OTOTOXICITY

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2014/08/15

Reference

- Bailey, Head & Neck Surgery - Otolaryngology, 5th Edition ; Chapter 160
- Johns Hopkins ABX guide-
  Diagnosis and Treatment of Infectious Diseases, 2012 3rd edition
- Molecular and genetic aspects of aminoglycoside-induced hearing loss-Drug Discovery Today: Disease Mechanisms Vol. 3, No. 1 2006
- Mitochondrial 12S rRNA mutations associated with aminoglycoside ototoxicity-Mitochondrion 11 (2011) 237–245
- New developments in aminoglycoside therapy and ototoxicity-Hearing Research 281 (2011) 28-37
- Mechanisms of cisplatin ototoxicity: theoretical review-The Journal of Laryngology & Otology (2013), 127, 536–541
- Drug-mediated Ototoxicity And Tinnitus: Alleviation With Melatonin-journal OF PHYSIOLOGY AND PHARMACOLOGY 2011, 62, 2, 151-157

- A. Introduction
- B. Aminoglycosides
- C. Platinum
- D. Other medication
- E. Topical agent
- F. Genetics
  - Aminoglycosides
- G.Genetics
  - Cisplatin
- H. Clinical Monitoring
- I. Summery

A. Introduction

- Ototoxicity-induced hearing loss
  - Significant disability
  - Young children
    - Speech and language development
- Vestibular system
  - Balance disorder
  - Impair even simple activities of daily life

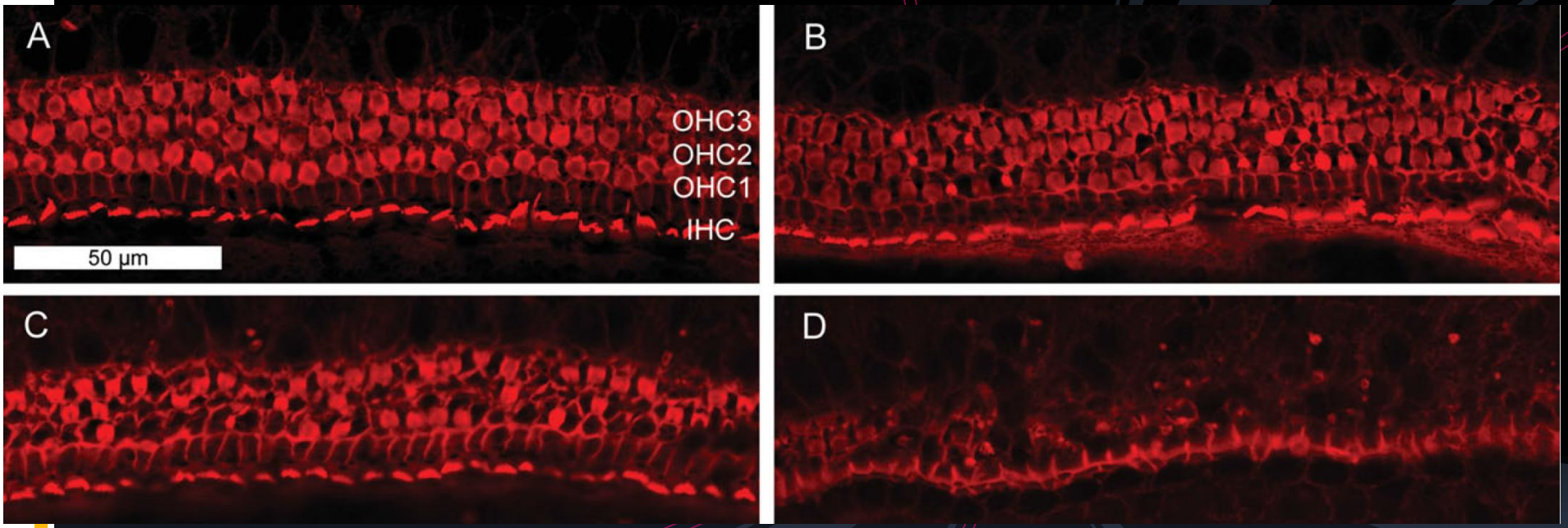
B. Aminoglycosides

B. Aminoglycosides

- Against P. aeruginosa and aerobic GNB
  - "-mycin" from *Streptomyces*
  - "-micin" from *Micromonospora*
  - Significantly cheaper
- Nephrotoxicity: 5~25%
- Hearing loss: 3~13%
- Vestibular impairment: 1~11%
- Most common cause of bilateral vestibular dysfunction

- Cochleotoxicity:
  - Neomycin>Gentamicin>Tobramycin>Amikacin>Netilmicin
- Vestibulotoxicity:
  - Gentamicin>Tobramycin>Amikacin>Netilmicin

- Johns Hopkins ABX guide-2012
  - Irreversible vestibular toxicity(4~6%)
    - Most pts compensate with visual and proprioceptive cues.
    - Monitor for nausea, vomiting, nystagmus, and vertigo(exacerbated in the dark)
  - Irreversible cochlear toxicity(3~14%)
    - Risk factors include repeated exposure(cumulative dose and duration of therapy), genetic predisposition, renal impairment, specific aminiglycoside, elderly, age, bacteremia, hypovolemia, degree of temperature elevation, and liver dysfunction
    - 62% of hearing loss was at frequency above 9kHz at a mean of 9 days of therapy.
    - Neomycin>Streptomycin>Gentamicin>Tobramycin>Amikacin >Netlimicin

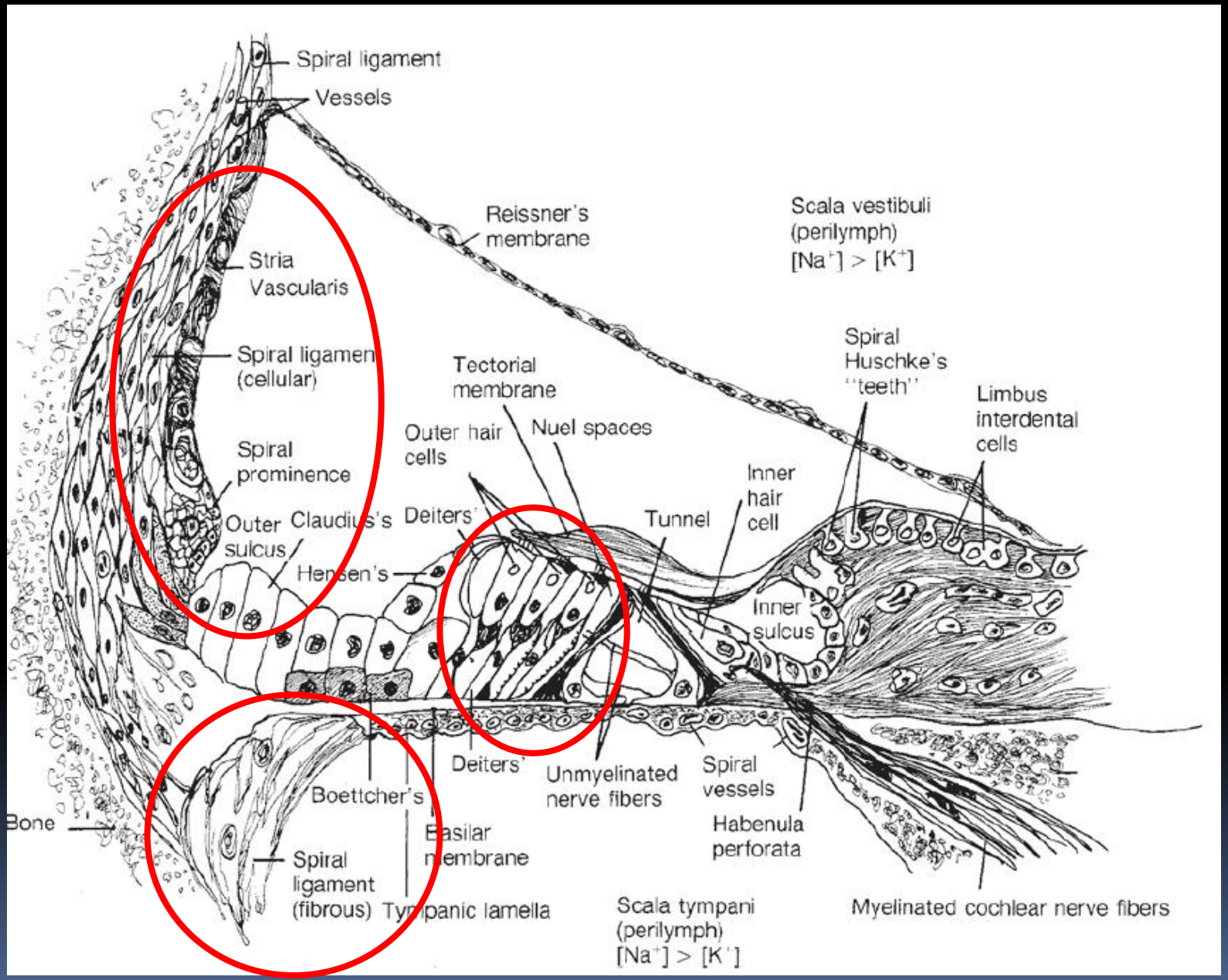


Cisplatin and Aminoglycoside Antibiotics: Hearing Loss and Its Prevention
The Anatomical Record 295:1837–1850 (2012)

