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Fundamental Mechanisms of Ototoxicity

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Disclosure

- Brian Zitelli has the following financial disclosures:
  - He is employed by UPMC Hillman Cancer Center
  - He is receiving an honorarium for this session

- Brian Zitelli has no non-financial disclosures
Learning Outcomes

The Learner will be able to:

- Describe key pharmacological concepts including: therapeutic index, receptor, and pharmacokinetics
- List the most common mechanisms of ototoxicity
- Explain the proposed mechanisms of otoprotective drugs and supplements

Topics for today

- Section 1: Pharmacology
- Section 2: Mechanisms of Ototoxicity
- Section 3: Chemical Otoprotection
Section 1: Pharmacology

Introduction to Pharmacology

Broadly, the study of medicines, including:

- Origin
- Chemistry
- Therapeutic use
- Mechanisms of action
- Pharmacokinetics/Pharmacodynamics
- Toxicology
Receptor Theory

- Drugs interact with biological molecules (receptors) to change the state of the molecule, producing a physiologic response
- Competition for active binding sites can result in different outcomes
  - Agonist - a drug binds to a receptor, leading to activation of a cellular process
  - Antagonist - a drug binds to a receptor, preventing the activation of a cellular process
  - Partial agonist - a drug binds to a receptor, but produces an effect below the theoretical maximum response

Receptor Theory - Consequences

- Drugs modify existing cellular processes
  - Traditional drug therapy (as opposed to gene therapy) does not fundamentally change cells
- Some receptor types are present in multiple tissues
  - This is at the root of many drug toxicities
- Manipulating receptors specific to a particular cell type is key to effective drug therapy
  - Penicillin interferes with bacterial cell walls
  - Many chemotherapy agents target dividing DNA, present in more cancer cells than normal cells
  - Some blood pressure medicines relax the smooth muscle in arteries, but do not interfere with voluntary muscle control
Selectivity

- Receptors for endogenous substances or drugs may exist in multiple tissues
- Multiple receptor types may respond to the same signal
  
  - Example: Alpha and Beta receptors
  - Receptor subtypes may exist that respond to differing degrees
  
  - Example: Beta 1 receptors in the heart, Beta 2 receptors in the lungs
  - Drugs may exhibit differing affinities for related receptors
  - A lack of selectivity is often manifested as toxicity
  
  - Example: Rapid heartbeat from albuterol

Pharmacokinetics (Absorption)

- Initial uptake of drug, regardless of route
Pharmacokinetics (Distribution)
- Dispersal of a drug throughout the body from the initial site of absorption

Pharmacokinetics (Metabolism)
- The actions of the body on a drug, most commonly by the liver
Pharmacokinetics (Elimination)

- Removal of the drug or metabolites, usually by the renal or hepatic pathways
Pharmacokinetic Profiles

Steady State

\[ AUC_t = \int_{0}^{t} C dt \]

\[ AUC_\infty = \int_{0}^{\infty} C dt \]
Pharmacodynamics

- The study of the relationship between drug concentrations and effects
  - The relationship is not always linear

- Includes the study of tolerance
  - Decreased efficacy with repeated usage of a drug
    - Ex. opioid painkillers

- The relationship between the probability of the desired outcome and toxicity is called **therapeutic index**

Toxicity - Adverse Drug Events

- An appreciably harmful or unpleasant reaction, resulting from an intervention related to the use of a medicinal product, which predicts hazard from future administration and warrants prevention or specific treatment, or alteration of the dosage regimen, or withdrawal of the product

**Notes:**

- All FDA approved drugs must publish the incidence of ADEs observed during their trial periods
- All drugs are subject to post-marketing surveillance, which is intended to identify ADEs not observed during the trial period

**Expected:**
- A potential consequence of drug therapy based on what is known about a given drug’s action

**Unexpected:**
- In some cases, patients may experience ADEs that are not listed in the available literature

**Note:**
- These can be reported to FDA MedWatch, which may lead to further investigation
Therapeutic drug monitoring

- Pharmacokinetics can be used to predict drug levels based on specific patient characteristics
- Therapies that may benefit from monitoring levels have:
  - A strong relationship between effect and plasma levels
  - Significant kinetic variability from patient to patient
  - An established concentration range
  - An affordable assay test to measure drug levels

