MCB 135K Review

Midterm – II
March 30, 2004
Jason Lowry
Outline

1. Aging of the Nervous System
2. Brain Disorders
3. Imaging of the Brain
4. Oxidants and Anti-Oxidants
5. Aging of the Visual System
6. Aging of the Cardiovascular System
7. Exercise and Aging
8. Aging of Muscles
9. Immune System
Aging of the Nervous System

- Structural Changes
  1. Changes in Brain Weight
  2. Neurons vs. Glial Cells
  3. Denudation
  4. Neuropathological Markers

- Biochemical Changes
  1. Neurotransmitters
  2. CNS Synapses
  3. Neurotransmitter Imbalance and Brain Disorders

- Brain Plasticity
  1. CNS Regenerative Potential
Changes in Brain Weight

Structural brain changes with aging
changes in brain volume

young  old
Neurons vs. Glial Cells

- Neurons
  - Cell Body
  - Axons
  - Dendrites
  - Synapses

- Glial Cells
  - Astrocytes
  - Oligodendrocytes
  - Microglial
Denudation

- Normal Aging
  - A, B, C
  - Small amounts of neuronal loss
  - Increased dendritic growth
- Degenerative Disease
  - D, E, F, G
  - Progressive loss of dendritic spines
  - Eventual Cell Death
Neuropathologies

• Lipofuscin
  – By-product of cellular autophagia
  – Linear increase with normal aging
  – Function in disease unknown

• Lewy Bodies
  – Present in normal aging (60+)
  – Increased accumulation in Parkinson’s Disease

• Neurofibrillary Tangles
  – Tangled masses of fibrous elements
  – Present in normal aging in hippocampus
  – Accumulation in cortex is sign of Alzheimer’s

• Paired Helical Filaments
  – Role in Neurofibrillary tangle formation
# Neurotransmitters

## TABLE 7-2 Neurotransmitters and Modulators in the Nervous System

<table>
<thead>
<tr>
<th>Amines</th>
<th>Amino Acids</th>
<th>Peptides</th>
<th>Others</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetylcholine</td>
<td>Glutamate</td>
<td>Enkephalin</td>
<td>Nitric Oxide</td>
</tr>
<tr>
<td>Catecholamines</td>
<td>Aspartate</td>
<td>Cholecystokinin</td>
<td>Carbon Monoxide</td>
</tr>
<tr>
<td>Norepinephrine</td>
<td>Glycine</td>
<td>Substance P</td>
<td>Zinc</td>
</tr>
<tr>
<td>Epinephrine</td>
<td>GABA</td>
<td>VIP*</td>
<td>Synapsins</td>
</tr>
<tr>
<td>Dopamine</td>
<td>Taurine</td>
<td>Somatostatin</td>
<td>Cell Adhesion Molecules</td>
</tr>
<tr>
<td>Serotonin*</td>
<td>Histamine</td>
<td>TRH*</td>
<td>Neurotropins</td>
</tr>
</tbody>
</table>

*Serotonin, 5-hydroxytryptamine, or 5-HT  
GABA or gamma-aminobutyric acid  
VIP or vasoactive intestinal polypeptide  
TRH or thyrotropin-stimulating hormone
Synapses

- Cholinergic
- Adrenergic
- Serotonergic
- Gabanergic
Brain Disorders

• Parkinson’s Disease
  1. Pathologies
  2. Symptoms
  3. Treatment Strategies

• Alzheimer’s Disease
  1. Symptoms and Signs
  2. Disease Progression
  3. Pathophysiology
  4. Treatment / Management
Parkinson’s Disease

• Loss of neuromelanin containing neurons in brain stem and presence of Lewy bodies in degenerating dopaminergic cells
Parkinson’s Disease

• Symptoms
  – Loss of motor function
  – Loss of balance
  – Speech and Gait abnormalities
  – Tremor
  – Rigidity