C. Platinum

C. Platinum

- Inhibit DNA replication
- Apoptosis and/ or necrosis
- Cisplatin
  - Stria vascularis, spiral ganglion cells, and outer hair cells (OHCs)
  - 9%~91%
  - Tinnitus
  - Bilateral symmetric high-frequency SNHL
    - Progression toward lower frequencies



Bailey, Head & Neck Surgery - Otolaryngology, 5th Edition

- OHCs are more susceptible than IHCs
  - Inhibited by broadspectrum inhibition of caspases
- Cisplatin
  - Degeneration of the stria vascularis
  - Marginal and intermediate cells ↓
  - Spiral ganglion cells ↓

Cisplatin

- Age(children)
- Cranial irradiation
- Renal disease
- IV bolus Cisplatin
- Cumulative dose cisplatin
- With aminoglycosides
- With loop diuretics
- Noise exposure
- Poor volume status
- Hx of hearing loss
- With other ototoxic chemotherapy
  - Cytarabine
  - Bleomycin
  - Nitrogen mustard
  - Vincristine
  - Vinorelbine

Other Platinum

- Carboplatin:
  - Inner hair cells (IHCs)
  - 1%
- Ototoxicity:
  - Cisplatin > Nedaplatin > Carboplatin > Oxaliplatin
  - Oxaliplatin
    - no nephrotoxicity
    - no ototoxicity

D. Other Medication

Vinca Alkaloids

- *Vinca rosea*
  - Vincristine, Vinblastine
- Semisynthetic
  - Venorelbine
- Sporadic reports
  - With Cisplatin?
- Vincristine
  - A rare otolaryngologic complication is vocal cord paralysis.

Loop Diuretics

- Risk:
  - Renal impairment
  - Prematurity
  - With aminoglycoside
- Dose-related
- Reversible reduction in endocochlear potential
- Bumetanide
  - More potent and less ototoxic than furosemide
  - Expensive

Macrolides

- Reversible
- Risk factor
  - Renal impairment
  - Hepatic impairment
  - Transplant recipients

- Johns Hopkins ABX guide-2012
  - Erythromycin – Occasional
    - Reversible ototoxicity especially with High Dose IV
  - Azithromycin - Occasional
    - Reversible dose-dependent hearing loss in 5% with mean exposure of 59g
  - Clarithromycin – Rare
    - Reversible hearing loss and tinnitus
  - Telithromycin - Nil
    - Occasional: 1.1% visual problem

Vancomycin

- 3.2~19%
- With an aminoglycoside
- Age extremes

Salicylates, NSAID, Quinine

- Aspirin, NSAID
  - 11/1,000 (1.1%)
  - Tinnitus – Earliest sign
  - Reversible bilaterally symmetric hearing loss
  - Recovery
    - 24~72 hours after cessation
- Quinine
  - Large doses
  - Reversible hearing loss and tinnitus

- Deferoxamine (DFO)
  - Iron-Chelating Agents
  - Thalassemia major
  - SNHL: 12~56%
- Heavy Metals
  - Murcury
  - Lead

E. Topical Agent

- Round window membrane
  - Potential access point in animal
- AAO-HNS panel in 2004
  - Free of potential ototoxicity
  - Only in infected ears
  - Patient/parent should be warned
  - Follow-up
    - if dizziness, vertigo, hearing loss, tinnitus
  - Intact eardrum-no risk

Aminoglycosides

F. Genetics

Genetics

- In Aminoglycoside
  - A1555G mutation in the mitochondrial 12S rRNA
    - China
      - 1/3 patients with aminoglycoside ototoxicity
    - U.S
      - 17% of patients with aminoglycoside ototoxicity
  - C1494T in 12s rRNA
    - Chinese
  - T1095C, 961delT+C(n), A827G