Therapeutic Index

![Graph showing the relationship between % Patients and Plasma Drug Concentration](image-url)
Therapeutic Index - Wide vs Narrow

End of Section 1

Questions?
Section 2: Mechanisms of Ototoxicity

Hearing Anatomy

- Auricle
- External Auditory Canal
- Tympanic Membrane
- Tympanic Cavity
- Round Window
- Eustachian Tube
- Stapes (attached to oval window)
- Maleus
- Incus
- Vestibular Nerve
- Semicircular Canals
- Cochlear Nerve
- Cochlea
Cochlear Anatomy

Common Mechanisms of Ototoxicity

Free Radical Damage
- Direct molecular damage to cells

Ion Gradient Disruption
- Between endolymph/perilymph

Metabolic Stress
- Decreased blood flow in the stria vascularis
Chemistry Review

- Atomic structure
  - Nucleus - protons and neutrons
  - Electrons - orbit the nucleus in predictable patterns called orbitals

- The “S” orbitals hold up to 2 electrons

Chemistry Review

- After the S orbital is filled, electrons are stored in “P” orbitals

There are 3 P orbitals - one for each axis of a graph (X,Y,Z)

The P orbitals can hold 6 electrons total (2 in each), S and P together hold 8

The highest occupied orbital is known as the valence shell

An unpaired electron is unstable
Free Radical

A missing electron creates a "Free Radical", highly reactive

Elemental Oxygen (O2) exists in nature as a pair of atoms sharing electrons. Energy is released by breaking the bond between these atoms.

If an electron becomes unpaired during a reaction, the resulting radical will react with nearby molecules to obtain one.
Free Radical Chain Reaction

initiation

\[
\text{A}^* + \text{B} \quad \text{(heat or light)}
\]

propagation

\[
\text{A} - \text{C} = \text{D} \quad \rightarrow \quad \text{A} - \text{C} + \cdot \text{D}
\]

\[
\text{D}^* + \text{E} - \text{F} \quad \rightarrow \quad \text{D} - \text{E} + \cdot \text{F} \quad \rightarrow \quad \text{etc.}
\]

termination

\[
\text{F}^* + \cdot \text{G} \quad \rightarrow \quad \text{F} - \text{G}
\]

Free Radicals

- In biological contexts, free radicals usually take the form of reactive oxygen species (ROS)
  - There are multiple subtypes of ROS, but all contain an oxygen atom with an unpaired electron
  - These ROS participate in chain reactions
    - Proteins, DNA, lipid membranes and other important cellular molecules are damaged
    - Chain reactions can be mitigated by molecules that are able to donate an electron without becoming unstable (Antioxidants)
  - Accumulated damage may result in cell apoptosis or necrosis
Drugs/Processes associated with ROS

- **Normal respiration and metabolism**
  - Some free radical generation is a normal consequence of our biology

- **Aminoglycosides**
  - Gentamicin, etc.

- **Radiation used for cancer treatment**
  - High energy waves split molecules

- **Many chemotherapy agents**
  - Cisplatin, etc.
  - It is important to note that in the case of cancer treatment, this type of oxidative damage is a necessary component of anti-tumor activity
Free Radical Damage

- Can result in damage to either the cochlea or the vestibular system
  - Cochlea – kills hair cells
  - Vestibular system – kills nerve cells of the vestibular ganglion

Connecting Concepts

Scenario: A young man is being treated with a CISplatin containing regimen for testicular cancer. Reducing the dose is not advised, as his treatment is likely to be curative, and efficacy may be compromised.

- Toxicity (ototoxicity and others) is expected. This is because CISplatin has a narrow therapeutic index.
- After administration, CISplatin is distributed throughout the body, not just to the tumor. It now comes into contact with the cells of the inner ear.
- As a consequence of its mechanism, CISplatin begins to generate ROS in the ear, ultimately leading to the death of hair cells.
Disruption of Necessary Gradients

- Maintenance of proper ion gradients between endolymph and perilymph is critical to proper function of the cochlea
  - This gradient is actively maintained by ion pumps in the membranes that separate the different scala
  - Ion pumps are proteins that may function as drug receptors
  - In the presence of certain drugs, these pumps may not function as intended. The result is impaired hair cell function.
    - Once the offending drug is eliminated, the gradient can be restored, and hair cell function usually returns with it

