Primary Cast Episode 18 - Nervous System Physiology

Host: Dr. Charlotte Durand
Guest: Dr. Aruna Shivam

1. **Skeletal Muscle Contraction**
   What is the sequence of events in the contraction of a skeletal muscle fibre, starting at the motor end plate?
   - Discharge of a motor neuron
   - Release of preformed acetylcholine at the motor endplate via exocytosis
   - Diffusion of Ach across the synaptic cleft
   - Binding of Ach to postsynaptic nicotinic Ach receptors
   - Increase Na and K conductance in the end plate membrane
   - Generation of the end plate potential
   - Generation of action potential in muscle fibres
   - Inward spread of depolarisation along the T tubules
   - Release of Ca from terminal cisterns of the sarcoplasmic reticulum and diffusion to thick and thin filaments
   - Binding of calcium to troponin C, uncovering myosin binding sites on actin
   - Formation of cross linkages between actin and myosin and sliding of thin on thick filaments, producing movement

   What is the sequence of events in relaxation of a skeletal muscle fibre
   - Calcium is pumped back into the sarcoplasmic reticulum
   - Release of calcium from troponin
   - Cessation of interaction between actin and myosin

   How does a tetanic contraction occur?
   - The contractile mechanism has no refractory period
   - Repeated stimulation before relaxation has occurred leads to a summation of contractions fast repeated stimulation causes a fused continuous tetanic contraction which can be complete or incomplete

2. **Smooth Muscle Contraction**
   Describe the sequence of events in contraction and relaxation of visceral smooth muscle
   - Binding of Ach to muscarinic receptors
   - Increased influx of calcium into the cell
   - Activation of calmodulin – dependent myosin light chain kinase
   - Phosphorylation of myosin
   - Increased myosin ATPase activity and binding of myosin to actin
   - Contraction
   - Dephosphorylation of myosin light chain phosphatase
   - Relaxation or sustained contraction

What factors influence intestinal smooth muscle contraction?

- Stretch of smooth muscle causes contraction in the absence of innervation
- Cold increases the activity
- Ach decreases smooth muscle potential and increases spike frequency resulting in more active muscle
- Adrenaline and noradrenaline increase smooth muscle potential and decrease spike frequency causing decreased muscle activity
- Neural mechanisms

3. **Cholinergic transmission**

Please describe the synthesis, release and action of acetylcholine at the nerve synapse

- Choline is synthesised in neurons and actively taken into cholinergic neuron
- Acetyl CoA and choline are used to form acetylcholine via choline acetyltransferase
- This is packaged in synaptic vesicles via transporter
- When the nerve is stimulated, the vesicles execytose the Ach into the synaptic cleft, where it binds the postsynaptic Ach receptor

Once released into the synaptic cleft, how is its effect terminated?

- Diffusion
- Catabolism by pseudocholinesterase in the circulation
- Acetylcholinesterase on the postsynaptic membrane
- Reuptake of choline into the presynaptic nerve terminal

Describe the differences between the two different types of acetylcholine receptors

- Divided into nicotinic and muscarinic
- Muscarinic – actions mimicked by muscarine and blocked by atropine. Found in smooth muscle, glands and brain. G protein coupled receptors.
- Nicotinic – actions mimicked by nicotine, found in the NMJ, autonomic ganglia and the central nervous system. They are ligand gated sodium ion channels.

4. **Adrenergic transmission**

Which catecholamines act as neurotransmitters?

- Noradrenaline
- Adrenaline
- Dopamine

Outline the biosynthesis of adrenaline

- Starts with tyrosine, converted to DOPA via tyrosine hydroxylase
- DOPA is converted to dopamine byb dopa decarboxylase
- Dopamine to noradrenaline by dopamine hydroxylase
- Norad to adrenaline via phenylethanolamine methyltransferase

Describe the sequence of events at the noradrenergic synapse, following stimulation of a sympathetic nerve

- Noradrenaline is stored in granulated vesicles in the nerve
- Released into the synaptic cleft by exocytosis once is is stimulated
- Acts on postsynaptic receptors
- **Action is terminated in 2 ways:**
    - Reuptake to the presynaptic neuron then metabolised by MAO to inactive derivatives
    - Catabolised in the synaptic cleft by COMT

5. **Nerve action potential**

Define resting membrane potential of a neuron

- The potential difference across a cell at rest, as a result of separation of positive and negative electrical charges across a cell membrane.
- Inside is negative relative to outside.
- The normal RMP is -70mV in a neuron.

How is the resting membrane potential generated?

