ALZHEIMER'S DISEASE PHARMACOLOGY

University of Hawai'i Hilo Pre-Nursing Program

NURS 203 – General Pharmacology

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LEARNING OBJECTIVES

- Understand how the proposed hypotheses for Alzheimer's Disease explains the drugs used to treat the symptoms
- Know which drugs belong to which class in the treatment of Alzheimer's disease
- Understand the pharmacologic differences between cholinesterase inhibitors that give individual drugs a place in therapy
- Know the pharmacologic characteristics of NMDA inhibitors and how they work for Alzheimer's Disease

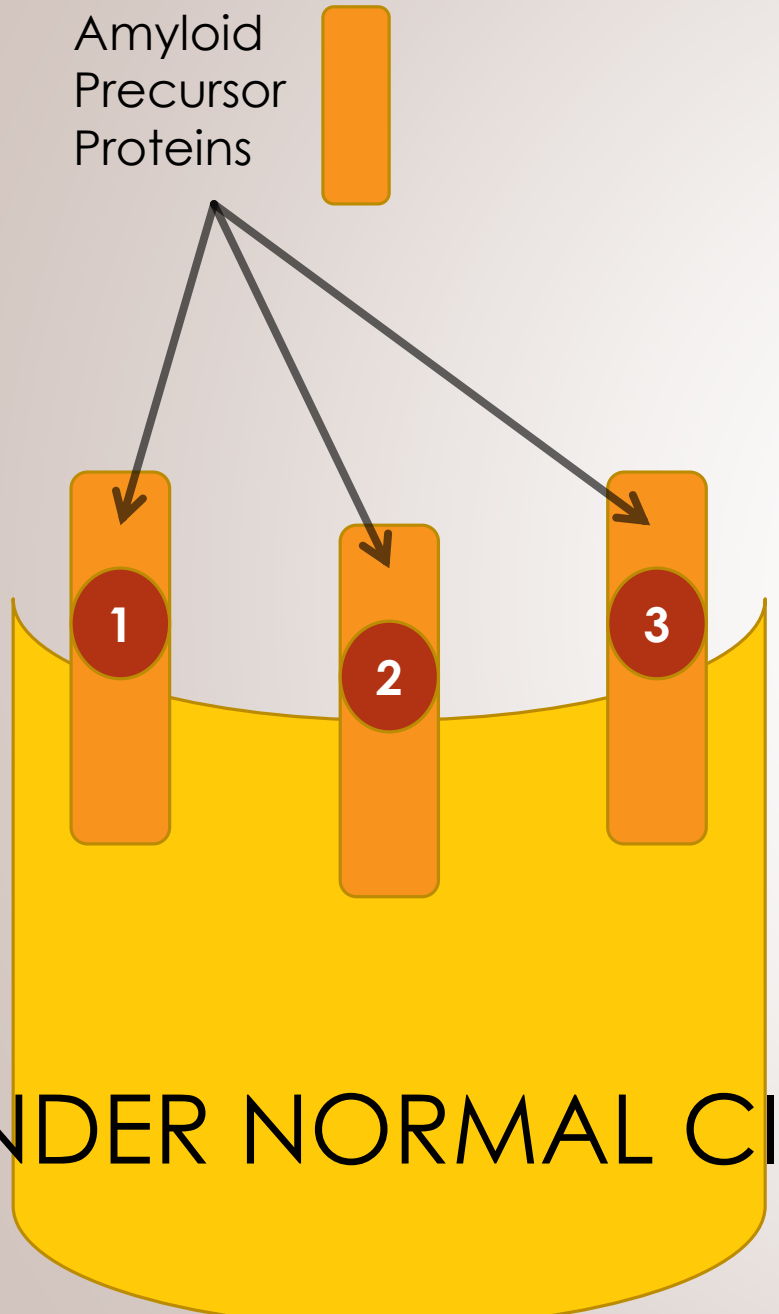
OVERVIEW

- Review of Alzheimer's Disease
- Hypotheses surrounding Alzheimer's Disease
- Drugs used to treat Alzheimer's disease

WHAT IS ALZHEIMER'S DISEASE?

