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ADVANCES IN ADULT AND PEDIATRIC EAR, NOSE, AND THROAT

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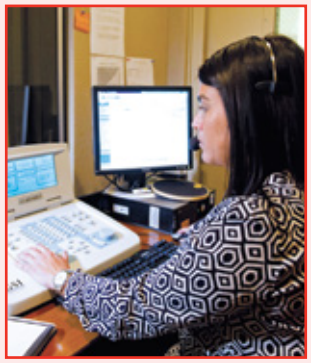

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Noise Induced Hearing Loss: Identifying Targets for Prevention

Accumulation of free radicals, which can be caused by environmental stress from intense noise, plays a key role in hearing loss and cell death in the inner ear. Otolaryngologist Kevin D. Brown, MD, PhD, Department of Otolaryngology – Head and Neck Surgery of NewYork-Presbyterian/Weill Cornell Medical Center, is trying to alter these outcomes through research he is pursuing on a class of molecules called sirtuins, specifically sirtuin 3 – an enzyme within the mitochondria of the cells.

"Mitochondria are responsible for producing the energy that makes cells work," says Dr. Brown. "They also respond to changes in energy requirements. Cells within the cochlea have high energy requirements. Any problems that exist within or put stress on the mitochondria then have a tendency to either acutely, or over time, affect hearing."

By focusing on the biological activities of sirtuin 3 and how they might be regulated, Dr. Brown seeks to identify therapeutic targets for preventing hearing loss.

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Dr. Kevin Brown and his colleagues are, in essence, utilizing a natural compound to stimulate the body's own machinery to protect against noise injury.

A New Perspective on Partial Versus Total Tonsillectomy

A joint retrospective study of factors contributing to cost in the performance of partial intracapsular and traditional total tonsillectomy by faculty members of the Departments of Otolaryngology – Head and Neck Surgery at NewYork-Presbyterian/Columbia University Medical Center and NewYork-Presbyterian/Weill Cornell Medical Center sheds new light on the time and resources involved for each method.

"This study examined two different techniques for doing a tonsillectomy, which at 300,000 to 400,000 a year, is the most common procedure performed in children in the country," says Vikash K. Modi, MD, a pediatric otolaryngologist with NewYork-Presbyterian/Weill Cornell. "The primary reason we remove tonsils is because children have difficulty with sleep. The tonsils become so large that they obstruct the airway. It has already been proven in multiple studies that patients do equally well with either surgery. However, the two techniques have never really been studied from a cost comparison standpoint."

"Some of the faculty in the Weill Cornell group were early adopters of the partial tonsillectomy technique, while the Columbia campus was more representative of what the rest of the country was doing with the standard technique, which was the total tonsillectomy," notes Eli Grunstein, MD, Assistant Director of Pediatric Otolaryngology at NewYork-Presbyterian/Columbia.

"Having two university-based tertiary care hospitals under the same umbrella institution gave us a good way to study the two procedures and their differences," says Dr. Modi. "We have the same PACU and discharge criteria, as well as the same ENT residents who travel to both campuses."

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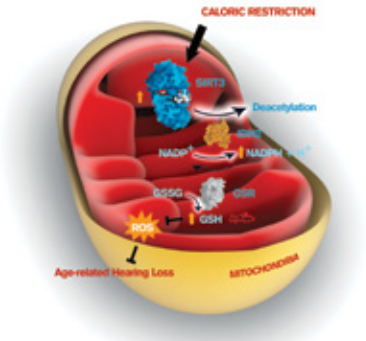
Noise Induced Hearing Loss: Identifying Targets for Prevention *(continued from page 1)*

Identifying the Role of Sirtuin 3

"One of the ways to activate sirtuins is to increase a particular energetic intermediate called NAD, which is nicotinamide adenine dinucleotide, found in all living cells," says Dr. Brown.

Dr. Brown and his colleagues used genetically modified mouse models to either produce more NAD or produce more sirtuin 3. They evaluated whether these animals were less likely to have hearing loss from noise exposure, and found that this was, in fact, the case. Animals that either had an increased capacity for producing NAD or an increased level of sirtuin 3 were protected against noise induced hearing loss. Dr. Brown, in collaboration with Weill Cornell colleague Anthony A. Sauve, PhD, Associate Professor of Pharmacology, then utilized a compound – nicotinamide riboside – synthesized by Dr. Sauve that could increase NAD, and administered it to the animals before they were subjected to noise exposure.