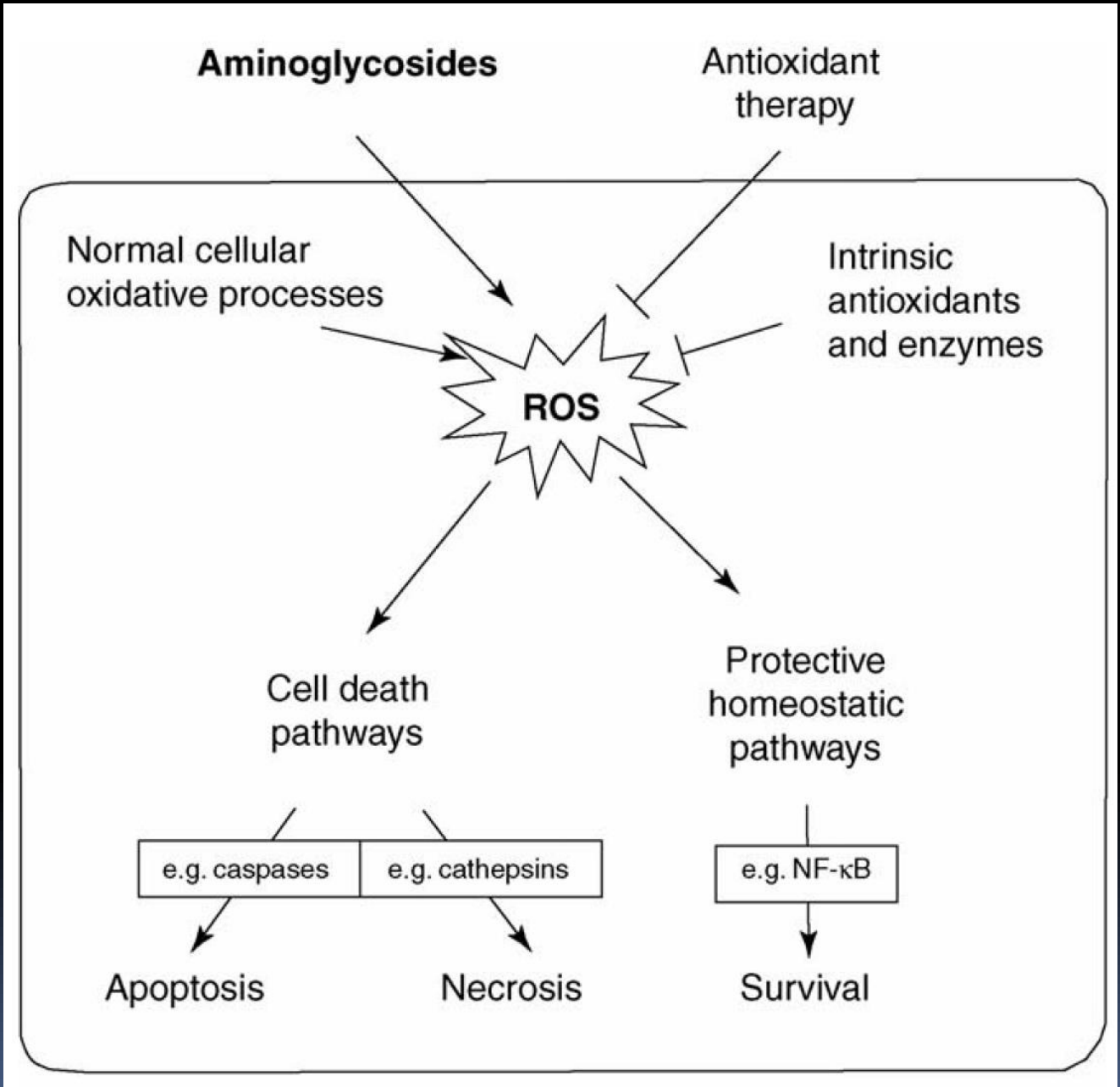
Journal

Molecular and genetic aspects of aminoglycoside-induced hearing loss

Andra E. Talaska
Jochen Schacht
Nathan Fischel-Ghodsian

Kresge Hearing Research Institute, University of Michigan

Drug Discovery Today: Disease Mechanisms Vol. 3, No. 1 2006



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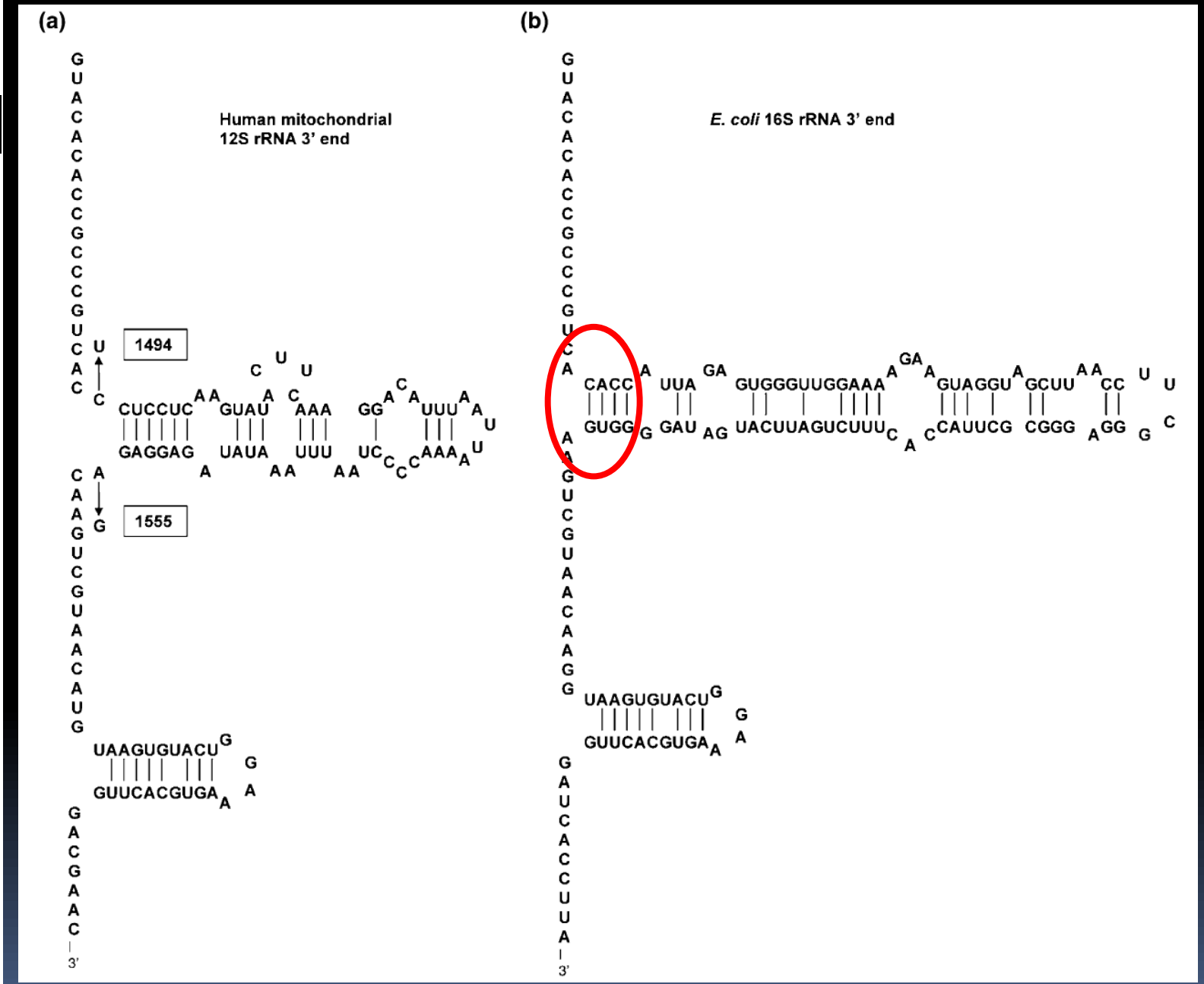

Molecular and genetic aspects of aminoglycoside-induced hearing loss-Drug Discovery Today: Disease Mechanisms Vol. 3, No. 1 2006

Journal

Mitochondrial 12S rRNA mutations associated with aminoglycoside ototoxicity

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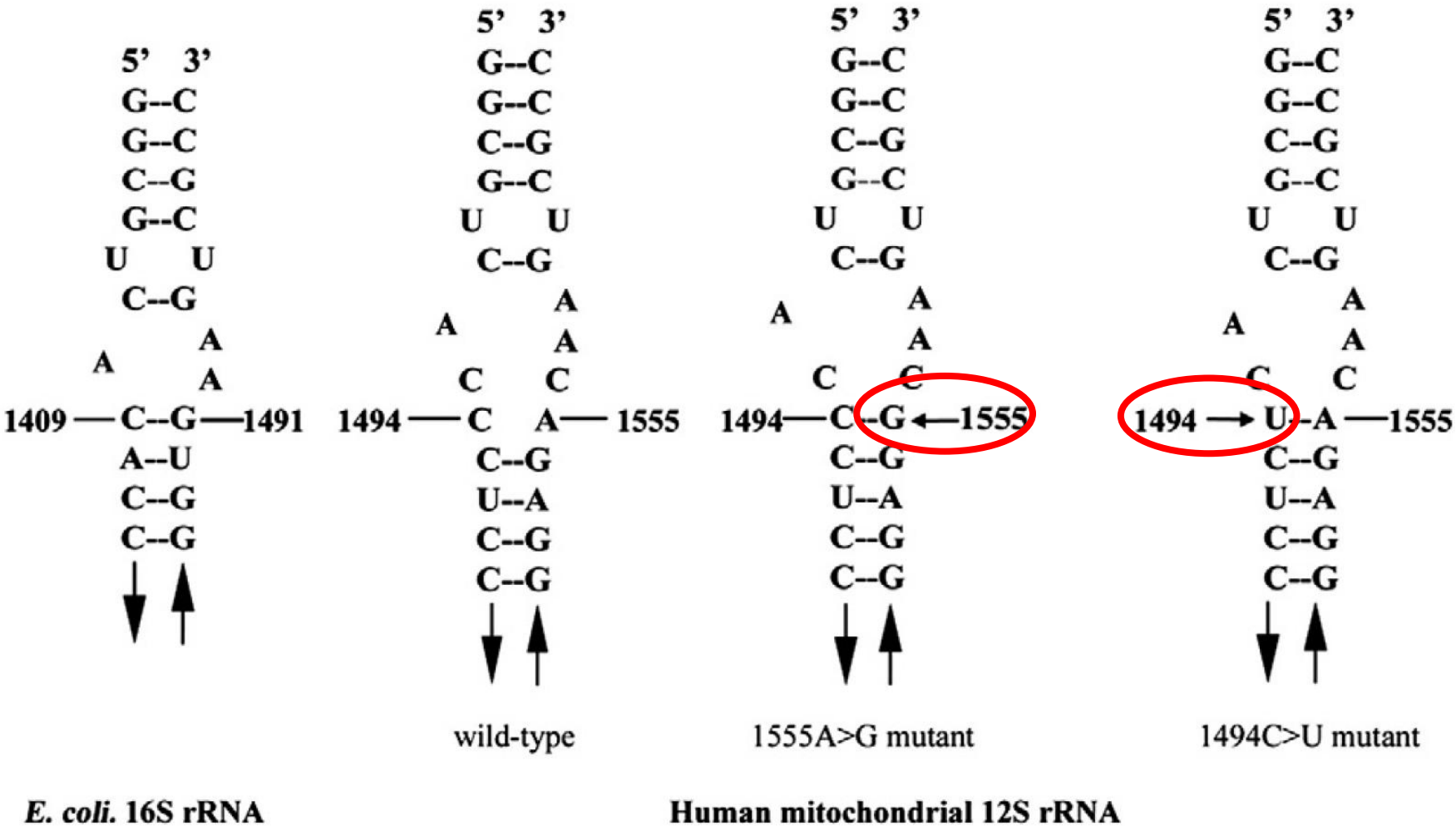
Division of Human Genetics and Center for Hearing and Deafness Research, Cincinnati Children's Hospital Medical Center