• Treatment Strategies
  – Pharmacological
    • Ldopa
  – Neuroprotective
  – Surgical
  – Cell Therapies
Alzheimer’s Disease

- **Risk Factors**
  - Apolipoprotein E4 on chromosome 19
  - Late-onset AD
  - APOE*4 allele ↑ risk & ↓ onset age in dose-related fashion
  - APOE*2 allele may have protective effect

- **Pathophysiology**
  - There are 3 consistent neuropathological hallmarks:
    - Amyloid-rich senile plaques
    - Neurofibrillary tangles
    - Neuronal degeneration
  - These changes eventually lead to clinical symptoms, but they begin years before the onset of symptoms
# Alzheimer’s Disease Progresses Through Distinct Stages

<table>
<thead>
<tr>
<th>Stage</th>
<th>Symptoms</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>Memory loss, Language problems, Mood swings, Personality changes, Diminished judgment</td>
</tr>
<tr>
<td>Moderate</td>
<td>Behavioral, personality changes, Unable to learn/recall new info, Long-term memory affected, Wandering, agitation, aggression, confusion, Require assistance w/ADL</td>
</tr>
<tr>
<td>Severe</td>
<td>Gait, incontinence, motor disturbances, Bedridden, Unable to perform ADL, Placement in long-term care needed</td>
</tr>
</tbody>
</table>

Dementia/Alzheimer’s Symptoms
TREATMENT & MANAGEMENT

• Primary goals: to enhance quality of life & maximize functional performance by improving cognition, mood, and behavior
  • Nonpharmacologic
  • Pharmacologic
  • Specific symptom management
  • Resources
Imaging of the Brain

- Types of Neuroimaging
- Neuronal Recruitment and Reaction Time
Oxidants and Anti-Oxidants

- **Oxidants**
  - Free Radicals (Table 5.1)
- **Anti-Oxidants**
  - Examples (Table 5.2)
- **Cellular Effects**
  - Metabolism
  - Homeostasis
  - Mitochondria
- **Modulation of Life Span**
  - Ionizing Radiation
  - Caloric Intake
Oxidants and Anti-oxidants

- **Oxidants (Table 5.1)**
  - Superoxide Radical
  - Hydrogen Peroxide
  - Hydroxyl Radical
  - Singlet Oxygen
  - Nitric Oxide
  - Peroxynitrite
  - Hypochlorite
  - Certain Transition Metals

- **Anti-Oxidants (Table 5.2)**
  - Vit C
  - Glutathione
  - Vit E
  - Carotenoids
  - Lipoic Acid
  - Superoxide Dismutase
  - Catalase
  - Many others
Oxidants and Anti-Oxidants

- **Free Radicals**
  - Produced when chemical bonds are broken
  - Attack other molecules indiscriminately
  - Initiate oxygen consuming chain reactions
  - Cause fragmentation and random cross-linking

- **Anti-Oxidants**
  - Reduce adverse impact of oxidants by:
    - Intercepting Oxidants before they react with vital biological agents
    - Prevent chain reactions
    - Prevent the activation of oxygen to highly reactive products
Oxidants and Anti-Oxidants

• Cellular Effects
  – Metabolism
    • Life span correlation with metabolic rate
    • Comparison involving different animal species having similar metabolic rate (Bats/Rats)
  – Homeostasis
    • Cells can adapt to increased oxygen up to a certain level and at a certain rate
    • Various other roles
  – Mitochondria
    • Leakage
    • Electron Transport Chain

• Modulation of Life Span
  – Ionizing Radiation
    • High levels cause animals to develop disease and do not allow study of oxidative damage
    • Low levels cause increased lifespan in mice
  – Caloric Intake
    • Decreased caloric intake lowers metabolic rate and increases life span
    • FSIRKO mice show an increased life span, with decrease fat, in the absence of caloric restriction
Aging of the Visual System
Aging of the Visual System