- Main ions involved are K and Na
- The Na/K ATPase creates an electrochemical gradient by pumping out 3 Na for every 2 K in
- Na and K diffuse down their concentration gradient across a semipermeable membrane (K wants to go out, Na wants to come in)
- The cell membrane is more permeable to K at rest – which is why the RMP is close to the equilibrium potential for K

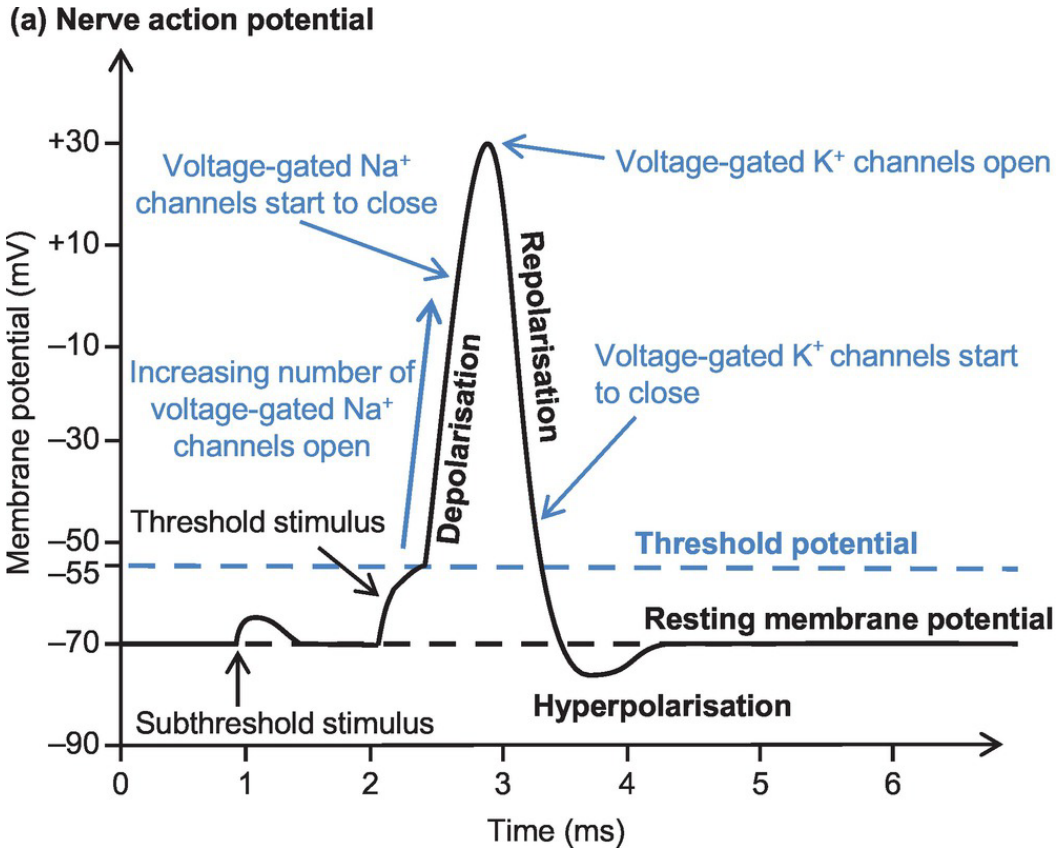
Why is a cell more excitable in hyperkalaemia?

RMP moves closer to the threshold potential for eliciting an action potential (it becomes less negative on the inside of the cell)

Please draw a nerve action potential and indicate the sequence of events that occur

Key Points you must include:

- Starts at -70mV
- After a depolarising stimulus occurs, voltage gated Na channels become active and Na enters the cell
- When the threshold potential is reached (-55mV) , the voltage gated Na channels overwhelm the K channels
- Entry of Na causes opening of more voltage gated Na channels and further depolarisation in a positive feedback loop, causing the upstroke of the action potential (peaks at +35mV)
- Voltage gated Na channels enter an inactivated state for a few milliseconds before returning to the resting state, this inhibits further Na movement
- The reversal of membrane potential causes opening of voltage gated K channels, resulting in repolarisation via K efflux and the end of the AP
- Slow return of K channels causes hyperpolarisation (below -70mV)
- Over time this is corrected and the cell returns to resting membrane potential



6. **Nerve Conduction**

Where are ion channels distributed in myelinated neurons?

Concentrated in the nodes of ranvier, Na channels are flanked by K channels

What factors affect conduction?

- Myelinated is quicker than demyelinated
- Size
- Direction of conduction

In the synapse, where can inhibition occur?

- Post synaptic – via direct or indirect inhibition (i.e. refractory periods or after hyperpolarisations)
- Pre-synaptic – mediated by neurons that end on excitatory endings (axo-axonal synapses)

What mechanisms are involved?

