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Effect of streptomycin on melanogenesis and antioxidant status in melanocytes

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Abstract Streptomycin is an aminoglycoside antibiotic with an antituberculosis activity commonly used in clinical practice due to its good antimicrobial characteristics. A well-known undesirable side effect of this drug is ototoxicity, which may be caused by overproduction of reactive oxygen species and loss of melanocytes in the inner ear. The aim of this study was to examine the effect of streptomycin on melanogenesis and antioxidant defense system in cultured normal human melanocytes (HEMa-LP). Streptomycin induced concentration-dependent loss in melanocytes viability. The value of EC_{50} was determined to be $\sim$5.0 mM. It has been shown that streptomycin causes inhibition of tyrosinase activity and reduces melanin content in human melanocytes in a concentration-dependent manner. Significant changes in the activity of cellular antioxidant enzymes: superoxide dismutase, catalase, and glutathione peroxidase were also stated. The results obtained in vitro may explain a potential role of melanocytes and melanin in the causative mechanisms of aminoglycosides ototoxic effects in vivo.

Keywords Streptomycin · Melanocytes · Melanization · Tyrosinase · Antioxidant enzymes

Introduction

Streptomycin was the first aminoglycoside antibiotic, identified by Waksman's group as a natural product of a soil bacterium, *Streptomyces griseus*. The aminoglycosides comprise a large group of naturally occuring or semisynthetic polycationic compounds. Most are bactericidal agents and share similar range of antibacterial activity, pharmacokinetic behavior, tendency to damage one or both branches of the eight nerve, and a propensity to cause renal damage [1, 2]. Aminoglycosides are potentially ototoxic to both the cochlear and vestibular functions, with such damage usually being permanent. Vestibulotoxicity is manifested by vertigo, especially on rising out of bed, ataxia, and oscillopsia. Cochleotoxicity presents as deafness, particularly to high tones [3, 4].

Aminoglycoside-induced generation of reactive oxygen species (ROS) is presumed to be a principal mechanism underlying sensory cells death [2, 5, 6]. However, it has been demonstrated that aminoglycosides are redox inactive compounds, and therefore a conversion to a redox-active form is necessary to induce ROS formation. Generation of free radicals by aminoglycosides cames from their ability to act as an iron chelator [7]. The production of ROS can be catalyzed by the redox-active iron (Fe^{2+})-aminoglycoside complex [8] in a reaction in which molecular oxygen is activated and subsequently reduced to the superoxide radical. Iron-catalyzed Fenton reactions can then lead to formation of other radicals, including the highly aggressive hydroxyl radical [9].

Mammalian pigment cells produce melanin as the main pigment. They differentiate from the neural crest and migrate to a variety of organs during development, including the skin (epidermis, dermis, and hair follicles), the eye (choroid, iris, and ciliary body), cardiac valves [10, 11] and the inner ear [12–14]. Melanin function has been described in the cochlear labyrinth, and it has been suggested that it protects the cochlea from various types of trauma, including the effects of ototoxic drugs, such as

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