- Neurodegenerative disease associated with
  - Impaired memory
  - Difficulty recognizing people, stimuli, & objects
  - Impaired writing & speech abilities
  - Depression, aggression, moodiness
  - Impaired motor skills

1. Plaques
2. Neurofibrillary tangles
3. Atrophy of brain areas
4. Decrease in acetylcholine
5. Excessive glutamate



1. Alpha secretase
   - Neuronal growth
   - Neuronal survival
   - Synaptic health
2. Beta secretase
   - Axon health through selective apoptosis (DR6 receptor)
3. Gamma secretase
   - Formation of plaques
     - Inflammation
     - Death receptor activation
     - Reactive oxygen species

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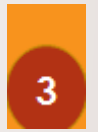
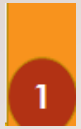


Aβ

UNDER NORMAL CIRCUMSTANCES

1. Alpha secretase
   - Neuronal growth
   - Neuronal survival
   - Synaptic health
2. Beta secretase
   - Axon health through selective apoptosis (DR6 receptor)
3. Gamma secretase
   - Formation of plaques
     - **Inflammation**
     - **Death receptor activation**
     - **Reactive oxygen species**



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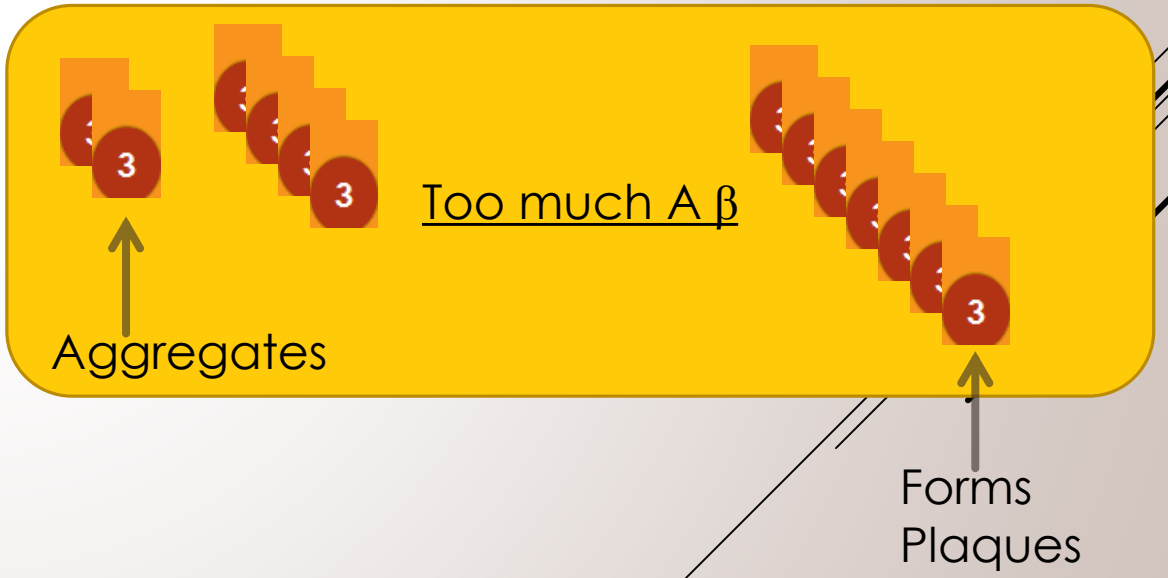
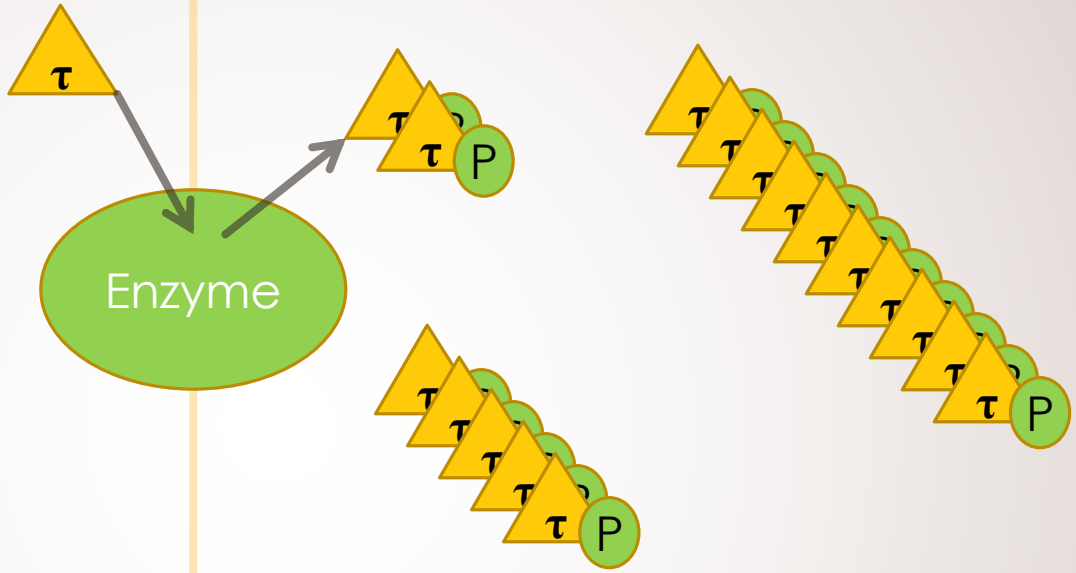


