INTRODUCTION

- Pathology/Mitochondria
- Relationships
- Importance!
NEURODEGENERATION

- Alzheimer’s is most prevalent affecting 5.4 million people last year
- Parkinson’s 2nd, affecting 1.5 million people
- Huntington’s Disease more rare affecting 30,000 people
- Amyotrophic Lateral Sclerosis affects 20,000 people

http://www.phrei.org/research_neurodegenerative.html
ALZHEIMER’S DISEASE

Pathology

► Characterized by neuritic plaques made of:
  ▶ Amyloid beta protein
  ▶ Neurofibrillary tangles of overly-phosphorylated tau protein

► Plaques found in cortex and especially in the hippocampus

Clinical Symptoms

► Dementia/Cognitive Decline
► Increased confusion
► Mood and personality changes
PARKINSON’S DISEASE

- Loss of neurons in the substantia nigra of the brain
- Inclusions: Lewy Bodies with accumulated alpha synuclein and ubiquitin proteins.
- Symptoms include tremors, decreased range of motion, and paralysis.

http://www.healthcentral.com/ency/408/guides/000051_1.html
HUNTINGTON’S DISEASE

Pathology
- Known for loss of long projection neurons in the cortex and striatum.
- Irregular polyglutamine addition in the N terminal of huntingtin protein

Symptoms
- Psychiatric problems
- Dementia
- Uncoordinated and changed movements
AMYOTROPIC LATERAL SCLEROSIS

- Degeneration of motor neurons in the cortex, brain stem, and spinal cord
- Accumulations of mutated copper and zinc superoxide
- Symptoms show progressive weakness and atrophy due to disuse

http://www.als-ny.org/index.php?page=als_about
THE MITOCHONDRIA

- Big roll in all cells
- Run metabolic systems
- Provide ATP
- Contain own circular DNA - mtDNA
- mtDNA accumulates mutations as person ages
- Dysfunction!
- Initiation and progression of neurodegeneraiton

http://www.doeaccimphal.org.in/m18/file.php/1/final%20contents/21/structure.html
REACTIVE OXYGEN SPECIES

- Accelerate aging/cause damage
- Mitochondria produce ROS
- Unpaired electron, redox reactive
- Oxidize proteins to disform enzymes and others
- Lipid peroxidation
- Mutates DNA

http://seallab.wordpress.com/research/7-cytotoxicity-measurements/
TYING IT TOGETHER

- When problems occur in the mitochondria, especially important metabolic centers, in concurrence with an excess of reactive oxygen species, we see an increase in the number of neurodegenerative cases.
MITOCHONDRIAL DYSFUNCTION

- **Causes**
  - Through Reactive oxygen species
  - Through mutations in mtDNA
    - Large scale deletions and point mutations

- **Consequences**
  - Loss of important enzymes
  - Glucose metabolism impaired
  - Less ATP
  - Decreased autophagy and lysosomal degradation
  - Loss of cell-cell communication
  - Unstable calcium levels
  - Increase in reactive oxygen species
  - Apoptosis!
APOPTOSIS

- Occurs in extreme cases
- Through opening of mitochondrial permeability transition pore
  - Increase in ROS
  - Decrease in ATP
  - Rise in CA
  - Loss of membrane potential
PROTEIN ACCUMULATION

- Protein accumulation seen in mitochondria as well
- Which is initiating damage?
  - Protein accumulation or mitochondrial dysfunction
- Example includes amyloid precursor protein in Alzheimer’s disease

http://www.nature.com/nrn/journal/v9/n7/box/nrn2417_BX1.html
ROS AND NEURODEGENERATION

- ROS and NOS
- NOS made by N-methyl-D-aspartate glutamate receptors.
  - Overactivation = accumulation
- Decrease in antioxidant agents
  - Superoxide diismutase, glutathione peroxidase, and glutathione reductase

OXIDATIVE DAMAGE

- ROS and NO damage chaperone and proteasomal proteins
- S-nitrosylation by NO disables these proteins
- Creates direct protein accumulation

http://www.springerimages.com/Images/RSS/1-10.1007_s10495-010-0476-x-0
THE VICIOUS CYCLE

- ROS made in mitochondria are able to damage mitochondria directly
- This mutates mtDNA
- Creates problems in respiratory chain leading to production of more reactive oxygen species
- Cycle continues!

