NIGMS Science Advance

Project Title:
NADH Fluorescence Lifetime-Based Analysis of Mitochondrial Dysfunction during Ototoxic Antibiotic Exposure

Institution and State:
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Background:
Over 100,000 individuals suffer from hearing loss (HL) and/or balance disorders after aminoglycoside (AG) antibiotic treatment for life-threatening bacterial infections. Numerous studies have shown the production and destructive actions of reactive oxygen species (ROS) are common features of multiple HL pathologies, including AG-induced ototoxicity, noise induced HL, and age-related HL. Although there is little doubt inner ear ROS cause hair cell damage and HL, the exact mechanism(s) responsible for ROS production is/are controversial. ROS are normal byproducts of cellular metabolism that can rise to lethal levels when mitochondrial metabolism is perturbed. Using NADH fluorescence lifetime imaging, these studies have identified rapid, significant changes in NADH metabolism in high-frequency sensory cells that are preferentially damaged during antibiotic treatment.

Advance:
These studies demonstrate that gentamicin, a representative aminoglycoside antibiotic, 1) rapidly alters mitochondrial metabolism, 2) differentially modulates sensory and supporting cell metabolism, and 3) provide evidence that GM-induced changes in mitochondrial metabolism are significant and greatest in high-frequency OHCs which are preferentially damaged and/or permanently lost during antibiotic-induced ototoxicity.

How NIGMS Grant Enabled Advance:
NIGMS financial support was critical for obtaining the laboratory equipment, supplies and access to the state-of-the-art imaging facility used for these studies.

Public Health Impact Statement:
Aminoglycoside antibiotics (AGs) are important for treating life-threatening bacterial infections. Unfortunately, more than 120,000 individuals treated with AGs develop deafness/balance disorders every year. This project identified a new mechanism capable of causing inner ear damage during AG treatment. Understanding antibiotic-induced metabolic changes in the inner ear is critical for developing optimized hearing loss prevention and treatment strategies.

NIH Director's theme(s) relevance*:
Reinvigorating the Biomedical Community. Advances in the biomedical community have the capacity to, and has, virtually eradicated global health risks such as polio and smallpox. Another global health risk is the progression of multi-drug resistant bacteria. Aminoglycoside antibiotics are one of the few remaining antibiotics capable of treating many of these infections. Regrettably aminoglycoside antibiotic efficacy and use are

currently correlated to ototoxic potential and hearing loss. By identifying key metabolic changes occurring during antibiotic treatment, these studies provide a new foundation for developing successful hearing loss prevention strategies during aminoglycoside treatment of bacterial infections.

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Key Words:
Aminoglycosides, hearing loss, NADH metabolism, mitochondria, ototoxicity

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***NIH Director's Themes: Genomics, Translational Research, Health Care Reform, Global Health, Reinvigorating the Biomedical Community.*
http://nexus.od.nih.gov/all/2009/09/01/five-themes-for-the-nih-3/
http://news.sciencemag.org/funding/2010/02/nih-director-bends-budget-fit-five-themes