Neurological disorders II

Degenerative disorders (14.9)

- **Transmissible spongiform encephalopathy**
  - E.g.: Bovine spongiform encephalopathy (BSE= mad cow disease) Creutzfeldt-Jakob disease, scrapie (animals only)
  - Sporadic: can be infectious or genetic
  - Caused by protein infectious agents (prions) found in neural membranes, important for synaptic function and myelin. Normal amino acid composition but **misfolding**
  - Symptoms similar to Alzheimer’s, but faster and deadlier
  - No known treatments in human, genetic manipulations in mice

- Scrapie can be treated by late onset destruction of (normal) Prions. Prions are useful for development. Treatment involves a prion-destructive protein produced after 12 weeks
  - Possible genetic therapies: selective activation of cell death in infected cells only. Use Caspases: enzymes that triggers cell death (aka *apoptosis*).

- **Parkinson’s disease: classified movement disorder**
  - Symptoms:
    - Rigidity, slow movement, absence of reflexes, tremors at rest (but not during sleep or voluntary movements), posture and walking abnormalities, bradykinesia, and akinesia
    - Initially, little intellectual impairments. As it progresses: speech impairments, decreased Short Term memory, slower problem solving and slower visual spatial skills.
    - Mood changes, including depression. Anxiety is also common.
    - In general, not hereditary. Sporadic. Affects 0.5% of adult population, slow progression (~20 years)
    - No single causes (genetic, strokes, tumors, infections…) no cure.
    - Mohmand Ali

Degeneration of the basal ganglia

- Neural structures affected:
  - Degeneration of pars compacta region of sub. Nigra  $\rightarrow$ basal ganglia
  - Caused by death of dopamine neurons
- Decreased activity of 4 areas that receive inputs from the basal ganglia:
  - 1. Motor cortex – look up in book

**Physiological mechanisms of PD**

- Lack of dopamine
  - Nigrostriatal dopaminergic neurons almost gone
- Lewy bodies: protein growth within dopamine cells
- Possibly due to a defect on Chromosome 4: the protein (a-synuclein) produced by misfolded
- Toxic gain of function: production of a toxic protein by a faulty gene
- Mutation on chromosome 6: Parkin gene
- Ubiquitin tags faulty/ misfolded protein
- Tagged proteins are destroyed by proteasomes
- Parkin gene helps in ubiquitin tagging
- Mutation → loss of Parkin function
- Not only genetic: other possible mechanisms include decreased mitochondrial activity and iron build up

Ubiquitin & misfolded protein → Tagged misfolded protein → proteasomes → amino acids

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**Parkinson's Disease**

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**Parkinson’s disease continued**

- **Treatments**
  - MAO inhibitors (e.g. deprenyl) prevents the destruction of monoamines, slows down progression of PD
  - Direct fetal dopamine cell transplantation in Basal Ganglia. Side effects – involuntary movements
  - **Pallidotomy**: precise lesions of Globus Pallidus
(-) Sub.Nigra (dopamine) → also (+) sub thalamic nucleus → glob. Pall → (-) motor systems
in Parkinson’s, it goes = subthalamic nucleus → glob Pall → motor systems
- Deep brain inhibitory stimulation of subthalamic nucleus (STN)
- Skip figure 14.13

Current research on PD
- Gene therapy: modified virus that inhibits STN → increase acidity in Supplemental Motor area → decrease PD symptoms
- Neuroprotective agents – chemicals that protect brain. Control a-synuclein

Degenerative disorders
- Huntington’s Disease

- Symptoms:
  - Uncontrollable and excessive movements. Uncoordinated activation of motor programs
  - Rare, associated with dementia. Symptoms appear after 35 years old, death 15 years after onset
  - 1630s witches of Bures (UK)

- Neural substrate: degeneration of caudate and putamen: affect GABA and Ach cells in the basal ganglia. Enlarged ventricles

Caudate Putamen → (GABA) → prefrontal cortex & motor cortex → motor activity
- Treatment
  - No treatment, 1/10000 people. Management therapies
  - Gene is identified and tests exits to determine whether it is present
  - Research focuses on gene therapy

- Alzheimer’s Disease
- Symptoms
  - Affects 10% of the 65 and up population 50% 85 and under
  - Not entirely hereditary
  - Progressive: depression, loss of memory and mental function (dementia) resemble anterograde amnesia of declarative memory
  - Down syndrome develops sometimes into Alzheimer’s
  - Terminal disease
Neural substrate
- Degeneration of Ach center (nuc. Basalis)
- Degeneration of the hippocampus, frontal and temporal cortices, raphe nucleus and locus coerules
- Issues with working memory sometimes
- Development of:
  - B- amyloid plaques: accumulation of B-Amyloid.. cell death
  - Neurofibrillary tangles. Dead microtubules. Also in down syndrome

skip figures 14.16-14.18 and page 380 (starting at APP) to 382 (before ALS)
- Treatment:
  - no cure.
  - Causes unclear.
  - Gene mutation on chromosome 21 (amyloid gene)
- Amyotrophic Lateral Sclerosis (Lon Gehrigs disease) (ALS)

- Symptoms:
  - Stiffness of movement, exaggerated reflexes muscular atrophy, paralysis, terminal disease (5-10 years after onset) no dementia
  - Mostly sporadic cases (1/20,000)
  - In some cases, related to chromosome 21
  - Neural substrate: degeneration of spinal cord, motor neurons and cranial nerves. Excitotoxicity
  - Treatment: no cure. Drug that decrease glutamate release, improve symptoms. Gene therapy