**ROS AND GLIAL CELL ACTIVATION**

**MICROGLIA**
- Glial cells detect damage by ROS
- Microglia activate to stimulate release of:
  - Cytokines
  - NO
  - NADPH oxidase
- Causes neuroinflammation and damage

**ASTROCYTES**
- Responsible for glutamate
- Overactivation = altered glutamate handling
  - Abnormal excitatory processes
  - Abnormal calcium signaling waves
- Increased death of dopaminergic neurons
MORE CONSEQUENCES OF ROS

- Initiate apoptosis
- Damage RNA and DNA
- Activate astrocytes to cause glutamate excitotoxicity:
  - Cell death through NMDA receptors
    - Influx of Ca, increase in NO, loss of membrane potential, damage to DNA, and cell death!
METABOLIC DERANGEMENTS

- Decline in glucose metabolism-hypometabolism
  - Key metabolic enzymes destroyed
- Insulin signaling defects
  - Important for glucose metabolism, memory skills, and synapse plasticity.
INSULIN RESISTANCE

HOW IT HAPPENS

- Activity of IR-tyrosine kinase being decreased
  - Errors in insulin signal transduction
- ROS damage

CONSEQUENCES

- Decrease in cognitive function
- Problems with acetylcholine formation
- Disruption in synaptic transmission
INSULIN AND PROTEIN ACCUMULATION

TAU PROTEIN
- Regulated by phosphorylation through kinases
- Kinases down regulated by insulin
- Insulin resistant brains = over-phosphorylation of tau protein and accumulation

BETA-AMYLOID PROTEIN
- Insulin helps with clearance of beta-amyloid protein
- Wide variety of hypotheses
INSULIN RESISTANCE

- Alteration in brain metabolism
  - Decrease in glucose metabolism
  - Insulin resistance

- Alteration in APP processing
  - Soluble Aβ↑
  - Aβ42:Aβ40 ratio ↑
  - Aβ plaque ↑
  - Aβ toxicity

- Defect in signal transduction (e.g. GSK3β)
  - Tau hyper-phosphorylation

- Oxidative stress (e.g. ROS, RNS)
  - Mitochondrial dysfunction
  - Defect in energy metabolism
  - Caspase activation

- Change in signal transduction in glial cells
  - Induction of pro-inflammatory gene
  - Inflammatory cytokines (e.g. IL-1β, IL-6, TNF-α)

- Neuronal cell death
NEURODEGENERATIVE DISEASE AND DOWN’S SYNDROME

- People with down’s syndrome have a greater chance of getting Alzheimer’s, Parkinson’s, or Huntington’s disease
- Brain of person with Down’s syndrome has abnormal neurons
  - Accumulation of ROS
  - Inflammation
  - Apoptosis
- Cause of decrease in cognition
NEURODEGENERATION AND DOWN’S SYNDROME

- Also compound called dual-specificity tyrosine- (Y)- phosphorylation regulated kinase 1A (Dyrk1A) overexpressed in Down’s syndrome brains
- Phosphorylates Alzheimer’s proteins
- Relates to pathological accumulation of other proteins
ALZHEIMER’S AND DIABETES MELLITUS

- Both show increased resistance to insulin
- If Diabetes is present, increased chance of neurodegeneration occurring
- Insulin resistance progresses protein accumulation
TREATMENT OF NEURODEGENERATION

- Thiazolidinediones
- mTOTS
- Insulin sensitizing hormones
- Other mitochondrial targets
- Antioxidant compounds
- Still looking!

http://www.rsc.org/chemistryworld/News/2012/January/alzheimers-parkinsons-neurodegeneration-linked-iron.asp
THIAZOLIDINEDIONES (TZDS)

- Used in treatment of Diabetes II
- Insulin sensitizer
- Directly activates the peroxisome proliferator-activated receptor-gamma
- Also decreases neuroinflammation
- Examples: Rosiglitazone and pioglitazone.
- Bad side effects!

http://www.pharmainfo.net/reviews/oral-hypoglycemic-agents-treatment-type-ii-diabetes-mellitus-review
MTOTS

- Mitochondrial target of thiazolidinediones
- Target protein located on inner membrane of the mitochondria
- Change in the nutrient sensing pathway
  - Activates AMPK
  - Decreases mTOR activity
  - Decrease in inflammatory kinase activation
- Leads to increased insulin sensitivity
- Compound in trial now, MSDC-0160, thanks to Metabolic Solutions Development Company.
MITOCHONDRIA AS A TARGET

- The dysfunctional mitochondria plus the aggregation of proteins inside of it makes it a good therapeutic target.
- Example would be reducing amount of p53 in the mitochondria, protecting against the mutant huntingtin protein.
- Also artificially increasing amount of ATP in the mitochondria has seen to help with neurodegeneration.
ANTIOXIDANTS

- Triphenylphosphonium-based antioxidants
- Foods and drinks
  - Curry spice, vegetables, green tea
- Melatonin

http://emilytodhunterwvudietetics.wordpress.com/2013/03/22/storage-life-of-fruits-and-vegetables/
CONCLUSION

- With a rising elderly population, number of neurodegenerative cases are rising.
- Mitochondrial dysfunction and reactive oxygen species play big rolls.
- Decreased glucose metabolism and increased insulin resistance also have a big effect on neurodegeneration.
- All the above are good targets for therapeutic compounds, which are being researched and tested.
THANK YOU FOR YOUR TIME!

Any questions?