Mitochondrion 11 (2011) 237–245


5' 3'
G--C
G--C
C--G
G--C
U U
C--G
A
A A
A
1409 — C--G — 1491
A--U
C--G
C--G
5' 3'
G--C
G--C
C--G
G--C
U U
C--G
A
A A
C C
1494 — C A — 1555
C--G
U--A
C--G
C--G
5' 3'
G--C
G--C
C--G
G--C
U U
C--G
A
A A
C C
1494 — C--G ← 1555
C--G
U--A
C--G
C--G
5' 3'
G--C
G--C
C--G
G--C
U U
C--G
A
A A
C C
1494 → U--A — 1555
C--G
U--A
C--G
C--G
wild-type
1555A>G mutant
1494C>U mutant
E. coli. 16S rRNA
Human mitochondrial 12S rRNA

- 1555A>G mutation
  - ~33% in two small Japanese cohorts
  - 13%, 10.4% and 5% in three Chinese cohorts
  - ~17% in two white cohorts from United States and Spain
- 1555A>G mutation + nonsyndromic hearing loss
  - 0.3% ~2.5% in white cohorts
  - 0.9% ~5.3% in Asian cohorts
- 1494C>T mutation + hearing impairment
  - 3/1642 Chinese pediatric subjects
  - 3/1340 Spanish hearing-impaired subjects
- 1095T>C mutation
  - 0.61%
- 961delT, 961insC, 961TNC
  - 1.8% in a large Chinese pediatric population

- 1555A>G
  - Filipino-American family
    - Premature graying
    - Depigmented patches
    - Digital anomalies
  - Cardiomyopathy
  - Leber's optical neuropathy(LHON)

- 1555A>G or 1494C>T
  - Bilateral SNHL at high tone
  - No apparent vestibular dysfunction
  - Age < 10 y/o
  - PTA: Sloping, flat, rising-shaped and U-shaped patterns
  - Age-at-onset
    - 5~ 30 years
    - Average 14.5 years

- 1555A>G or 1494C>T mutation
  - Mitochondrial protein synthesis ↓ 30~40%
- G1555–C1494 or A1555–U1494
  - Binding pocket of 12S rRNA for aminoglycosides
  - Impair mitochondrial translation in cochlear cells
  - Worsening of mitochondrial translation
  - Subsequent respiration defect
- Aminoglycosides caused an additional 30% decrease in the rate of mitochondrial protein synthesis
  - Mitochondrial translation rate down to and below the minimal level required for normal cell function, thus inducing the deafness phenotype

Environmental factors

(Aminoglycosideantibiotics, noise, etc)

↓ATP synthesis

↑Free radicals

Redoximbalance

Primary mtDNA mutation

Mitochondrial dysfunction

Cochlear or/and vestibular cells

Apoptosis

Loss of function

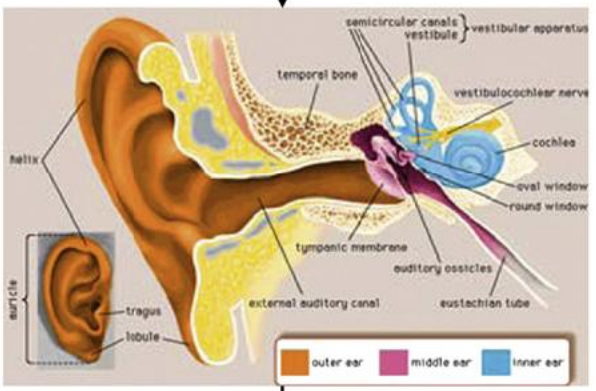
Genetic factors

Mitochondrial genomes

Nuclear modifier genes

mtDNAvariants/haplotypes

TRMU, *MTO1*, *GTPBP3* and other nuclear modifier genes



Hearing failure

- Mutations in MTO1, MSS1/GTPBP3 and MTO2/TRMU
  - Modifier factor
  - Failure in mitochondrial tRNA metabolism
  - Worsening defects in mitochondrial protein synthesis in cells carrying the 1555A>G or 1494C>T mutation
- Mutated TRMU
  - Modifier factor
  - Phenotypic manifestation of the 1555ANG or 1494CNT mutation

- 1555A>G, mtDNA
  - Chinese haplogroups A, B, C, D, F, G, M, N, R, Y
  - Spanish haplogroups H, I, J, K, T, U, V, L
- Furthermore, the 1494C>T mutation among Chinese and Spanish families occurs in the various mtDNA haplogroups.
- These suggested that the 1555A>G or 1494CNT mutation occurred sporadically and multiplied through the evolution of the mtDNA

- 1555A>G or 1494C>T
  - Decline in ATP production in the cochlear and vestibular cells
  - Defects in oxidative phosphorylation
    - Reactive oxygen species (ROS) ↑
    - Damaging mitochondrial and cellular proteins, lipids and nuclear acids
  - Mitochondrial permeability transition pore opens
  - Activates apoptosis
- Ototoxic 12S rRNA mutations account for at least 17% of cases with aminoglycoside ototoxicity.

Journal

New developments in aminoglycoside therapy and ototoxicity

Jing Xie
Andra E. Talaska
Jochen Schacht

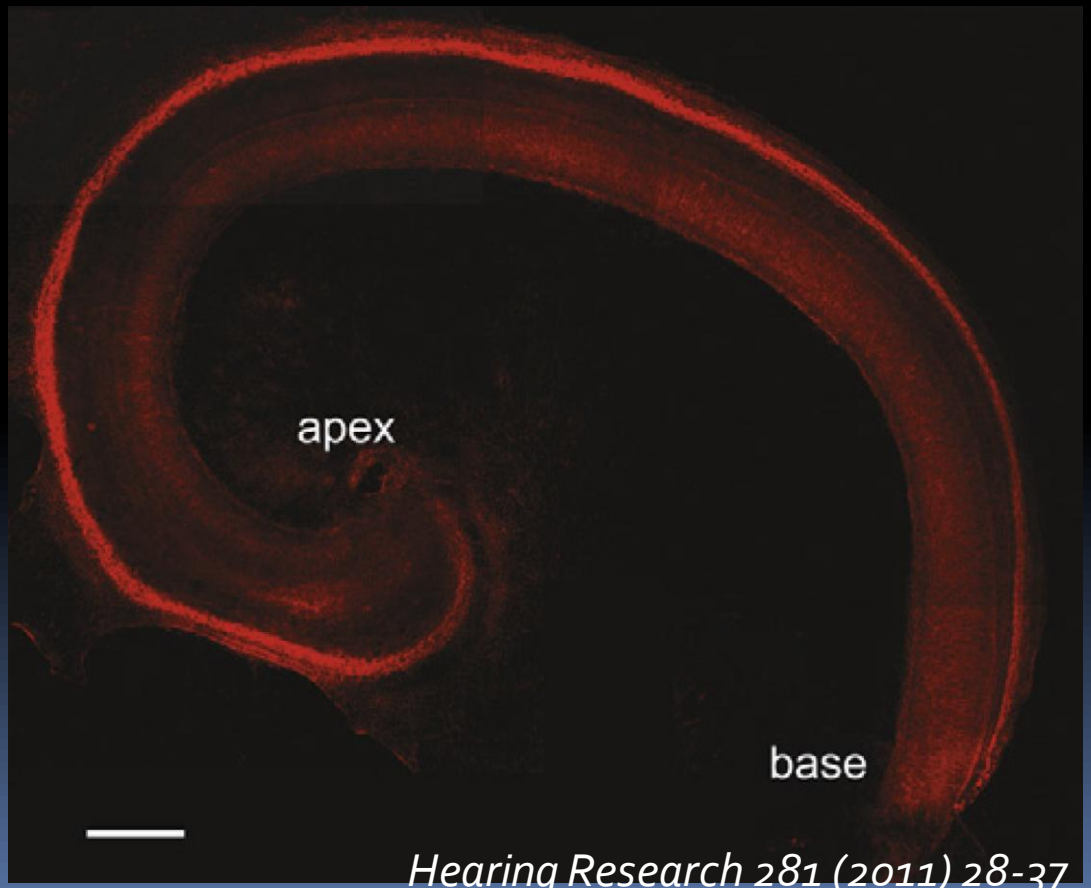
Kresge Hearing Research Institute, University of Michigan