"We were able to demonstrate in a mouse model that the administration of this compound effectively prevented them from having both the short-term transient loss as well as the long-term loss of hearing that occurs with noise exposure," says Dr. Brown. "This was really quite incredible. Nicotinamide riboside is metabolized to NAD, which in turn activates the enzymatic activity of sirtuin 3. Sirtuin 3 then acts as master regulator of mitochondrial metabolism, bringing the mitrochondria to a more favorable state that enables them to continue to function during periods of stress.



Using genetically modified mouse models, Dr. Kevin Brown and his colleagues found that animals that had an increased level of sirtuin 3 were found to be protected against noise induced hearing loss.

Dr. Brown then wished to determine the mechanism by which NAD prevents hearing loss. "One of the features of NAD seen in models of neurodegeneration is that if NAD is over-expressed or added exogenously, you tend to prevent the breakdown of the connections [axons/neurites] between nerve cells and their targets," explains Dr. Brown. "We therefore investigated the connection between the spiral ganglion neuron and the inner hair cell in the cochleas that were treated with nicotinamide riboside to see if there was a difference in the degree of degeneration of their neurites. We found that deterioration in the noise-treated animals was prevented by administration of nicotinamide riboside. It therefore appears that this compound is preventing breakdown of connections between nerve cells and inner hair cells in the cochlea following noise injury."

Exploring Other Conduits of Hearing Loss

With the goal of providing a pharmacologic approach to prevent or treat the damage associated with acute inner ear injury, whatever the cause, Dr. Brown and his colleagues are now exploring other toxic pathways that lead to degeneration in the hearing system. "We are looking at whether this same compound can prevent ototoxicity associated with the common antibiotic gentamicin and of cisplatin, a chemotherapy agent," says Dr. Brown.

The compound used in these experiments is basically a vitamin, notes Dr. Brown. "The questions now are how much do we give to a human to equal the amount that we're giving to mice and what are the associated toxicities. One of the more exciting alternatives is the possibility that we could deliver the drug at sufficient quantity with minimal side effects intratympanically through the eardrum into this middle ear space so that it can be absorbed into the cochlea. This may enable us to prevent, in a very logical fashion, injuries to the inner ear – whether from Meniere's disease, noise exposure, aging, or other causes – from leading to permanent hearing loss."

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A New Perspective on Tonsillectomies *(continued from page 1)*

The study included the review of records of two groups of patients, 289 who had a partial tonsillectomy and 289 patients who had a full tonsillectomy, with the average age being five years in both groups. The researchers looked specifically at children who only had enlargement of their tonsils resulting in difficulty with sleep and did not include those who had recurrent infections.

"A total tonsillectomy is very different from a partial tonsillectomy," says Dr. Modi. "In a total tonsillectomy a raw muscle bed is left behind. As a result kids tend to have a lot of pain, and they often don't want to eat or drink anything. Recently published guidelines recommend a postoperative admission for children undergoing a total tonsillectomy who are younger than three years old because of this risk of dehydration. The other issue is that there is a 1 to 3 percent risk of bleeding after a total tonsillectomy. Once again, if there is bleeding after surgery they'll have to come back to the hospital and possibly revisit the operating room. With a partial tonsillectomy, where you leave a little tonsil tissue behind, the recovery is not as painful and there is a lower risk of bleeding after surgery."

"The benefit of the partial technique is that the recovery seems to be quicker," adds Dr. Grunstein. "In particular, our study showed that the average time in the OR was slightly less – 32 minutes for full tonsillectomies and 26 minutes for partial. And even more striking, the average time in the PACU was significantly less – 174 minutes compared to 91 minutes."

"When you decrease operative time, you're saving dollars," says Dr. Modi. "The study also showed that after a total tonsillectomy 21.5 percent of patients were admitted to the hospital as compared to 1.7 percent for partial. The number of patients requiring care in the PICU, hospital readmissions, and postoperative visits to the ED were all lower as well for those undergoing partial tonsillectomies."