Drugs linked to gradient disruption

- Loop diuretics
  - Furosemide, etc.
    - Loop diuretics interfere with strial adenylate cyclase and Na+/K+-ATPase and inhibit the Na-K-2Cl cotransporter in the stria vascularis (Ding et al)
      - Disrupts the gradient directly at the pump level
      - Disrupts indirectly by depriving the enzymes of the energy needed to function properly
    - Loop diuretics also cause potassium wasting
Metabolic Stress

- The stria vascularis supplies critical blood flow to the cochlea
  - Supplies needed nutrients
  - Removes waste
- Vasoconstriction is a common condition that leads to decreased blood flow in the stria vascularis

Drugs associated with metabolic stress

**Non-steroidal anti-inflammatory drugs (NSAIDS)**
- Aspirin, Ibuprofen, etc.
  - Vasoconstriction is believed to be a major contributor to NSAID ototoxicity
  - Usually the result of repeated dosing
  - Characterized by tinnitus and reversible hearing loss

**Loop diuretics**
- In addition to interfering with gradients
  - Secondary effect; decreased blood volume can induce constriction
End of Section 2

Questions?

Section 3:
Chemical Otoprotection
Potential Mechanisms for Otoprotection

- Reduction of free radicals
- Alleviating biological stress

Antioxidants

- Antioxidants are molecules that are able to donate an electron to another molecule, without becoming unstable
- The human body produces some molecules with antioxidant properties naturally
- Antioxidants may also come from the diet or be taken as a supplement
Antioxidants Being Studied (a few of many)

- **D-methionine**
  - An amino acid that can be reversibly oxidized, neutralizing ROS

- **N-acetylcysteine**
  - Precursor of glutathione, an endogenous antioxidant

- **Molecular Hydrogen**
  - Direct electron donor

Limitations of antioxidants as therapy

- **Efficacy depends on adequate concentration in susceptible tissues**
  - Intravenous/Oral administration may fail to deliver adequate concentrations in the ear
    - May require injection directly into the ear
  - High dose systemic therapy may interfere with treatments that depend on ROS generation for efficacy
    - Chemotherapy/radiation
  - Pharmaceutical companies possibly reluctant to take on the cost of bringing drugs to market
    - None commercially available with the indication of otoprotection
Anti-inflammatory agents

Inflammation is a stressful biological state
- Swelling/Edema
  - Increased metabolic activity
  - Proliferation of signalling that may lead to cell death

Drugs already exist that may be useful
- Steroids - dexamethasone
- TNF blockers
- NSAIDS

Anti-inflammatory drugs

**Dexamethasone**
- Potent steroidal anti-inflammatory
  - Thought to reduce apoptosis by down-regulation of pro-apoptotic signalling from immune cells

**Etanercept**
- Binds to and neutralizes Tumor Necrosis Factor Alpha (TNF)
  - TNF is a pro-inflammatory marker
  - May lead to increased apoptosis

**Salicylate**
- Component of aspirin
  - May behave as an antioxidant
  - Reduces inflammation by inhibiting cyclooxygenase pathways
Limitations of Anti-Inflammatory Therapy

- These drugs are not free of toxicity!

Steroids
- Systemic therapy associated with:
  - Increased blood glucose, swelling, hormone disruption, immune suppression

TNF Blockers
- Immunosuppressive
  - Latent infections can be reactivated
  - Expensive

End of Section 3

Questions?
A Note About Supplements...

- Supplements are subject to a different regulatory process than drugs
  - Do not require FDA approval
  - “This statement has not been evaluated by the Food and Drug Administration. This product is not intended to diagnose, treat, cure, or prevent any disease.”
    - Unlike drugs, supplements are not required to prove efficacy or safety
    - Permissible claims are limited to:
      - Nutritional claims
      - Claims of well being
      - Health claims (evaluated by FDA)
      - Structure or Function claims
        - “Supports a healthy immune system”

Supplements (Additional Reading)

An in depth look at supplements for tinnitus:

Robert M. DiSogra, Au.D
Guide to OTC Tinnitus Relief Products
(https://docplayer.net/46917450-Guide-to-over-the-counter-tinnitus-relief-products.html)
Thank You

- Questions?
  - Contact me at: zitellib@upmc.edu