Hearing Research 281 (2011) 28-37

Aminoglycoside	Specific Therapy (FDA-approved and off-label indications)
Streptomycin[a]	Given IV or IM for tuberculosis, brucellosis, tularemia, and pneumonic, septicemic, and bubonic plagues caused by Yersinia pestis, among others
Neomycin	Topical application for skin infections from minor wounds, orally for as an adjunct for hepatic encephalopathy (of questionable efficacy) or hypercholesterolemia
Kanamycin[a]	Intraperitoneal application for post-operative perontinitis, IV or IM for tuberculosis, gonorrhea, orally for necrotizing enterocolitis in fetus or newborn, or hepatic encephalopathy
Paromomycin	Taken orally for intestinal amebic infections, tapeworms, giardiasis, leishamaniasis, trichomoniasis, and hepatic encephalopathy
Gentamicin	Administered IV or IM for meningitis, pneumonia, Pseudomonas infections, septicemia, E. coli infections, Staphylococcus infections, listeria, tularemia, brucellosis, endocarditis, respiratory tract infections, urinary tract infections, bone infections, cystic fibrosis, diverticulitis, neutropenia, and sepsis and necrotizing entercolitis in newborns, among others. Oral or intraperitoneal treatment for peritonitis, topical treatment for burns and skin infections, opthamalic drops for eye infections, intratympanic injection for Meniere's disease
Tobramycin	Administered IV for lower respiratory infections, osteomyelitis, some recurrent urinary tract or abdominal infections, meningitis, and skin and bone infections. Nebulized for infections in cystic fibrosis.
Amikacin	Administered IV or IM for some highly drug resistant gram-negative organisms, as well as meningitis and uncomplicated urinary tract infections
Netilmicin[a]	Given IV or IM for Pseudomonas infections, skin, bone, or abdominal infections, gonorrhea, lower respiratory infections, and urinary tract infections
Spectinomycin	Administered IM for gonorrhea

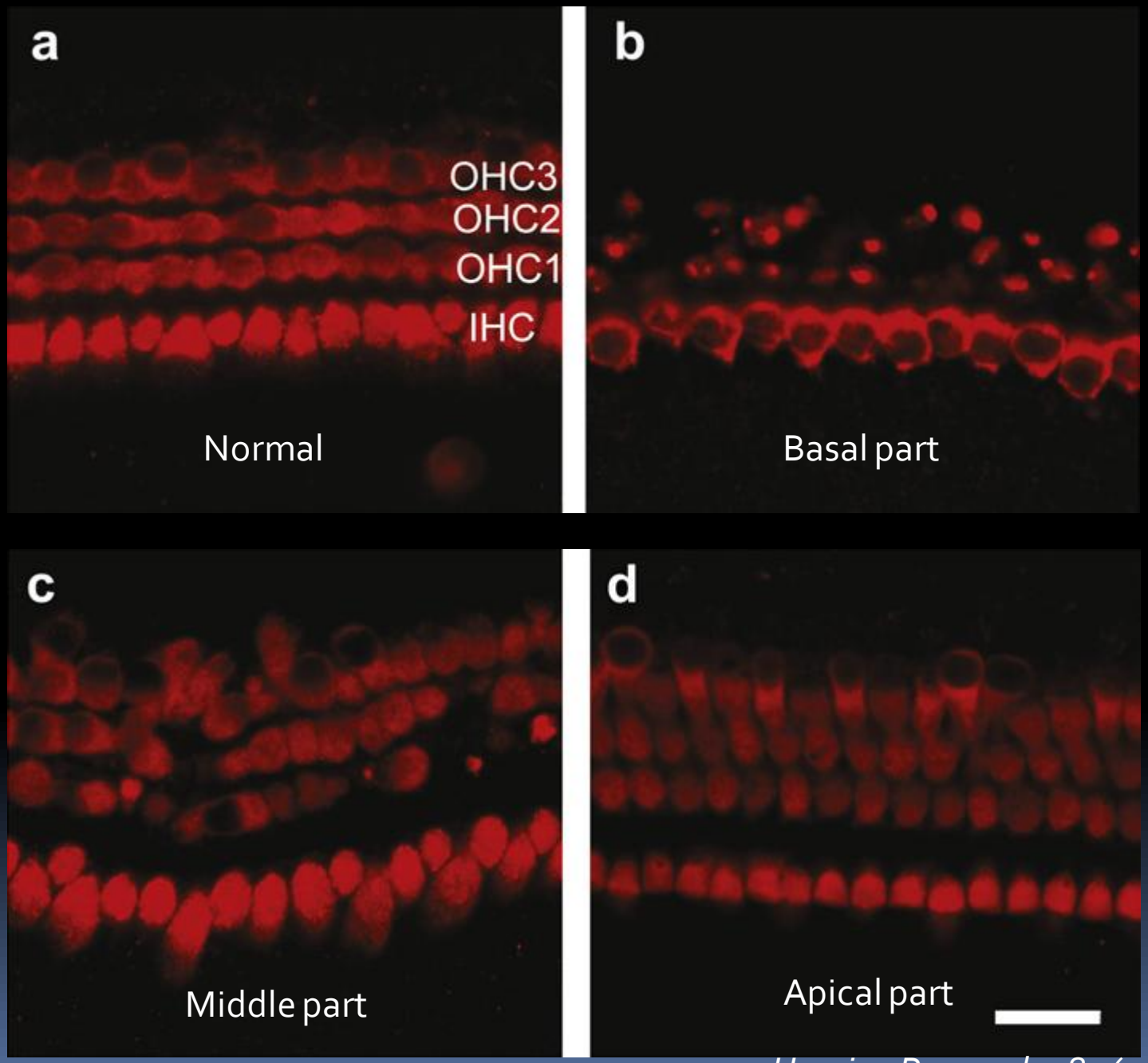
- Neomycin
  - Most highly toxic
  - Gentamicin, kanamycin, and tobramycin
- Amikacin and netilmicin
  - Least toxic
- Amikacin, neomycin, dihydrostreptomycin
  - More cochleotoxic
- Gentamicin, streptomycin
  - Vestibular sensory epithelium

- Degeneration of nerve fibers, spiral ganglion neurons, and supporting cells generally follow hair cell death in the same regions.



Organ of Corti explant from a post-natal day 3 mouse(F-actin)