- Increased Cl conductance (reduced Ca influx and the amount of excitatory transmitter release)
- Voltage gated K channels – K also decreases Ca entry
- Direct inhibition regardless of Ca

7. **Serotonergic Transmission**

What are the functions of serotonin?

- Regulation of the vomiting reflex
- Regulation of mood
- Control of respiration
- Platelet aggregation and smooth muscle contraction
- GI secretion and peristalsis
- Regulation of circadian rhythms

What are the steps in the synthesis and catabolism of serotonin?

- Hydroxylation and decarboxylation of tryptophan to form serotonin
- Released serotonin from serotonergic neurons is recaptured by an active re-uptake mechanism and inactivated by MAO to form metabolite 5HIAA (5 hydroxy indoleacetic acid) – which is secreted in the urine

8. **Hearing (from 2013)**

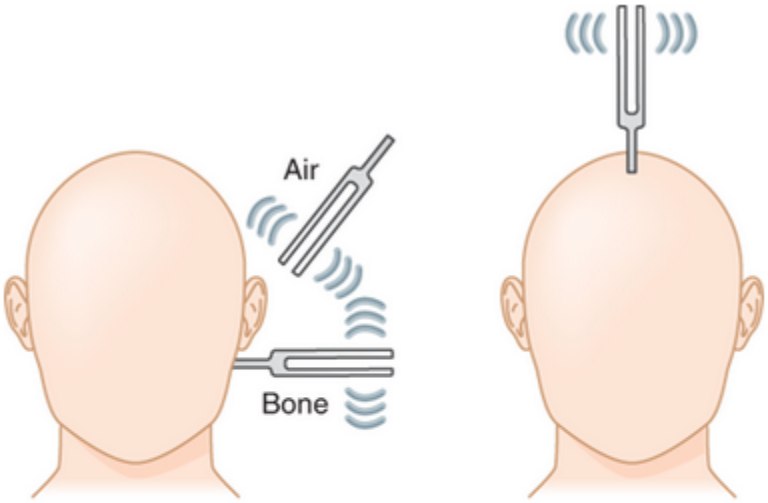
What are the two major mechanisms of deafness?

- Conductive deafness – due to impaired sound transmission in the external or middle ear, affects all frequencies. Examples: wax, perforated TM, otitis media
- Sensorineural deafness – due to loss of cochlear hair cells (most common) or problems with CNVIII or within central auditory pathways. Only affects some frequencies. Examples: noise exposure, aminoglycosides

How can you differentiate between them?

Weber and Rinne can both be done using a 512hertz tuning fork

Weber - place on the forehead, rinne on the mastoid



Hearing loss	Rinne test (Conduction)	Weber test (Localization)
None	Air > bone	Midline
Sensorineural	Air > bone	Normal ear
Conductive	Bone > air	Affected ear

9. **Temperature Regulation**

What is the body's response to hot and cold environments?

Mechanisms activated by cold (posterior hypothalamus)

- Increased heat production: shivering, hunger, voluntary activity, noradrenaline and adrenaline release

- Decreased heat loss: skin vasoconstriction, curling up, body hair stands on end

Mechanisms activated by heat:

- Decreased heat production: anorexia, apathy, inertia
- Increased heat loss: vasodulation, sweating, increased respiration

10. Nystagmus

What is nystagmus?

- Characteristic jerky movement of the eye seen at the start and end period of rotation
- Different types - the direction of eye movement is identified by the direction of the quick component
    - Horizontal
    - Vertical
    - Rotatory

Why does nystagmus occur?

- There is a reflex that maintains visual fixation on stationary points while the body rotates, though this is not initiated by visual impulses
- When rotation starts the eyes move slowly in the direction opposite to the direction of rotation, maintaining visual fixation
- When the limit of this movement is reached, the eyes quickly snap back to a new fixation point and then again move slowly in the other direction

How is nystagmus mediated?

- Slow component initiated by impulses from the labyrinths
- Quick component is triggered by a centre in the brain stem

11. Optic pathways

Describe the neural connections of the visual pathways

- Begins with the retina
- Optic nerve
- Optic chiasm
- Optic tract
- Lateral geniculate body (in the thalamus)
- Then fibres to the primary visual cortex in the occipital lobe
- Other connections
    - The lateral geniculate nucleus also sends information to the pretectal midbrain (to control papillary reflexes, eye movements)
    - To frontal cortex (refined eye movements, near point response)
    - Optic chiasm to thalamic suprachiasmatic nucleus (endocrine and circadian responses to the day/night cycle)

How is visual acuity measured?
Using a Snellen chart viewed at a distance of 6m (20 feet)

What does a result of 6/24 mean?
Reduced visual acuity. Means that at 6m this person can see something they should be able to see from 24m.

