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Review

Mitochondrial 12S rRNA mutations associated with aminoglycoside ototoxicity

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ABSTRACT

The mitochondrial 12S rRNA is a hot spot for mutations associated with both aminoglycoside-induced and nonsyndromic hearing loss. Of those, the homoplasmic 1555A>G and 1494C>T mutations at the highly conserved decoding region of the 12S rRNA have been associated with hearing loss worldwide. In particular, these two mutations account for a significant number of cases of aminoglycoside ototoxicity. The 1555A>G or 1494C>T mutation is expected to form a novel 1494C–G1555 or 1494U–A1555 base-pair at the highly conserved A-site of 12S rRNA. These transitions make the human mitochondrial ribosomes more bacteria-like and alter binding sites for aminoglycosides. As a result, the exposure to aminoglycosides can induce or worsen hearing loss in individuals carrying one of these mutations. Biochemical characterization demonstrated an impairment of mitochondrial protein synthesis and subsequent defects in respiration in cells carrying the A1555G or 1494C>T mutation. Furthermore, a wide range of severity, age-at-onset and penetrance of hearing loss was observed within and among families carrying these mutations. Nuclear modifier genes, mitochondrial haplotypes and aminoglycosides should modulate the phenotypic manifestation of the 12S rRNA 1555A>G and 1494C>T mutations. Therefore, these data provide valuable information and technology: (1) to predict which individuals are at risk for ototoxicity; (2) to improve the safety of aminoglycoside antibiotic therapy; and (3) eventually to decrease the incidence of hearing loss.

Contents

1. Introduction

Hearing loss is one of the most common human health problems, affecting one in 700–1000 newborns (Morton, 1991, 2002; Mehl and Thomson, 2002). Hearing loss can be classified as genetic or nongenetic, prelingual or postlingual, and syndromic or nonsyndromic. About 50% of hearing loss cases have a genetic etiology or predisposition with autosomal dominant, autosomal recessive, X-linked or maternal patterns of inheritance. These have rapidly been defined at molecular levels (Van Camp and Smith, 1998; Petit et al., 2001; Morton, 2002; Friedman and Griffith, 2003). Hearing loss can result from mutation(s) in a single gene or from a combination of mutations in different genes. Hearing loss can also be caused by environmental factors, including

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perinatal infection, acoustic or cerebral trauma affecting the cochlea or ototoxic drugs such as aminoglycoside antibiotics (Petit et al., 2001; Morton, 2002). Additionally, hearing loss can result from the interaction of hereditary and environmental factors.

Aminoglycosides, such as gentamicin and tobramycin, are of great clinical importance for the treatment of bacterial infections. These antibiotics are composed of amino sugars linked to a 2-deoxystreptamine ring (Fig. 1, ring II). The conserved elements among aminoglycosides are rings I and II, and particularly the amino groups at positions 1 and 3 within ring II. These elements are essential for binding to the decoding site of bacterial 16S rRNA (Recht et al., 1996). The 2-deoxystreptamine ring is substituted most commonly at position 4 and 5, as in the neomycin class, or at position 4 and 6, as in the kanamycin and gentamicin class (Fig. 1). They are particularly active against aerobic, gram-negative bacteria and act synergistically against certain gram-positive organisms. In the developed countries, these drugs are mainly used in the treatment of hospitalized patients with aerobic gram-negative bacterial infections, particularly in patients with chronic infections such as cystic fibrosis or tuberculosis (Sande and Mandell, 1990; Lortholary et al, 1995). However, in developing countries, aminoglycosides are more routinely used, even for relative minor infections. These drugs are highly polar cations, which are not easy to be metabolized (Chamber and Sande, 1996).

Glomerular filtration rapidly clears aminoglycosides from the majority of tissues and organs (Chamber and Sande, 1996; Edson and Terrell, 1991). However, these drugs may become concentrated in renal tubular cells, and the perilymph and endolymph of the inner ears (Henley and Schacht, 1988). The use of these drugs can frequently lead to toxicity, which involves the renal, auditory and vestibular systems (Fischel-Ghodsian, 2005; Guan, 2005). The renal impairment is usually reversible, whereas the auditory and vestibular ototoxicity is usually irreversible. Although all aminoglycosides affect cochlear and vestibular functions, some (streptomycin and gentamicin) produce predominately vestibular damage, while others (neomycin and kanamycin) cause mainly cochlear damage. On the other hand, tobramycin affects both equally (Sande and Mandell, 1990; Lortholary et al, 1995).

