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Review

The mitochondrion: A perpetrator of acquired hearing loss

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ABSTRACT

Age, drugs, and noise are major causes of acquired hearing loss. The involvement of reactive oxygen species (ROS) in hair cell death has long been discussed, but there is considerably less information available as to the mechanisms underlying ROS formation. Most cellular ROS arise in mitochondria and this review will evaluate evidence for mitochondrial pathology in general and dysfunction of the mitochondrial respiratory chain in particular in acquired hearing loss. We will discuss evidence that different pathways can lead to the generation of ROS and that oxidative stress might not necessarily be causal to all three pathologies. Finally, we will detail recent advances in exploiting knowledge of aminoglycoside–mitochondria interactions for the development of non-ototoxic antibacterials.

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1. Introduction

1.1. Mitochondria and ROS in health and disease

Mitochondria are the givers of aerobic life and the mediators of cell death. This dual role is intrinsic in their basic and most important function, namely to reduce oxygen in the electron transport chain and provide energy in the form of ATP. However, this process also produces potentially cell-damaging reactive oxygen species (ROS). Probably through this lifelong exposure to ROS as well as through noxious environmental influences, mitochondrial DNA (mtDNA) is at risk to sustain mutations that can impede the function of these organelles (Lee and Wei, 2012).

Dysfunction of mitochondria is not only a phenomenon associated with the aging process but also contributes to the pathogenesis of many diseases, including neurodegenerative diseases such as Alzheimer's, Parkinson's, and amyotrophic lateral sclerosis (Martin, 2012). The central role for mitochondria in cellular life and death makes them suspects in many more disorders, including hearing loss. The genetic aspects of "mitochondrial deafness" are well-documented (Fischel-Ghodsian, 2003; Kokotas et al., 2007; Berrettini et al., 2008) and will not be addressed here. Instead, this review concerns itself with the involvement of mitochondria in acquired hearing loss. First, however, we want to consider some basic issues of mitochondrial energy metabolism.

1.2. Mitochondrial energy metabolism and ROS formation

When we discuss mitochondrial energy metabolism and the role of ROS, we should not overlook that ROS are essential molecules in cellular physiology. They are normal products of biochemical pathways and serve as regulatory messengers in a multitude of processes, ranging from proliferation and survival to gene expression and apoptosis, as well as being signaling molecules for homeostatic adaptation under stress conditions (Ray et al., 2012; Finkel, 2012). Not only do ROS serve multiple physiological roles, they also arise from multiple sources. ROS can be generated as radicals or pro-radicals by, among others, NADPH oxidase, nitric oxide synthase, and mitochondrial, peroxisomal, or microsomal pathways.

The process of mitochondrial ROS formation itself is complex (Adam-Vizi, 2005; Dröse and Brandt, 2012), potentially involving several of the four complexes of the respiratory chain. In brief, the production of ATP is linked to the reduction of oxygen (O_2) to water, a process that requires the coordinated addition of two electrons. The respiratory chain is highly efficient in this coordination but not completely so. During regular metabolism 1–4% of oxygen is estimated to be incompletely reduced in a one-electron transfer, yielding superoxide as the primary radical. In addition to the electron transport chain, monoamine oxidase in the outer membrane and the α-ketoglutarate dehydrogenase complex in the matrix are potential contributors to mitochondrial ROS.

Abbreviations: ROS, reactive oxygen species; mtDNA, mitochondrial DNA; SOD, superoxide dismutase; rRNA, ribosomal RNA.

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While mitochondria can generate ROS, their intrinsic antioxidants also guard against damaging ROS escaping into the cell. Superoxide has a very short half-life and is dismutated to hydrogen peroxide (H_2O_2) either by the mitochondrial superoxide dismutase (Mn-SOD; SOD2) or its cytosolic counterpart, Cu–Zn–SOD (SOD1). Hydrogen peroxide is not a radical by itself but a pro-radical capable of yielding the highly reactive hydroxyl radical (·OH) in the presence of transition metals such as iron (Fe^{2+}) in a non-enzymatic Fenton-type reaction. Normally, however, H_2O_2 is rendered harmless by reacting with glutathione or converted to water by catalase or glutathione peroxidase.

Under basic metabolic conditions the intrinsic mitochondrial and cytosolic antioxidant machinery can maintain redox homeostasis, the steady state between oxidative and reductive forces. The situation, however, may change if ROS are being produced in excess creating oxidative stress that might affect various organelles and pathways in the cell, ultimately leading to apoptosis or other forms of cell death. In addition, ROS may damage the mitochondria themselves, affecting the mitochondrial membrane potential and energy metabolism.