WHAT MIGHT BE HAPPENING IN AD - PLAQUES

Under normal circumstances

- Tao – Protein involved in the stabilization of microtubules

Alzheimer's Disease

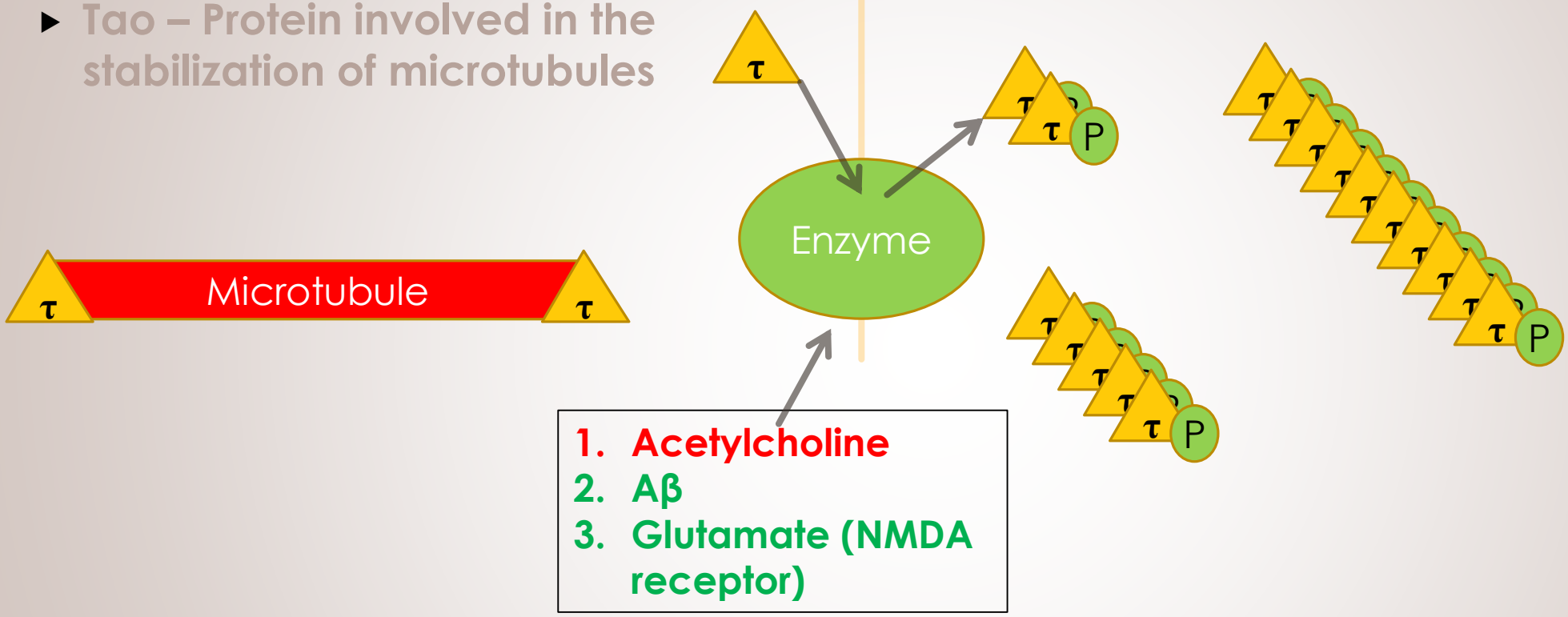


WHAT MIGHT BE HAPPENING IN AD - TANGLES

Under normal circumstances

- Tao – Protein involved in the stabilization of microtubules

Alzheimer's Disease



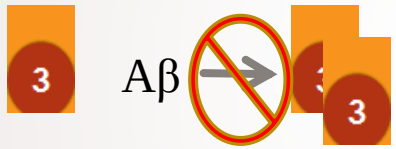
1. Acetylcholine
2. Aβ
3. Glutamate (NMDA receptor)

WHAT MIGHT BE HAPPENING IN AD - TANGLES

WHAT MIGHT BE HAPPENING IN AD – PLAQUES & TANGLES

Cholinergic deficits

1. **Acetylcholine**
2. **Aβ**
3. **Glutamate (NMDA receptor)**



Acetylcholine

Glutamate excess

Glutamate

Na & Ca

ATP depletion

Activation of the Calpain enzyme

Apoptosis

Cholinesterase Inhibitors

- Tacrine (Cognex)
- Donepezil (Aricept)
- Rivastigmine (Exelon)
- Galantamine (Razadyne)

NMDA Antagonists

- Memantine (Namenda)

