1. Define the following terms used to describe the Nervous System and explain how they interact with each other:
   a. Central Nervous System
   b. Peripheral Nervous System
   c. Autonomic nervous System
   d. Somatic Nervous System

2. List the major causes of neurological disorders and give examples.
3. State the difference in the regenerative capacity of injured axons between the CNS and PNS.
4. Describe the main components of a standard neurological examination.
5. Outline the main electrophysiological and imaging techniques used in neurological diagnosis, noting the main advantages and disadvantages.

Main Causes

- **Trauma**, e.g. skull fracture, spinal cord injury
- **Cerebrovascular accident**, e.g. stroke
- **Neoplasia**, e.g. glioma
- **Infection**, e.g. meningitis
- **Metabolic disorders**, e.g. diabetic neuropathy
- **Genetic disorders**, e.g. Down’s syndrome
- **Environmental factors**, e.g. heavy metal encephalopathies
- **Immunological factors**, e.g. multiple sclerosis

**Trauma**

- Neurones once lost cannot be replaced
- Neurones are highly differentiated so cannot return to the cell cycle, therefore small loss of neurones or neurone function can lead to devastating effects on tissue
- E.g. spinal cord injury → quadriplegia and complete loss of sensation
- Damage to the DESCENDING tract damages MOTOR neurones, which results in loss of effector function e.g. movement below the damage point
- Damage to the ASCENDING tract damages SENSORY neurones, which results in a loss of sensation
- Damage to the CNS is permanent, i.e. there is no regeneration of axons

**Cerebrovascular accident**

- The brain is highly metabolically active, therefore requires a large supply of energy
- Loss of blood supply will lead to degeneration of the brain tissue within a few minutes
- E.g. cerebrovascular infarct- area of brain tissue completely deprived of oxygen, resulting in cell death
- Asymmetry between the two hemispheres indicates an abnormality
- Damage to the left hemisphere of the brain results in a loss of sensation and movement on the right side of the body. This is described as a CONTRALATERAL relationship.
Neoplasia

- Presence of TUMOURS in nervous tissue
- Within the skull, ½ of the tumours will be METASTASES; primary tumours will be present in other body locations
- ⅔ of tumours present in nervous tissue will develop from the surrounding membranes or GLIAL cells (OLIGODENDROCYTES)
- Tumours cannot result from differentiated cells, i.e. neurones
- E.g. menigiomas- space occupying lesion evolved from MENINGES surrounding brain
- This can lead to an increase in INTRACRANIAL PRESSURE and movement of the MIDLINE towards on hemisphere, therefore try to limit swelling/growth of the tumour
- Different between infarct and tumour; how quickly do symptoms develop? Infarcts usually develop rapidly, whereas tumours may grow slowly.

Infection

- E.g. meningitis- infection of the MENINGES which can rapidly spread
- VIRAL meningitis does not stimulate a full immune response and has a low mortality rate
- BACTERIAL meningitis rapidly develops with a high mortality rate
- Oedema, and increased WBC count and fever can be observed rapidly with bacterial meningitis

Metabolic disorders

- E.g. diabetes
- Decreased blood sugar levels can lead to a hypoglycaemic coma which can lead to brain death
- Also can lead to PERIPHERAL NEUROPATHY, and has effects on retinal function

Genetic disorders

- Involving development e.g. Down’s Syndrome
- A small mutation (Trisomy 21) can lead to a big effect
- Some genetic disorders don’t present till adulthood, e.g. Huntington’s – degeneration of CAUDATE and PUTAMEN nuclei leads to uncontrolled movement
- A person may have already passed this genetic disorder onto their children, although screening tests are available for family members of the patient- with this screening test, genetic counselling is strongly recommended

Environmental factors

- E.g. heavy metal encapholopathy i.e. lead poisoning
- The developing brain is very sensitive to heavy metals, and for this reason the levels of exposure should be tightly controlled
- Other factors: mobile phones, smoking, diet etc

Immunological factors

- Abnormal immune response → neurological disorder
- E.g. multiple sclerosis
- The DEMYELINATION of axons means that they are less efficient at nerve conduction
Syndromes