Hearing Research 281 (2011) 28-37



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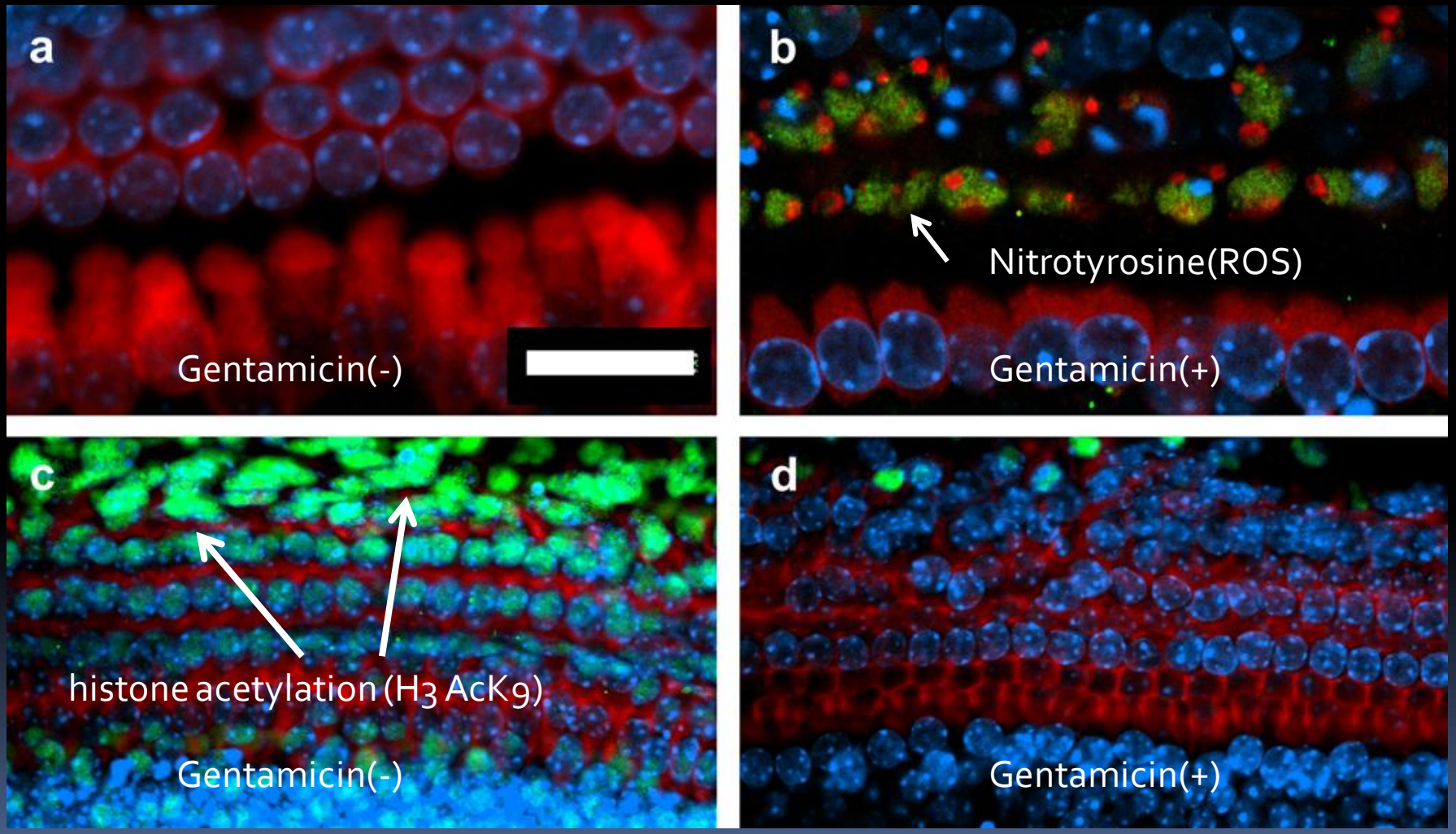

Hearing Research 281 (2011) 28-37

- Aspirin (acetyl salicylate) vs Gentamicin
  - First protectant successfully tested
  - Double-blind RCT(Sha et al., 2006)
    - 3% vs 13%
  - Protective heat shock proteins ↑ (Ramesh and Reeves, 2004)
  - Inhibition of TNFα(Ishihara et al., 2003)
    - Cisplatin nephrotoxicity
- N-acetylcysteine vs Gentamicin
  - Hemodialysis + bacteremia (Feldman et al., 2007)
    - Hearing loss ↓
- Vitamin E vs Gentamicin
  - No significant protection (Kharkheli et al., 2007)

Cisplatin

G. Genetics

- Glutathione S-transferases (GST)
  - Detoxification
  - Catalyzing the conjugation of potentially damaging electrophiles
  - GSTM1, GSTP1, GSTT1 – Cisplatin
    - Cisplatin-induced hearing impairment ↑
- Thiopurine S-methyl transferase (TMPT)
- Catechol-O-methyl transferase (COMT)
  - TMPT / COMT ↑
    - Earlier onset / greater severity of cisplatin-induced hearing loss
- Cellular uptake of cisplatin
  - Copper and cisplatin can prevent the uptake of each other

Cisplatin and Aminoglycoside Antibiotics: Hearing Loss and Its Prevention
The Anatomical Record 295:1837–1850 (2012)

- Copper transporter-like 1 (CTR1) gene
  - CTR1 increased cellular uptake of cisplatin by 50%
- Copper-transporting adenosine triphosphatases 7A / 7B (ATP7 A / ATP7B)
  - Cytoplasmic cisplatin sequestration
  - Export out of the cell
- OCT2
  - Cisplatin excretion in the kidneys
  - OCT1/2 double knockout mice
    - protected from cisplatin-induced ototoxicity
- CTR-1 and OCT2 are present in the stria vascularis
- CTR1, ATP7A, ATP7B, OCT2
  - Highly expressed in the choroid plexus

Bailey, Head & Neck Surgery - Otolaryngology, 5th Edition

Journal

Mechanisms of cisplatin ototoxicity: theoretical review

M S GONÇALVES
A F SILVEIRA
A R TEIXEIRA
M A HYPPOLITO

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Department of Morphology/Health Sciences Center, Federal University of Santa Maria

The Journal of Laryngology & Otology (2013), 127, 536–541

Platinum on cochlear function

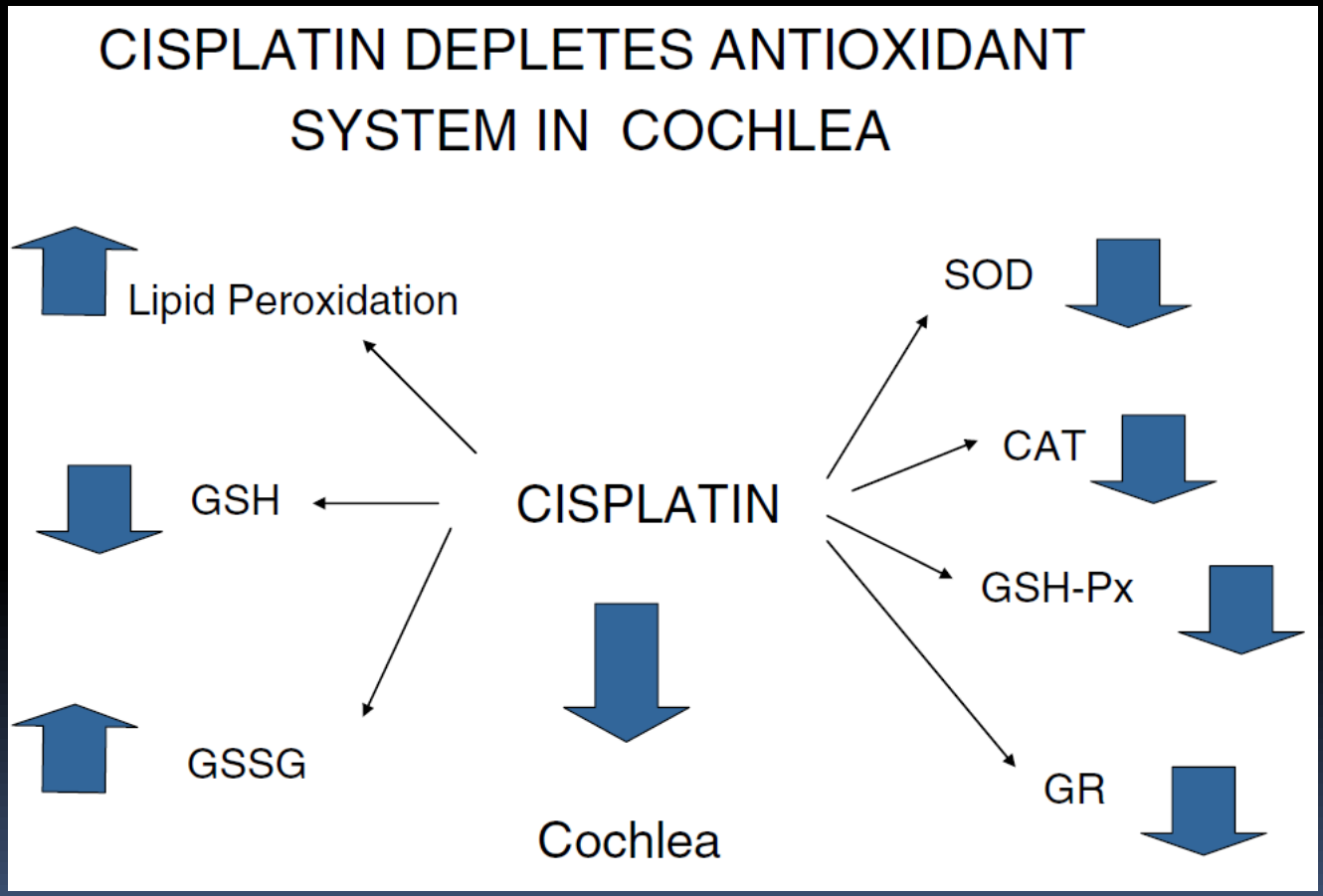
- Animal experiments
  - Endocochlear potential (EP) ↓
  - Thresholds ↑
    - Compound action potential (CAP)
    - Cochlear microphonic (CM)
    - Amplitude: CAP ↓ ↓ ,CM ↓
  - Detachment of the myelin sheath of spiral ganglion cells
    - Alteration of hair cell function and reduction of the EP
  - DPOAEs ↓
  - ABR Thresholds ↑
    - Greatest effects in the higher frequencies

Effects on cochlear morphology

- 3 major tissue targets in the cochlea
  - Organ of Corti
    - primarily the outer hair cells
  - Spiral ganglion cells
    - Type I spiral ganglion cells undergo detachment of their myelin sheaths
  - Lateral wall (stria vascularis and spiral ligament)
    - Strial edema, bulging, rupture
    - Compression of the marginal cells
    - Depletion of organelles from the cytoplasm
    - Shrinkage in the area of the stria
    - Gerbil type I spiral ligament cells also undergo significant apoptosis after cisplatin exposure in cell culture.

