence of tinnitus duration on stimulation parameter choice and maximal tinnitus suppression. Otol. Neurotol., 147: 495–501.

Densert, O. (1974) Adrenergic innervation in the rabbit cochlea. Acta Otolaryngol. (Stockh.), 78: 345–356.

Dobie, R.A. (1999) A review of randomized clinical trials in tinnitus. Laryngoscope, 109: 1202–1211.

Eggermont, J.J. (2005) Tinnitus: neurobiological substrates. Drug Discov. Today, 10: 1283–1290.

Emmett, J.R. and Shea, J.J. (1980) Treatment of tinnitus with tocainide hydrochloride. Otolaryngol. Head Neck Surg., 88: 442–446.

Fowler, E.P. (1942) The illusion of loudness of tinnitus: its etiology and treatment. Ann. Otol. Laryngol., 52: 275–285.

Gerken, G.M., Hesse, P.S. and Wiorkowski, J.J. (2001) Auditory evoked responses in control subjects and in patients with problem tinnitus. Hear. Res., 157: 52–64.

Gerken, G.M., Saunders, S.S. and Paul, R.E. (1984) Hypersensitivity to electrical stimulation of auditory nuclei follows hearing loss in cats. Hear. Res., 13: 249–260.

Gerken, G.M., Solecki, J.M. and Boettcher, F.A. (1991) Temporal integration of electrical stimulation of auditory nuclei in normal hearing and hearing-impaired cat. Hear. Res., 53: 101–112.

Gothelf, D., Farber, N., Raveh, E., Apter, A. and Attias, J. (2006) Hyperacusis in Williams syndrome: characteristics and associated neuroaudiologic abnormalities. Neurology, 66: 390–395.

Hallam, R., Rachman, S. and Hinchcliffe, R. (1984) Psychological aspects of tinnitus. In: Rachman S. (Ed.), Contributions to Medical Psychology. Pergamon Press, Oxford, pp. 31–53.

Hebert, S. and Lupien, S.J. (2007) The sound of stress: blunted cortisol reactivity to psychosocial stress in tinnitus sufferers. Neurosci. Lett., 411: 138–142.

Henry, J.A., Dennis, K.C. and Schechter, M.A. (2005) General review of tinnitus: prevalence, mechanics, effects, and management. J. Speech Lang. Hear. Res., 48: 1204–1235.

Hildesheimer, M., Sharon, R., Muchnik, C., Sahartov, E. and Rubinstein, M. (1991) The effect of bilateral sympathectomy on noise induced temporary threshold shift. Hear. Res., 51: 49–53.

Hoffmann, H.J. and Reed, G.W. (2004) Epidemiology of tinnitus. In: Snow J.B. (Ed.), Tinnitus: Theory and Management. B.C. Decker, Hamilton, pp. 16–41.

Jastreboff, P.J. (1989) An animal model of tinnitus: development, present status, perspectives. Hear. J., 42: 58–63.

Jastreboff, P.J. (1990) Phantom auditory perception (tinnitus): mechanisms of generation and perception. Neurosci. Res., 8: 221–254.

Jastreboff, P.J., Brennan, J.F., Coleman, J.K. and Sasaki, C.T. (1988) Phantom auditory sensation in rats: an animal model for tinnitus. Behav. Neurosci., 102: 811–822.

Jastreboff, P.J. and Jastreboff, M.M. (2000) Tinnitus retraining therapy (TRT) as a method for treatment of tinnitus and hyperacusis patients. J. Am. Acad. Audiol., 11: 162–177.

Jastreboff, P.J. and Jastreboff, M.M. (2004) Decreased sound tolerance. In: Snow J.B. (Ed.), Tinnitus: Theory and Management. B.C. Decker, Hamilton, pp. 8–15.

Jastreboff, P.J. and Jastreboff, M.M. (2006) Tinnitus retraining therapy: a different view on tinnitus. ORL J. Otorhinolaryngol. Relat. Spec., 68: 23–29.

Kaltenbach, J.A. (2000) Neurophysiologic mechanisms of tinnitus. J. Am. Acad. Audiol., 11: 125–137.

Kaltenbach, J.A. and Afman, C.E. (2000) Hyperactivity in the dorsal cochlear nucleus after intense sound exposure and its resemblance to tone-evoked activity: a physiological model for tinnitus. Hear. Res., 140: 165–172.