1.3. Oxidative metabolism in the cochlea

From the very early investigations into cochlear respiration we learned that the stria vascularis has by far the highest metabolic rate of all inner ear structures (Hughes and Chou, 1964; Marcus et al., 1978) commensurate with its task of establishing the endocochlear potential and the driving force for transduction. Hair cells have a rather low metabolic rate, estimated to be even lower than that of supporting cells based on histochemical studies of enzymes involved in energy metabolism (Nakai and Hilding, 1968). This fact has led to speculations of a high glycolytic ("anaerobic") metabolism in outer hair cells, but quantitative determination of the contributions of glycolysis and oxidative phosphorylation have clearly established that their metabolism is primarily aerobic (Puschner and Schacht, 1997) and, hence, their fate subject to mitochondrial function or dysfunction as much as other cell types. In fact, outer hair cells may be even more susceptible to oxidative stress due to a lower content of antioxidants (Sha et al., 2001).

1.4. Mitochondria and oxidative stress in acquired hearing loss

Oxidative stress, the failure to maintain redox homeostasis permitting cell death pathways to proceed, has been associated with many forms of disease as well as the aging process (Lenaz et al., 2006). Oxidative stress also figures prominently in the pathology of acquired hearing loss and several recent review articles have addressed ROS-based and other mechanisms of toxicity in drug-induced, noise-induced, and age-related hearing loss (Warchol, 2010; Huth et al., 2011; Op de Beeck et al., 2011: Xie et al., 2011). A causal relationship linking ROS to hearing loss has been inferred for both drug-induced and noise-induced hearing loss as the co-administration of antioxidants effectively prevents or attenuates morphological and functional damage in animal models. As we will discuss later, the case for ROS as the basis for age-related hearing loss is more tenuous, although oxidative stress can be documented in the aging cochlea (Jiang et al., 2007).

While ROS are formed by several cellular reactions, most ROS production is due to mitochondrial metabolism. Therefore, this review will explore the evidence for mitochondrial involvement in acquired hearing loss and, more specifically, mitochondria as primary targets of ototoxic actions. Mitochondria also harbor the mediators of cell death pathways that have been implicated in acquired hearing loss, for example the release of cytochrome c and activation of Bcl-2 family proteins and caspases, leading to apoptosis. While such pathways are important in an overall consideration of mitochondrial involvement in disease or acquired hearing loss, this review will bypass these downstream consequences of mitochondrial injury in favor of a close look into presumed primary events.

2. Noise-induced hearing loss

ROS emerge following noise exposure in cochlear tissues (Yamane et al., 1995; Ohinata et al., 2000) and spill into inner ear fluids (Ohlemiller et al., 1999), suggesting that they can leave the site of their original production to impact surrounding structures. Although their formation is almost immediate, there is also delayed ROS production that persists for extended periods of time (days) after cessation of noise exposure, spreading from the base of the cochlea to the apex (Yamashita et al., 2004) and widening the area of morphological damage. Antioxidants, when given prior to or shortly after noise exposure, can attenuate both hair cell death and threshold shifts (see Oishi and Schacht, 2011), a fact that suggests a causal relationship between oxidant stress and noise-induced hearing loss.

2.1. Mitochondria and noise-induced hearing loss

Mitochondria have long been speculated as being involved in noise trauma and the source of ROS. Spoendlin (1971) observed mitochondrial damage in outer hair cells of guinea pigs following exposure to noise, but such gross pathology may depend very well on the conditions of the trauma. If severe enough, noise exposure may lead to major intracellular derangements as well as mechanical destruction of cochlear structures; metabolic effects, although possibly leading to cell death, will be more subtle and not necessarily morphologically obvious. Metabolic effects signifying mitochondrial involvement in the initial events after noise exposure might include, for example, a rapid depletion of ATP levels (Chen et al., 2012). Genetic evidence also points to a link between mitochondria, oxidative stress, and noise. Factory workers exposed to occupational noise were at higher risk for hearing loss when they carried a specific single nucleotide polymorphism in the mitochondrial Mn-superoxide dismutase gene (Liu et al., 2010) compromising their ability to effectively inactivate mitochondria-generated superoxide.

It has been argued (Henderson et al., 2006) that the exposure to noise induces a higher metabolic rate in the affected cochlear cells, "overstimulates" mitochondrial energy metabolism, and thereby increases the rate of leakage of ROS. However, it appears unlikely that an enhanced metabolic rate *per se* should lead to a surge in ROS sufficient to overwhelm the cells' considerable antioxidant defenses. An enhanced metabolism might even lower ROS formation by making better use of energy-supplying substrates. In fact, it is not stimulation but selective inhibition of the electron transport chain (in particular, of complex I) that produces the largest excess of ROS under stress situations (Sipos et al., 2003). Therefore, we need to look for alternative explanations of the elevation of ROS in noise trauma.

2.2. A mechanism for noise-induced ROS generation

The most likely trigger for elevated ROS is calcium. Free Ca^{2+} increases in outer hair cells immediately after acoustic overstimulation (Fridberger et al., 1998), probably both via entry through ion channels and liberation from intracellular stores. In agreement with calcium as a decisive factor in noise trauma is the success of attenuating noise-induced hearing loss through a blockade of L-type (Heinrich et al., 1999) or T-type voltage-gated calcium