"We still give parents the option of either technique after providing them with the indications, risks, alternatives, and benefits of each," says Dr. Grunstein. "Interestingly, many of our families

Obesity in Teenagers Tied to Hearing Loss

Obesity in children is a serious public health concern, with such known consequences as cardiovascular disease and type 2 diabetes. An increased risk of sensorineural hearing loss has now been added to a growing list of disorders affecting children with a body mass index greater or equal to 95 percent, according to a recent study conducted by Anil K. Lalwani, MD, Vice Chair for Research and Chief of Otology, Neurology and Skull Base Surgery for the Department of Otolaryngology – Head and Neck Surgery at NewYork-Presbyterian/Columbia University Medical Center.

"We know that obesity is a factor for hearing loss in adults," says Dr. Lalwani. "However, to our knowledge, there had been no previous national study investigating the relationship between obesity and sensorineural hearing loss in a pediatric population."

Dr. Lalwani and his colleagues examined data from 1,488 adolescents, 12 to 19 years of age, compiled from the National Health and Nutrition Examination Survey (2005 to 2006). "Obesity was found to be associated with higher hearing thresholds across all frequencies and an almost two-fold increase in the odds of having unilateral low-frequency hearing loss," notes Dr. Lalwani. "It is possible that the unilateral hearing loss identified in adolescents with obesity represents an early stage of injury, and with time, hearing loss would progress to affect both ears."

The study, published in *The Laryngoscope*, is the first to show that obesity is associated with hearing loss in adolescents. The researchers further demonstrated that it is low-frequency hearing loss, not high frequency, which is linked to obesity – a finding similar in studies of adults. In fact, the rates for low-frequency hearing loss were nearly double in obese adolescents compared to non-obese adolescents.

"Obesity may directly or indirectly lead to hearing loss," says Dr. Lalwani. "Although additional research is needed to determine the mechanisms involved, we theorize that obesity-induced inflammation may contribute, as low plasma levels of the anti-inflammatory protein adiponectin, which is secreted from adipose tissue, have been found in children who are obese. This fat tissue secretes pro-inflammatory cytokines. People who are obese have more inflammatory proteins being secreted into the blood, which can cause many problems, including organ damage and hearing loss."

Obesity also may contribute indirectly to hearing loss as a result of its comorbidities, including type 2 diabetes, cardiovascular disease, and high cholesterol – all of which have been reported to be associated with loss of peripheral hearing.

"These results have several important public health implications," adds Dr. Lalwani. "Because previous research found that 80 percent of adolescents with hearing loss were unaware of having hearing difficulty, adolescents with obesity should receive regular hearing screening so that they can be treated appropriately to avoid cognitive and behavioral issues."

Reference Article
Lalwani AK, Katz K, Liu YH, Kim S, Weitzman M. Obesity is associated with sensorineural hearing loss in adolescents. *The Laryngoscope.* 2013 Jun 11. [Epub ahead of print]

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A New Perspective on Tonsillectomies *(continued from page 2)*

still choose total removal because it is what they are used to. For children with recurrent infections, we lean more toward total tonsillectomy in which we will remove any tissue that could potentially continue to be the source of throat infections."

Rather than calculating actual costs or charges in dollars in the study, the researchers directly compared the factors that would contribute to hospital cost. The study demonstrated statistically significant differences in favor of partial intracapsular tonsillectomies in surgical time, time in the operating room, PACU time, percent admitted postoperatively, number requiring PICU stay, number of readmissions after discharge, and number of postoperative ED visits separate from those requiring readmission.

The research has already had effects locally. "Since our study and as a natural consequence of partial tonsillectomies catching on in the country, we have been performing more partial tonsillectomies at the Columbia campus," says Dr. Grunstein.

Reference Article
Stucken EZ, Grunstein E, Haddad J, Modi VK, Waldman EH, Ward RF, Stewart MG, April MM. Factors contributing to cost in partial versus total tonsillectomy. *The Laryngoscope.* 25 Mar 2013. [Epub ahead of print]

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Comparison of Partial Versus Total Tonsillectomy
NewYork-Presbyterian Hospital – January 2007 through June 2010

N = 578	Operative Time	Time in PACU	Percent Admitted Postoperatively	Number Requiring PICU Stay	Readmissions After Discharge	Postoperative ER Visits
Partial Tonsillectomy	26.4 minutes	91.6 minutes	1.7%	0.3%	0.3%	0%
Total Tonsillectomy	32.4 minutes	174 minutes	21.5%	3.5%	3.5%	4.8%

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