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Nervous System Disease and Neuron Excitability

Dravet's Syndrome

Symptoms: Severe myoclonic epilepsy in infancy (SMEI), polymorphic epilepsy in infancy (PMEI), epilepsy with polymorphic seizures

Treatments: Daily Anticonvulsant Medication (ex. clobazam, clonazepam, leviteracetam), Alternative Treatments (Intravenous Immunoglobulin Therapy, Vagus Nerve Stimulation, ketogenic diet)

Why Interesting? Most often caused by a mutation in a gene that encodes a sodium ion channel in the brain

MSG and Glutamate Excitotoxicity

Excitotoxicity implicated in:
- Stroke
- Huntington's Disease
- Neuropathic pain
- Drug dependency

Cocaine Addiction

Short-term symptoms:
- Euphoria/anxiety
- Energy/mentally alert
- Increased sympathetic responses (HR, BP, T)
- Muscle twitches
- Heart attack, seizure, sudden death

Long-term symptoms:
- Craving
- Increased tolerance
- Increased irritability
- Paranoid psychosis

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Why Interesting?
Amyotrophic Lateral Sclerosis

“Lou Gehrig’s Disease”

- Most common Motor Neuron Disease (MND)
- Progressive degeneration of one or more of the following:
  - Corticospinal tracts
  - Anterior horn cells
  - Bulbar motor nuclei (brainstem, cranial nerves)

Common Symptoms (early → late):
- No energy, weakness, muscle atrophy of hands or feet, spreading up limbs
- Chronic pain, spasticity
- Fatigue
- Difficulty controlling tongue movements (impaired speech, facial expression)
- Inappropriate affect (involuntary laughing or crying)
- Death by asphyxiation (failure of respiratory musculature)

Treatment/Prognosis:
- No cramps, weakness, muscle atrophy of hands or feet, spreading up limbs
- Clumsiness, spasticity
- Fatigue
- Difficulty controlling tongue movements (impaired speech, facial expression)
- Inappropriate affect (involuntary laughing or crying)
- Death by asphyxiation (failure of respiratory musculature)

Amyotrophic Lateral Sclerosis (ALS)

- Idiopathic fatal motor neuron disease affecting voluntary muscle movements
- Symptoms: signs of both upper and lower motor neuron damage
  - UMN damage: stiff muscles, exaggerated reflexes
  - LMN damage: muscle weakness and atrophy, muscle cramps, fasciculation (twitches)
- Late symptoms: inability to walk, move limbs, swallow, chew, or breathe

Possible Causes:
- Excess glutamate in the spinal fluid and serum → glutamate-induced excitotoxicity incites neurodegeneration through activation of calcium-dependent enzymatic pathways.
  - Free radical generation, which can cause damage to intracellular organelles.
  - SOD1 mutation

Treatments:
- None, to undo motor neuron damage, just prevent further damage
  - Riluzole (Rilutek) → decreases glutamate release to avoid further motor neuron damage

Amyotrophic Lateral Sclerosis

= Lou Gehrig’s disease

Motor Neuron Diseases

Syndromes:
- Rapidly progressive weakness, muscle atrophy, fasciculation, muscle spasticity, difficulty speaking, difficulty swallowing, difficulty breathing.

Causes:
- Hereditary (chromosome 21), mutation of SOD1

Pathophysiology:
- Death of both upper and lower motor neurons in motor cortex of brain

Hench Wu and Yi-Yun Ho
Autosomal Dominant Nocturnal Frontal Lobe Epilepsy (ADNFLE)

- Epileptic disorder characterized by violent seizures during sleep
- Usually begins in childhood, decreasing in severity with age
- Mutations of nicotinic ACh receptors
  - CHRNA4
  - CHRN2
  - CHRNA2
- Treated by anti-epileptic drugs, vagal nerve stimulation

Multiple sclerosis, a demyelinating disease

- Autoimmune disorder that affects multiple parts of the CNS.
- The myelin sheath is damaged by an auto-inflammatory reaction provoking demyelination.
- Affects signal transduction.
- Degenerative.
- Many symptoms, the most common are:
  - Decrease in sensitivity (fingers, toes).
  - Loss of mobility.
- No cure but some drugs can reduce the reactivity of the immune system.
- Mainly affects females under 30.

Parkinson’s Disease

- Symptoms
  - Tremor
  - Bradykinesia
  - Impaired posture
- Cause
  - Degeneration of dopaminergic neurons in the substantia nigra pars compacta (SNc) results in dopamine (DA) imbalance
  - DA imbalance causes reduced excitation of striatum and eventually motor cortex
  - Reduced activity of motor cortex causes the symptoms of Parkinson’s Disease
- Treatment
  - Dopamine supplement
    - L-DOPA, a dopamine precursor
  - Dopamine agonist
  - Deep brain stimulation

Diabetic Neuropathy

- A progressive neurodegenerative disease that causes denervation of axon by eating away at the myelin sheath.
- Diabetic neuropathy is a negative response to hyperglycemia
- Denervation causes a “cross-talking” between nerves that causes an increase in sodium channels at site of denervation
- Increase in sodium channels creates Long Term Potentiation that causes a burst of electrical stimulation, called Hyperexcitability, into the dorsal horn in the Central Nervous System
- Hyperexcitability causes a release of Glutamate at the synaptic junction in the dorsal horn causes neuronal depolarization which increases signaling to the brain that registers the increase in dorsal horn signaling as pain

Sources:
Childhood Absence Epilepsy

**Symptoms:**
- Onset 4-10 yrs, peak 5-7 yrs
- Short lasting (~10 s) seizures
- Sudden impairment of consciousness
- Interruption of ongoing activity
- Upward blank stare

**Prognosis:** Most patients “grow out” of it

**Hypothesized Cause:**
- Genetic mutations alter T-type calcium channel properties (e.g., lower voltage activation)
- Found often in thalamus
- Open near resting potential
- Create low-threshold spikes after EPSPs
- Depolarize beyond threshold for Na-dependent APs

- Hyperexcitable T-type channels
- Inappropriate oscillations in thalamus
- Seizures

**Drug:**
- Zarontin (ethosuximide)
- Prevents absence seizures
- Although debated, commonly believed to be T-type channel blocker

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Neuromyotonia

**Description**
- Peripheral nerve hyperexcitability causes spontaneous muscular activity and may cause excessive stiffness and twitching

**Mechanism**
- Cause is still not 100% understood; one prominent explanation suggests an autoimmune origin for the disease; it is believed that certain antibodies bind to the potassium channels in peripheral nerves resulting in continuous hyperexcitability

Mark and Dinan

John and Andrew