Why is the fovea important for visual acuity?

- It is the point where visual acuity is the greatest
- Fovea is the centre of the macula, a thinned out, rod-free portion of the retina where cones are densely packed and each synapses on a single bipolar cell which, in turn, synapses on a ganglion cell, providing a pathway to the brain.

What factors influence visual acuity?

- Optical factors: state of the image forming mechanisms e.g. presence of cataracts, keratitis, astigmatism, myopia or hyperopia
- Retinal factors: the state of the cones,, affected by retinopathies, optic neuritis
- Stimulus factors e.g. illumination, brightness of the stimulus, contrast between stimulus and background.

12. Pain conduction

Describe how pain is transmitted from the periphery to the brain

- Sense organ - naked nerve endings
- Transmission via type 2 fibre types - small myelinated A-delta fibres or larger, slower, unmyelinated c fibres.
- Spinal cord - both fibre groups end in the dorsal horn of the spinal cord
- From the spinal cord, fibres go to the brain via second order neurons in the ventrolateral system to the thalamus
- then via third order neurons on to the cerebral cortex

How can acute pain be modulated?

- Gate theory – stimulation of large touch/pressure afferents causes inhibition of pain pathways in the dorsal horn of the spinal cord
- Stress induced analgesia i.e. in trauma
- Drugs i.e. opiates
- Higher centre interpretation and modulation

What sites do opioid medications act on?

- Receptors in afferent nerve fibres, in the dorsal horn of the spinal cord and in the periaqueductal grey matter of the brain

What is referred pain?

- Irritation of a visceral organ which causes pain at a somatic site other than the location of the stimulus
- Due to the somatic structure being from the same embryonic segment or dermatome as the structure from which the pain originates
- i.e. arm pain in a myocardial infarction, the loin to groin pain of renal colic, diaphragmatic pain referred to the shoulder

13. Spinal Tracts

What are upper motor neurons?

Usually refers to corticospinal neurons that innervate spinal motor neurons.

What clinical features can be seen when they are injured?

Damage initially causes muscles to become weak and flaccid but eventually leads to spasticity, hypertonia, hyperactive stretch reflexes and abnormal plantar extensor reflex (seen as an upgoing plantar reflex)

What is the physiological basis for clonus?

There is a loss of descending cortical input to inhibitory neurons (called Renshaw cells), therefore loss of inhibition of antagonists, resulting in a repetitive sequential contraction of the ankle flexors and extensors

14. Reflexes

Describe the components of the stretch reflex

- A monosynaptic reflex where skeletal muscle is stretched with contraction of the muscle as a response.
- Sense organ is the muscle spindle impulse via an afferent nerve (monosynapse on motor neurone) effector (intrafusal fibres)
- Example of this is the kneejerk reflex

How is it different from the withdrawal reflex?

- Withdrawal is a polysynaptic reflex
- Has afferent and efferent limbs as in the stretch reflex. But the sensory organ is a nociceptor and responds to painful stimulus
- The central integrator (between the afferent and efferent limbs) consists of polysynaptic connections in the spinal cord

- Efferent limbs are motor nerves to effector muscles on the ipsilateral and contralateral sides
- Flexion and withdrawal of the ipsilateral limb and extension of the contralateral limb

15. Thermoregulation

How is heat lost from the body?

- Radiation and conduction (70%)
- Vaporisation of sweat (27%)
- Respiration (2%)
- Urination/defacation (1%)

How is fever produced in the body?

- Endotoxins, inflammation and other pyrogens that act on monocytes, macrophages and other cells to produce cytokines (e.g. interleukins and TNF)
- Cytokines act on the pre-optic areas of the hypothalamus. Local release of prostaglandins raises the set point

16. Thirst

Where is thirst regulated?

Hypothalamus

What factors increase thirst?

- Increased osmotic pressure in the plasma – sensed by osmoreceptors in the anterior hypothalamus
- Decreased ECF volume (i.e. in haemorrhage) – sensed by the baroreceptors in the heart and blood vessels, increased renin which acts on central receptors to increase thirst
- Psychological i.e. psychosis
- Others – habitual intake of liquids when eating, other GI hormones may influence but this is poorly understood

In what situations may thirst be blunted?

- Hypothalamic disease
- Direct head trauma
- Altered mental state
- Psychosis
- Lesion of the anterior communicating artery – supplies the hypothalamus
- High protein diet – promotes diuresis