- Structural Changes (See handout)
  - Tear Film:
    - Dry eyes or tearing
  - Sclera:
    - Fat deposits – yellowing
    - Thinning – blueing
  - Cornea
    - Diameter does not change after age 1
    - Shape changes
  - Retina
    - Photoreceptor density decreases; other layers become disordered
    - Illuminance decreases with age
  - Lens
    - Increased size and thickness
    - Becomes more yellow
Aging of the Visual System

• Function
  – Corneal and Lens
    • Decreased accommodation power
    • Increased accommodation reflex latency
    • Refractive error becomes more hyperopic with age
    • Corneal sensitivity decreases
    • Scatter increases
  – Retinal
    • Decreased critical flicker frequency
    • Visual acuity declines
    • Visual Field decreases
    • Color vision changes
    • Darkness adaptation is slowed
    • Increased glare problems
    • Decreased light reaches retina
Aging of the Visual System

- Recommendation to Accommodate Problems:
  - Wear appropriate optical correction
  - Increase ambient light
  - Make lighting even and reduce glare
  - Improve contrast in critical areas
  - Avoid rapid changes in light level
  - Avoid Pastel
  - Allow more time
Aging of Cardiovascular System

- Atherosclerosis
  - Characteristics
  - Disease Results
  - Arterial Changes
  - Atherogenesis
  - Contributing Factors
  - Age Changes in Vascular Endothelium
Atherosclerosis

- Characteristics
  - Universal
  - Progressive
  - Deleterious
  - Irreversible …but (?)
Atherosclerosis

• Disease Manifestation
  – Myocardial Infarct
  – Stroke
  – Aneurysm
  – Gangrene
Arterial Changes

• Morphological Characteristics of the Arterial Wall
  – Intima – inner most layer of endothelial cells
  – Media
    • Elastica interna – formed by elastin fibers
    • Smooth Muscle cells
    • Vasa vasorum (penetrates media)
    • Elastica externa
  – Adventitia – outer most layer of collagen bundles
    • Vasa vasorum – provide blood

• Read Pages 287-289
Atherogenesis

- Fatty Streak (Intima)
  - Increased LDL and oxidized LDL
  - Accumulation of LDL in endothelial space
  - Alter and breakdown of Elastic fiber
  - Alerts immune system
  - Monocytes → macrophages
  - Phagocytose LDL and elastic fibers
  - Macrophages become full of LDL and appear as foam cells after staining
Atherogenesis

- Fibrous Plaque (Intima and Media)
  - Damaged smooth muscle cells take up LDL
  - Increase foam cells
  - Defense mechanism create scar tissue
  - Problem for metabolic exchange later
Atherogenesis

- **Atheroma**
  - Alteration of endothelial cells
  - Decreased number of cell
  - Platelets seal off area where there was a loss of cells
    - Increased growth factors
    - Increased RBC
    - Results in thrombus
Aging of Cardiovascular System

- Atherosclerosis
  - Theories
- Coronary Heart Disease
  - Risk Factors
  - Risk Assessment
  - Treatment
Lipids and Apolipoproteins

- Major Categories
- Risk Factors in Atherosclerosis
- Lipoprotein Synthesis
- Apolipoproteins
- Lipolytic Enzymes
- Receptors
Lipids and Apolipoproteins

• Categories
  – Chylomicrons and VLDL
    • High triglycerides
  – IDL and LDL
    • High cholesterol
  – HDL
    • High proteins
    • High phospholipid
LIPOPROTEINS
MAJOR PROTEIN AND MAJOR LIPID

Legend: CM = chylomicron
        VLDL = very low density lipoprotein
        IDL = intermediate density lipoprotein
        LDL = low density lipoprotein
        HDL = high density lipoprotein
        TG = triglyceride
        CE = cholesterol ester
Lipids and Apolipoproteins