Biochemical & molecular effects

- Reactive oxygen species (ROS)
- Antioxidant ↓ in cochlear
  - Direct binding of cisplatin
  - Depletion of copper and selenium
    - Superoxide dismutase / glutathione peroxidase activities ↓
  - ROS ↑ and organic peroxides
    - Inactivate antioxidant enzymes
  - Depletion of glutathione and the cofactor NADPH
    - Glutathione peroxidase / glutathione reductase activities ↓
- Cisplatin
  - Apoptosis in spiral ligament fibrocytes of the lateral wall
    - K+ channels ↑
    - K+ efflux
    - Intracellular ionic and osmotic strength ↓



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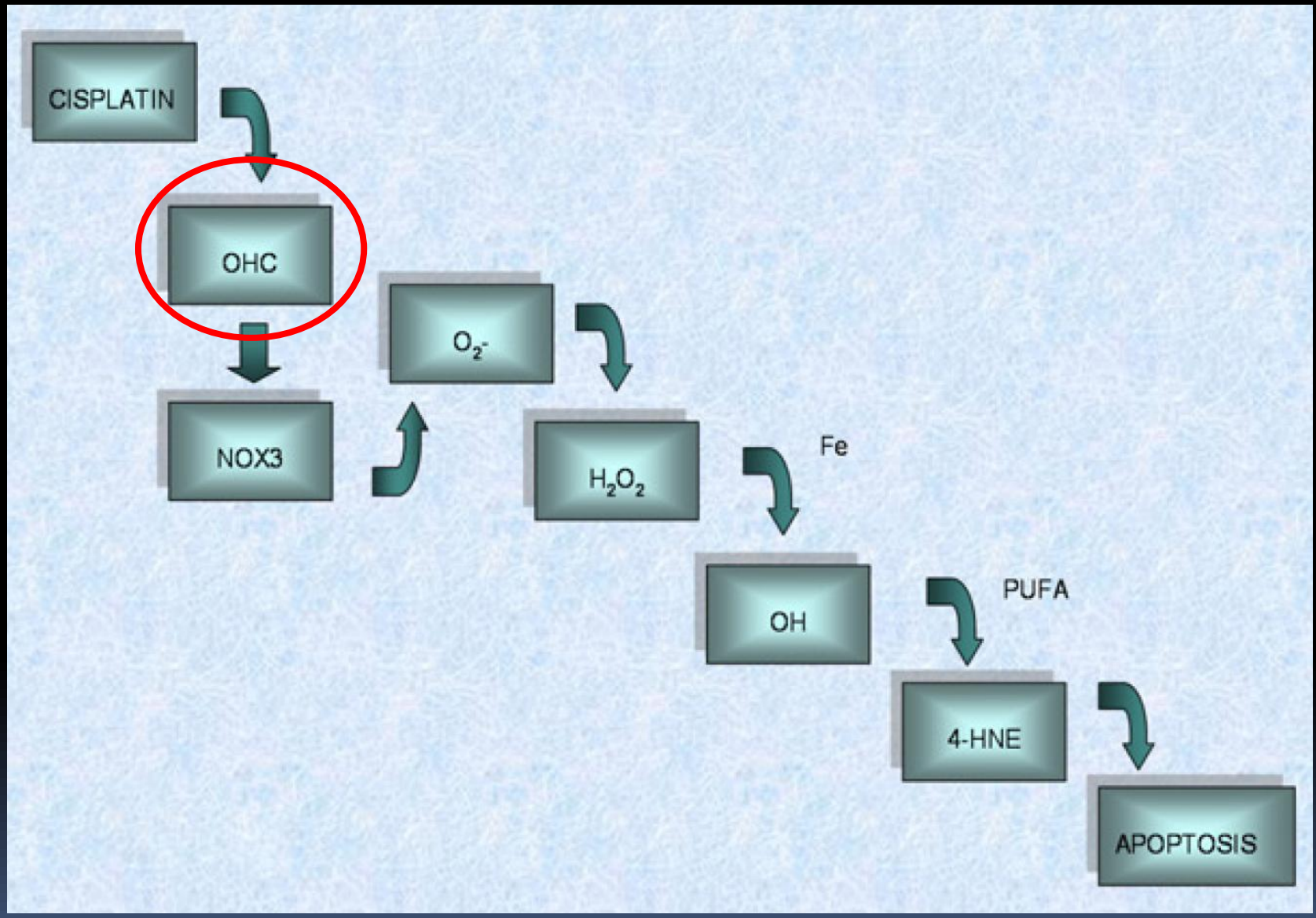

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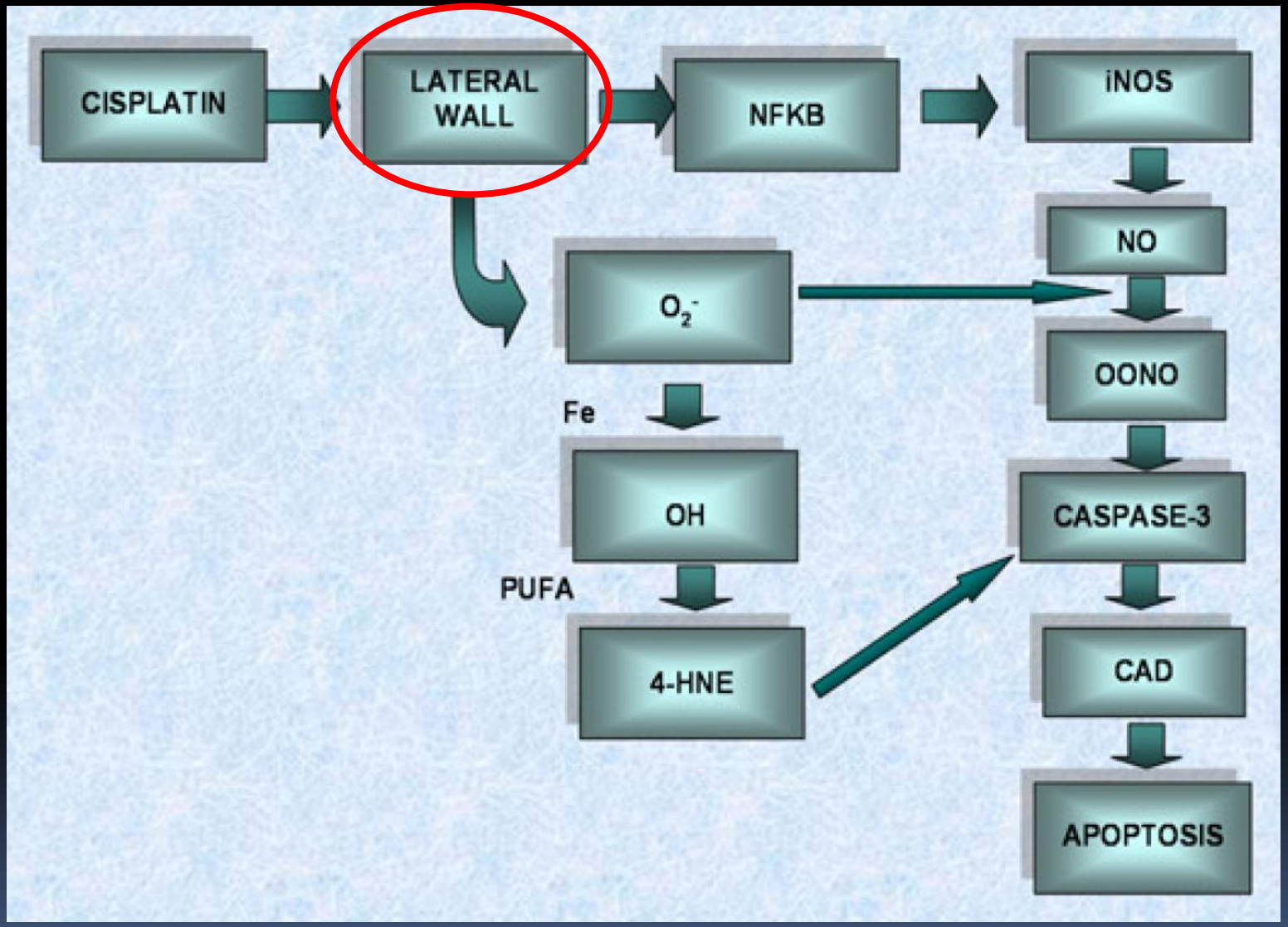