Kaltenbach, J.A., Zacharek, M.A., Zhang, J. and Frederick, S. (2004) Activity in the dorsal cochlear nucleus of hamsters previously tested for tinnitus following intense tone exposure. Neurosci. Lett., 355: 121–125.

Kanold, P.O. and Young, E.D. (2001) Proprioceptive information from the pinna provides somatosensory input to cat dorsal cochlear nucleus. J. Neurosci., 21: 7848–7858.

Keay, K.A., Clement, C.I., Depaulis, A. and Bandler, R. (2001) Different representations of inescapable noxious stimuli in the periaqueductal gray and upper cervical spinal cord of freely moving rats. Neurosci. Lett., 313: 17–20.

Kim, J.J., Gross, J., Potashner, S.J. and Morest, D.K. (2004) Fine structure of long-term changes in the cochlear nucleus after acoustic overstimulation: chronic degeneration and new growth of synaptic endings. J. Neurosci. Res., 77: 817–828.

Kleinjung, T., Eichhammer, P., Langguth, B., Jacob, P., Marienhagen, J., Hajak, G., Wolf, S.R. and Strutz, J. (2005) Long-term effects of repetitive transcranial magnetic stimulation (rTMS) in patients with chronic tinnitus. Otolaryngol. Head Neck Surg., 132: 566–569.

Lenarz, T. (1986) Treatment of tinnitus with lidocaine and tocainide. Scand. Audiol. (Stockh.), 26: 49–51.

Levine, R.A. (1999) Somatic (craniocervical) tinnitus and the dorsal cochlear nucleus hypothesis. Am. J. Otolaryngol., 20: 351–362.

Levine, R.A., Abel, M. and Cheng, H. (2003) CNS somatosensory-auditory interactions elicit or modulate tinnitus. Exp. Brain Res., 153: 643–648.

Lobarinas, E., Yang, G., Sun, W., Ding, D., Mirza, N., Dalby-Brown, W., Hilczmayer, E., Fitzgerald, S., Zhang, L. and Salvi, R. (2006) Salicylate- and quinine-induced tinnitus and effects of memantine. Acta Otolaryngol. Suppl., 556.

Lockwood, A., Salvi, R., Coad, M., Towsley, M., Wack, D. and Murphy, B. (1998) The functional neuroanatomy of tinnitus: evidence for limbic system links and neural plasticity. Neurology, 50: 114–120.

Lumb, B.M. (2002) Inescapable and escapable pain is represented in distinct hypothalamic-midbrain circuits: specific roles of Ad- and C-nociceptors. Exp. Physiol., 87: 281–286.

Ma, W.L., Hidaka, H. and May, B.J. (2006) Spontaneous activity in the inferior colliculus of CBA/J mice after manipulations that induce tinnitus. Hear. Res., 212: 9–21.

Masterton, R.B., Granger, E.M. and Glendenning, K.K. (1994) Role of acoustic striae in hearing: mechanism for enhancement of sound detection in cats. Hear. Res., 73: 209–222.

May, B.J. (2000) Role of the dorsal cochlear nucleus in the sound localization behavior of cats. Hear. Res., 48: 74–87.

McKerrow, W.S., Schreiner, C.E., Snyder, R.L., Merzenich, M.M. and Toner, J.G. (1991) Tinnitus suppression by cochlear implants. Ann. Otol. Rhinol. Laryngol., 100: 552–558.

Melcher, J.R., Sigalovsky, I.S., Guinan Jr., J.J. and Levine, R.A. (2000) Lateralized tinnitus studied with functional magnetic resonance imaging: abnormal inferior colliculus activation. J. Neurophysiol., 83: 1058–1072.

Melzack, R. and Wall, P.D. (1999) Textbook of Pain (4th ed.). Churchill Livingstone, Edinburgh.

Miyamoto, R.T. and Bichey, B.G. (2003) Cochlear implantation for tinnitus suppression. Otolaryngol. Clin. North Am., 36: 345–352.

Møller, A.R. (1984) Pathophysiology of tinnitus. Ann. Otol. Rhinol. Laryngol., 93: 39–44.

Møller, A.R. (1998) Vascular compression of cranial nerves I: history of the microvascular decompression operation. Neurol. Res., 20: 727–731.