DRUGS USED TO TREAT ALZHEIMER'S DISEASE

CHOLINESTERASE INHIBITORS

CHOLINESTERASE INHIBITORS - TACRINE

- MOA – Centrally active reversible inhibitor of acetylcholinesterase
- Dosage forms – oral
- Kinetics
  - High first pass effect - ~17% oral bioavailability
  - **Food decreases drug concentrations**
  - **Metabolism – CYP1A2, has an active metabolite**
  - Half-life – 2-4 hours
  - Excretion - urine
- ADRs
  - Nausea, vomiting, diarrhea, weight loss, dizziness, headache
  - Severe: hepatotoxicity
- Interactions
  - Antipsychotics (increase in EPS), **inhibitors of CYP1A2 (fluoroquinolones, antifungals, cimetidine, fluvoxamine**)
  - **Bioavailabiltiy reduced by food**

CHOLINESTERASE INHIBITORS - DONEPEZIL

- MOA – Reversible and noncompetitive inhibitor of central acetylcholinesterase
- Dosage forms
  - **Oral – 10 mg & 23 mg tablet, ODT 5mg &10 mg**
- Kinetics
  - Absorption – well absorbed
  - Distribution – large Vd, lipophilic
  - Protein binding – 96%
  - Metabolism – **extensive via CYP2D6 & 3A4, metabolites (inactive & active)**
  - Half-life – **70 hours (15 days to steady state)**
  - Time to peak – 3 hours, 8 hours
  - Excretion – urine 57% (17% unchanged drug), feces 15%
- ADRs
  - Insomnia, nausea, vomiting, diarrhea, infection, accidental injury, headache, dizziness, weight loss, fatigue, arrhythmia, **rhabdomyolysis**
- Interactions
  - Anticholinergic & cholinergic medications, beta blockers, inhibitors of CYP2D6 & 3A4, **statins**
  - Pregnancy category - C
  - Breast milk – not known

CHOLINESTERASE INHIBITORS - RIVASTIGMINE

- MOA – Reversible inhibition of the hydrolysis of acetycholine by cholinesterase
- Dosage forms
  - **Oral – tablet & solution**
  - **Transdermal patch**
- Kinetics
  - Absorption – oral, rapid & complete (fasting), transdermal 30-60 minutes
  - Protein binding - ~40%
  - **Metabolism – hydrolysis by cholinesterase in the brain, demethylation & conjugation in the liver (minimal CYP)**
  - Half-life – oral 1.5 hours, patch ~ 3 hours upon removal
  - Time to peak – oral 1 hour, patch 6-8 hours after applied
  - Excretion – urine (97% metabolites)
- ADRs
  - Headache, agitation, falling, weight loss, nausea, vomiting , diarrhea, abdominal pain, tremor, fatigue, insomnia, confusion, dyspepsia, UTI
  - **Transdermal**
    - **decreased incidence of ADRs overall**
    - **Redness at application site**
- Interactions
  - **Avoid use with beta blockers (other agents that can cause bradycardia), avoid use with metoclopramide**, cholinergic agents & anticholinergic agents, antipsychotic agents (severe EPS)
  - Pregnancy category – B
  - Breast milk – not known
  - **Food delays absorption but increases bioavailability**

CHOLINESTERASE INHIBITORS - GALANTAMINE

- MOA – Competitive & reversible central cholinesterase inhibitor, **may also increase glutamate & serotonin levels**
- Dosage forms
  - Oral – solution & tablet (IR & ER)
- Kinetics
  - Distribution – large
  - Protein binding – low
  - Metabolism – CYP2D6 & 3A4 (minor)
  - Bioavailability – 90%
  - Half-life – 7 hours
  - Time to peak – 1 hour (2.5 with food), 4.5-5 hours
  - Excreted – urine (20%)
- ADRs
  - **Nausea**, vomiting, headache, diarrhea, weight loss
- Interactions
  - Anticholinergics & cholinergic agents, antipsychotics, beta blockers & other agents that slow heart rate **(high incidence of interaction with drugs that prolong QT interval)**
  - Pregnancy category – C
  - Breast milk – not known

NMDA ANTAGONISTS - MEMANTINE

- MOA – noncompetitive antagonist of the N-methyl-D-aspartate (NMDA) receptor for glutamate, decreases glutamate activity under conditions of excessive excitation (does not effect normal neurotransmission), antagonized 5HT & nicotinic receptors, agonist at DA receptors
- Dosage forms
  - Oral – solution & tablet (IR&ER)
- Kinetics
  - Absorption – well absorbed
  - Protein bound - ~45%
  - Metabolism – Liver (not CYP), minor - inactive metabolites
  - Half-life – 60-80 hours
  - Time to peak – 3-7 hours, 9-12 hours (IR/ER)
  - Excretion – urine (unchanged)
- ADRs
  - Hypertension & hypotension (IR/ER), dizziness, confusion, headache, anxiety, diarrhea, constipation
- Interactions
  - Minor
  - Pregnancy category – B
  - Breast milk – not known