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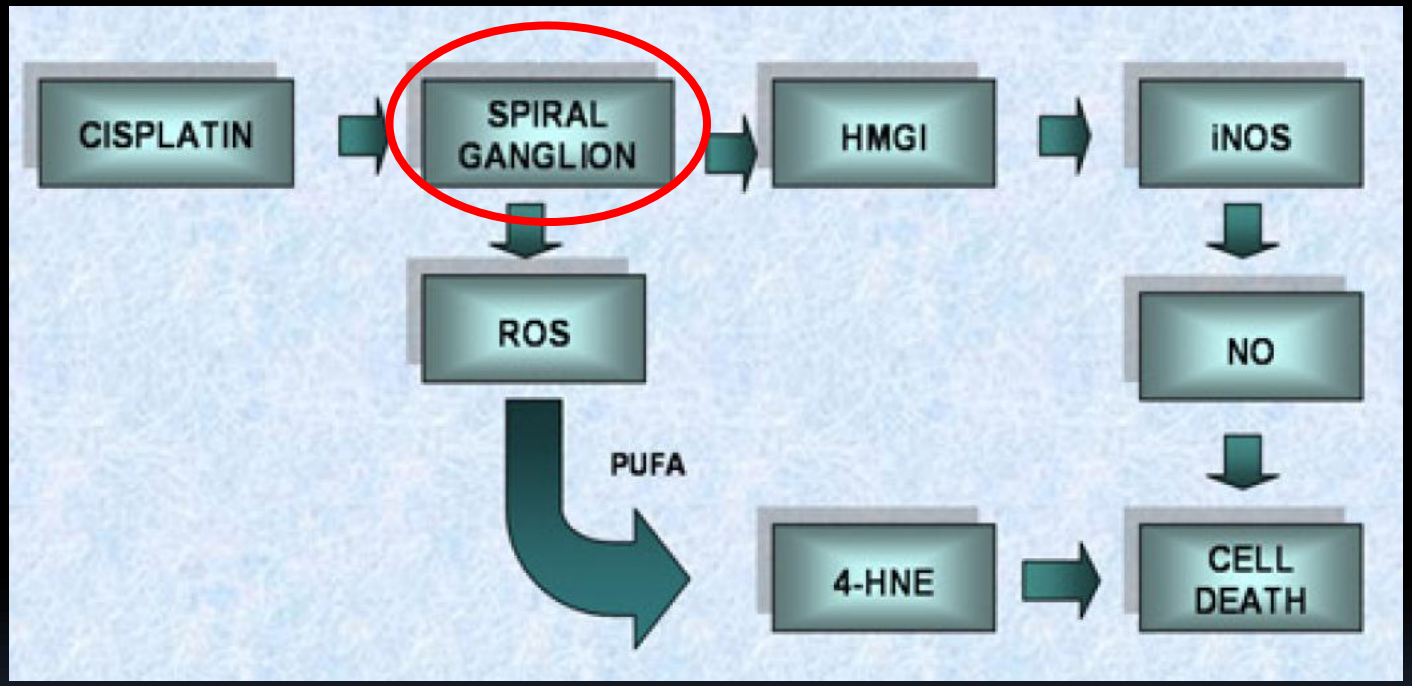

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Prevention of ototoxicity

- Protective molecules
  - Glutathione and the antioxidant enzymes
  - Heat shock proteins
  - Adenosine A1 receptors
  - NRF2 and heme-oxygenase-1
  - kidney injury molecule (KIM-1)
- Free radical scavengers
  - Sodium thiosulfate
  - Diethyldithiocarbamate
  - D- or L-methionine
  - Methylthiobenzoic acid
  - Lipoic acid
  - N-acetylcysteine
  - Tiopronin
  - Glutathione ester
  - Amifostine

Interference with cisplatin

- Sodium thiosulfate and N-acetylcysteine
  - Covalently bind to platinum→Inactive
  - Displace cisplatin after it is bound to target molecules
  - Delayed administration of sodium thiosulfate after cisplatin
    - Reduces ototoxicity
    - Not reduce antitumor activity
  - Coadministration of N-acetylcysteine
    - Reversed the cytotoxic and apoptotic effects of cisplatin
    - Route and timing can be adjusted to maintain the efficacy of cisplatin therapy

- Amifostine
  - Lowered the dose-normalized AUC for cisplatin
  - Adversely affect cisplatin pharmacokinetics
  - Failed to provide the protection against cisplatin ototoxicity
- IT or round window administration
  - L-methionine
    - Round window
    - Not compromise antitumor efficacy(rats)
  - D-methionine and N-acetylcysteine
    - Round window membrane prevented cisplatin ototoxicity(Rodent)
- Systemic sodium salicylate
  - Against cisplatin ototoxicity and nephrotoxicity
  - Without altering its antineoplastic efficacy(rats)

- Thiols(sodium thiosulfate)
  - Highly effective in antagonizing cisplatin ototoxicity
  - Some thiols also reduce its antitumor efficacy
    - IT injection→ Not effective
    - Delayed administration(PO / IV)→Could be useful
- Adenosine A1 receptor agonists
  - Only round window application
  - Avoid potential interference with antineoplastic effects
- Pifithrin or caspase inhibitors
  - Unintended side effects
  - Enhancement of tumor growth

- (PO)Ebselen + allopurinol
  - Against cisplatin ototoxicity
  - Preserving/enhancing antitumor activity of cisplatin(Animal)
  - Clinical trials?
- Sodium butyrate
  - Effective protective agent
  - Anticancer activity of its own
- Salicylates
  - Highly effective against cisplatin in animals.
  - Trial in China
    - Prevent aminoglycoside ototoxicity
  - Gastrointestinal upset
  - Cisplatin Thrombocytopenia→Bleeding

H. Clinical Monitoring

- Pure-tone thresholds (250 ~ 8,000 Hz)
  - Air / bone conduction
  - Tympanometry
  - Baseline assessment prior to ototoxic drug
- High-frequency audiometry (HFA)
  - > 8k Hz
  - Detect aminoglycoside-induced / cisplatin-induced ototoxic losses
    - OHCs of the basal cochlear
  - Before changes become evident on conventional audiometry

- OAEs
  - Distortion product OAEs(DPOAEs)
  - Transient Evoked OAEs(TEOAEs)
  - Widely used ototoxicity grading systems incorporating DPOAE and TEOAE do not currently exist
  - Cannot be reliably used to determine ototoxicity without a normal tympanogram
  - Helpful for early detection of ototoxicity

- 1994 ASHA criteria
- National Cancer Institute Common Terminology Criteria for Adverse Events, Ototoxicity Grades
  - Adults
  - Inconsistencies
- Brock's Hearing Loss Grades
  - Children
  - Underreport

I. Summery

- Most common ototoxicity
  - Aminoglycosides and platinum
- Symptoms of ototoxicity
  - High tone hearing loss, tinnitus, balance impairment.
- Topical agents
  - Nonototoxic FQ if perforated eardrum
- A1555G in mitochondrial 12S rRNA - aminoglycosides.
- TPMT and COMT - cisplatin
- Antioxidant
  - N-acetylcysteine / sodium thiosulfate
- Monitor ototoxicity
  - PTA, HFA, OAEs

THANKS FOR LISTENING