Nearly four million courses of aminoglycosides are administrated annually in the United States (Price, 1986) and it is estimated that at least 2–5%, of patients treated with these antibiotics develop clinically significant hearing loss (Moore et al., 1984; Rybak, 1986). The problem of ototoxic side effects is more acute in developing countries, where highly effective and low cost drugs such as aminoglycosides are often prescribed without adequate monitoring. The use of these antibiotics has been widespread in China and the administration of various aminoglycosides was believed to account for 22% of all deaf-mutes in one Shanghai district alone (Hu et al., 1991). Of these, 28% had relatives with aminoglycoside ototoxicity (Hu et al., 1991). Recently, we showed that 28% of 1642 Chinese pediatric deaf subjects could be the result of aminoglycoside treatment (Lu et al., 2010b). The type and doses of aminoglycoside medication, the length of treatment, and age of drug administration also contribute to the severity of hearing impairments in some subjects. At the highest doses of the drugs, most individuals exhibit toxicity. By contrast, some patients developed aminoglycoside-induced hearing loss after treatment with conventional doses or even a single dose over a short period. These cases of aminoglycoside ototoxicity may have a genetic etiology or predisposition with autosomal dominant, autosomal recessive, X-linked or mitochondrial patterns of inheritance. In particular, susceptibility to aminoglycoside-induced hearing loss is maternally inherited in humans in a significant proportion of cases (Fischel-Ghodsian, 2005; Guan, 2005). Hu et al. described 36 Chinese families with maternally transmitted predisposition to aminoglycoside ototoxicity (Hu et al., 1991), while Higashi reported that 26 of 28 Japanese families with streptomycin-induced deafness had maternally inherited transmission (Higashi, 1989).

These drugs are known to exert their antibacterial effects by directly binding to 16S ribosomal RNA (rRNA) in the 30S subunit of the bacterial ribosome, causing mistranslation or premature termination of protein synthesis (Davis and Davis, 1968; Noller, 1991). In particular, the aminoacyl-tRNA-binding site (A-site) of small rRNA has been shown to be the primary target site for aminoglycoside antibiotics (Moazed and Noller, 1987; Purohit and Stern, 1994; Fourmy et al., 1998). As the mitochondria are evolved from bacteria, mitochondrial ribosomes share more similarities to bacterial ribosomes than do cytosolic ribosomes (Hutchin et al., 1993; Ruiz-Pesini and Wallace, 2006). Therefore, it is suggested that one of the primary targeting sites for the aminoglycoside antibiotics is the small submit of mitochondrial ribosomes (Fischel-Ghodsian, 2005; Guan, 2005). In fact, in familial cases of ototoxic deafness, the aminoglycoside hypersensitivity is often maternally transmitted, suggesting that mutation(s) in mitochondrial DNA (mtDNA), particularly in 12S rRNA (MT-RNA1) gene, could be the molecular basis for this susceptibility (Fischel-Ghodsian, 2005; Guan, 2005). Thus, it has been proposed that the exposure of aminoglycosides leads to an impairment of mitochondrial translation in susceptible subjects by interacting with the binding sites of mitochondrial 12S rRNA (Hutchin et al., 1993; Prezant et al., 1993; Guan, 2005).

2. Identification of mitochondrial 12S rRNA mutations associated with aminoglycoside ototoxicity

Prezant et al. first investigated the molecular basis of this disorder by mutational analyses of the mitochondrial genome of three Chinese families with maternally transmitted aminoglycoside ototoxicity and a large Arab-Israeli family with maternally inherited nonsyndromic deafness (Prezant et al., 1993). As a result, the A-to-G transition at position 1555 (m.1555A>G) in the 12S rRNA gene was identified

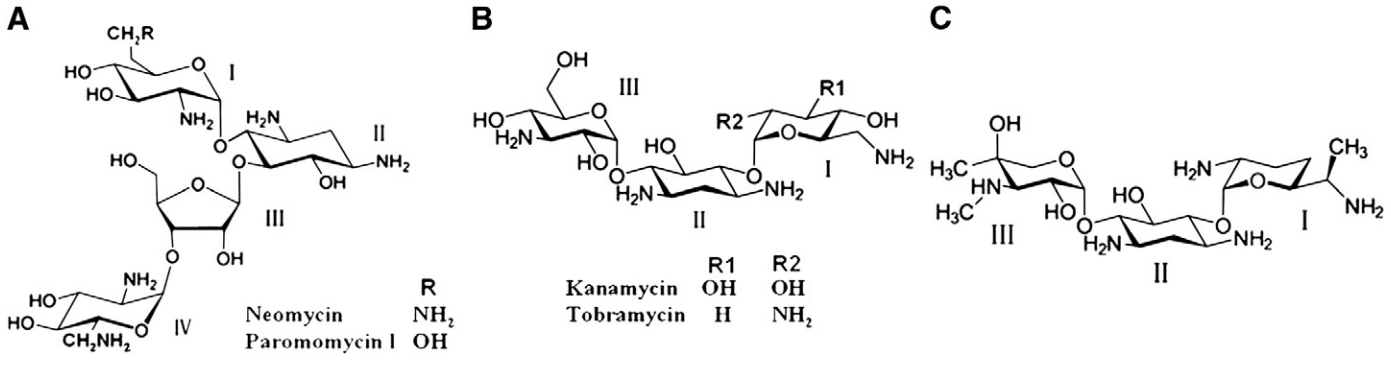

Fig. 1. Aminoglycosides that interfere with the decoding process and with ribozyme catalysis. (A) Neomycin-class antibiotics with a 2-deoxystreptamine (ring II), distributed at positions 4 (ring I) and 5 (rings III and IV). (B) Kanamycin-class antibiotics and (C) Gentamicin C1A with substitutions at positions 4 (ring I) and 6 (ring III).