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Pharmacological Strategies for Prevention and Treatment of Hearing Loss and Tinnitus

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The goal of this special issue is to focus on major developments related to the biological mechanisms that underlie noise, drug and age-related hearing loss and tinnitus and to review some of the new pharmacologic approaches to prevention and treatments of hearing loss and tinnitus. Hearing loss and tinnitus have long been recognized as serious and pervasive health problems. In industrialized societies where noise levels are increasing, hearing loss in the young and middle aged builds up over many years as a result of incessant exposure to moderate levels of noise in the work place (e.g., machinery) or recreational environments (e.g., loud music, motor cycles). In some cases, the onset of hearing loss and tinnitus occur almost immediately after extremely high level impact (e.g., jack hammer) or impulse noise (e.g., gun fire, explosion). Nowhere is the problem more serious than in the military where approximately 30% of combat personnel develop significant hearing loss or tinnitus. The Veterans Administration rank hearing loss and tinnitus among its 10 most common disabilities.

Drugs used to treat life threatening infections or malignant tumors may prolong an individual's life, but at the expense of developing severe high frequency hearing loss and tinnitus. Cisplatin, which is widely used to treat many forms of cancer leads to irreversible high-frequency hearing loss in approximately 30% of children and in adults the incidence of hearing loss ranges from 4% to 91%. Aminoglycoside antibiotics, which are extremely effective in treating gram negative bacterial infections are seldom used in the West because they are both ototoxic and nephrotoxic. However, aminoglycoside antibiotics are among the most widely used antibiotics in third world countries because of their low cost and therapeutic efficacy.

Those who manage to avoid hearing loss in early life cannot escape the ravages of age. By age 65, approximately 31% of the population has significant age-related hearing loss or presbycusis. By age 75, the prevalence increases to nearly 50%. Hearing loss is often accompanied by tinnitus, the ringing, rushing, buzzing or clicking sensation that occurs in the absence of sound. Approximately 12 million American seek medical treatment for tinnitus; and of these, 2 million experience tinnitus that is severe and disabling.

For more than 50 years, the prevention and treatment of hearing loss and tinnitus has largely focused on prevention, avoiding ototoxic drugs and high level noise that cause hearing loss or wearing hearing protectors. However, during the past decade scientists in many disciplines, including those working on the inner ear, have made enormous progress in understanding the biochemical events that can trigger the death of hair cells and spiral ganglion neurons either by necrosis or the carefully orchestrated biochemical cell death process known as apoptosis.

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A common theme that has emerged from recent studies of hearing loss from noise, ototoxic drugs or aging is that hearing loss is initiated by oxidative stress involving the overproduction of reactive oxygen species that overwhelm the cell's antioxidant defense system. In order to dissect out the role of cellular antioxidant enzymes in noise, drug or age-related hearing loss, researchers have used gene therapy approaches or transgenic or knockout mice that over or under express antioxidant enzymes or genes that enhance or inhibit apoptosis. Others have used pharmacologic strategies to upregulate antioxidant defenses or to block specific cell death pathways.

While the signaling pathways that modulate or regulate cell death from noise exposure, ototoxic drugs and aging are likely to share some similarities there may be important differences. Pharmacologic compounds that protect against aminoglycoside ototoxicity may or may not protect against cisplatin, acoustic trauma or aging. The biological pathways that lead to noise, drug or age related hearing loss may vary with the degree of stress imposed by a particular agent. Compounds that protect against low levels of stress may be ineffective at higher levels of stress. Animal studies have illustrated the important role that genetic factors have on age-related hearing loss as well as noise and drug-induced hearing loss. Knowledge of the role specific genes play in hearing loss may one day lead to individualized pharmacological treatments for preventing hearing loss.

Armed with the knowledge that oxidative stress is an important factor in noise, age and drug induced hearing loss, auditory scientists and clinicians have tested a host of compounds designed to scavenge or inactivate ROS, boost or upregulate cellular antioxidant defense systems or block apoptotic pathways. Animals studies of noise, drug or age-related hearing loss that have shown promise in the laboratory are gradually making their way into translational research studies aimed at evaluating the clinical efficacy of different therapeutic approaches.

Tinnitus is a continuously growing problem in all societies and often occurs together with hearing loss. Tinnitus is also accompanied by hyperacusis, and sometimes depression, indicating altered processing of both auditory information and non-auditory information, as well as altered expression of neural plasticity. At present, there is no general treatment for tinnitus, but there are several treatments that can alleviate or reduce the tinnitus in some patients. Antidepressant drugs have been successfully used to treat tinnitus in some patients with and without depressive symptoms. The basis for this therapy is based on the interplay between non-auditory brainstem structures and the central auditory pathways. Attempts to develop effective tinnitus therapies will benefit from a greater understanding of how the activity in the auditory pathway is altered by different states of activation of these non-auditory brainstem structures and vice versa. Pharmacological strategies for tinnitus have been hampered by the lack of suitable animal models. Salicylate-induced tinnitus is one of the animal models used over many years and is yielding information on the mechanisms responsible for this disorder. Reviewed in this Special Issue is a combination of new theoretical and experimental approaches, together with clinical findings that are increasing our understanding of tinnitus, its origin, underlying causes and its suppression.

The organizers, with cooperation from the National Institute for Occupational Safety and Health, believed that research on cochlear therapeutics had advanced to the state that it would be interesting and useful to arrange a meeting of leading scientists and representatives from the pharmaceutical industry. The U.S. Army, with guidance provided by Col. Nancy Vause, recognized the importance of the meeting very early in the planning stages and arranged financial support for the invited speakers and guidance for future development. The meeting was held in Niagara Falls, Ontario in October, 2005. In this special issue of *Hearing Research* are key papers that were presented at the meeting. The intellectual design was to

review the states of conventional protection strategies and then move into pharmacological prevention of noise-induced hearing loss, drug induced hearing loss and tinnitus.

Meeting Sponsors

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