- Risk Factors
  - Total cholesterol to HDL ratio above 4.0
  - Family history
  - Elevated LDL; Low HDL
  - Diabetes Mellitus
  - Age
  - Hypertension
  - Obesity
  - Smoking
Lipoprotein Synthesis

• Intestine
  – CM
  – Nascent HDL
• Liver
  – VLDL
  – IDL
  – LDL
  – Nascent HDL
Apolipoproteins

• Definition:
  – Markers on lipid cell surface that determines metabolic fate of lipids

• Roles in Metabolism
  – apoA-I
    • HDL
    • Reverse Cholesterol Transport
  – apoB-100
    • VLDL, IDL, LDL
    • Sole protein on LDL
    • Necessary for assembly and secretion in liver
    • Ligand for LDL receptor
Apolipoproteins and RCT

• apoA-I is important in reverse cholesterol transport (review figure 17.3)
  – Process whereby lipid free apoA-I and subclasses of HDL mediate the removal of excess cholesterol
Enzymes

- Lipoprotein Lipase
  - Catabolizes CM and VLDL → produces glycerol and fatty acids
  - Requires apoC-II for activation
- Hepatic Triglyceride
- LCAT
  - Essential for normal maturation of HDL
  - Associates with discoidal HDL and is activated by apoA-I
  - Forms hydrophobic cholesteryl ester that moves to core and gives spheroid shape (active)
Receptors

• LDL
  – Responsible for internalization of LDL
  – Also known as apoB-E receptor
  – Regulates cholesterol synthesis
• Macrophage Scavenger (SR-A1)
  – Recognizes oxidized LDL
  – Role in atherogenesis
• SR-B1
  – Docking protein for HDL
  – Role in selective uptake for steroid hormone production
  – Role in catabolism and excretion from liver
Exercise and Aging

- Cardiovascular Fitness
- Metabolic Fitness
- Muscular Strength
- Anti-oxidant defenses
Exercise and Aging

- Cardiovascular Fitness
  - Maximal oxygen consumption
  - VO$_2$ Max increased by regular exercise
    - Declines with aging
  - Decreases morbidity
  - Decreases mortality
Exercise and Aging

• Metabolic Fitness
  – Control age related increases in body fat
  – Decrease risk of diabetes
  – Maintain Ideal BMI
  – Exercise at 45-50% of VO₂ Max to facilitate fat loss (utilize fat as energy source)
Aging of Muscles

- **Sarcopenia**
  - Age associated loss of muscle mass
  - Most significant contributing factor in the decline of muscle strength with age
  - Lean body mass decreases between 35 and 75
    - 45% muscle mass → 15% muscle mass
Aging of Muscles

• Etiology of Sarcopenia
  – Decrease in mitochondrial mass
  – Reduced protein synthesis
  – PNS and CNS changes
  – Hormonal changes
  – State of inactivity (most prominent)
Muscle Fibers and Aging

• Type I – slow fibers
• Type II – fast fibers
  – Type II decrease much more with aging than Type I
  – Explains why older people can have increased stamina at slow pace activities (hiking)
• Bed rest results in 1.5% loss per day and 2 weeks to recover for 1 day bed rest
The Aging Heart

• Heart ages well in absence of disease
• Age associated changes
  – Heart rate decreases
  – No change in stroke volume
  – Contractility decrease with exercise
  – No change in ejection fraction
  – Heart rate – to max rate of increase with exercise “220- age”
  – Blood pressure increases due to increased peripheral vascular resistance
The Aging Heart

• Heart Failure: - insufficient cardiac output
  – Due to:
    • Impediments to forward ejection
    • Myocardial Failure
    • Impaired cardiac filling
    • Volume overload

• Cardiomyopathies
  – Dilated – leads to systolic dysfunction
  – Hypertrophic – marked with ventricular hypertrophy
  – Restrictive – excess rigidity of the walls
Immune System

• To be discussed in discussion section
Discussion

• Wednesday/Thursday
  – 1st half-hour – immune system review
  – 2nd half-hour – open office hours