- A neurological disorder with a collection of symptoms with a distinct cause
- E.g. Epilepsy- abnormal synchronous firing of neurones
- Often pharmacologically controlled
- Neurones usually have synchronised action potentials with high firing rates
- On an EEG recording (electrodes placed on skull in different positions), EPILEPTIC SPIKES indicate a group of neurones firing simultaneously leading to an increased amplitude
- Can be diagnosed without symptoms
- If this simultaneous firing spreads to other areas other than the brain, this may cause a SEIZURE which may lead to unconsciousness or an abnormal response of the SENSORY CORTEX (feeling pain, pressure, coldness etc)

Neurological and Psychiatric Disorders

- Nervous tissue is more vulnerable than other tissues and therefore injury or disease is likely to have a greater effect
- This VULNERABILITY is due to:
  - Lack of replacement of lost tissue
  - No AXONAL REGENERATION in the CNS
  - High energy requirement and low energy store in the brain
  - Limited space in the cranial cavity
- The cause of many neurological disorders is not known
- A neurological disorder may display both loss of function (negative sign) and abnormal function (positive sign)
- Psychiatric disorders involve altered behaviour often with no demonstrable signs of altered brain function or pathology
- Neurology and psychiatry may overlap considerably

The Neuronal network

- Most neurones have a highly branched axons
- Nerve conduction is along the axon from the cell body towards the dendrites/synapse
- There can be many neurones that reach one synapse, or vice versa
- SYNAPSE: “decision points”- which point of the network is active at any one time, and which part will be stimulated?
- Can be thought of many different systems intertwining, e.g. motor, visual, sensory, auditory etc
Basic Organisation of the Nervous System

The Normal Nervous System

**Structural Divisions**
- CNS: brain and spinal cord
- PNS: nerves and ganglia

**Functional Divisions**
- Somatic: controls motor and sensory function for body wall
- Autonomic: controls VISCERAL FUNCTION

The CNS consists of:
- Cerebrum
- Cerebellum
- Brain stem
- Spinal cord

The CNS carries out “housekeeping” functions by processing sensory and motor information and maintaining the internal environment. It also supports higher functions such as perception, cognition, emotion and memory.

The ANS regulates/controls internal organs, blood vessels, glands, structures in the eye and genitalia.

To a large extent, there is localisation of function within the NS, but a FUNCTIONAL SYSTEM e.g. the motor system, may consist of several structures at some distance from each other, connected by pathways.

Each cerebral hemisphere has a CONTRALATERAL RELATIONSHIP with the side of the body it controls.

Some higher functions, such as language, are represented in one hemisphere only.

Neurones are the functional units of the nervous system. They have a cytoplasmic process, called an AXON, which conducts impulses away from the cell body towards other neurones or muscle fibres.

The point of contact with other cells is called a SYNAPSE. The resulting network contains many pathways that usually consist of multiple neurones. A neural pathway is usually represented diagrammatically (see pp).

Axons that are grouped together in peripheral nerves regenerate after injury, although functional recovery is often compromised by non-specific target REINNERVATION.

Axons within the CNS do not generally regenerate over long enough distances to be useful. This appears to be due to the presence of inhibitory factors and the absence of some guidance cues in the mature CNS environment, but also may involve INTRINSIC NEURONAL DIFFERENCES.

Diagnostic Methods

1. **Patient History**
2. **Neurological Examination**
3. **Specific Methods**

**Patient History**

- Symptoms
- Duration of symptoms
- Other illnesses
- Social situation etc.
• This is a very good opportunity for OBSERVATION of the patient, to observe any apparent “abnormalities”

Neurological examination

• Level of consciousness (very alert – normal – complete coma)
• Speech
• Mental state and cognitive function
• Sensory function
• Motor function
• Cranial nerve function

Specific methods

➤ Neurophysiology/electrophysiology
- Electroencephalography (EEG)
  o Measures electrical potentials at scalp generated by underlying neurones
  o Particularly useful at diagnosing epilepsy and coma
- Electromyography (EMG) & Nerve Conduction Studies (NCS)
  o Examine integrity of muscle, peripheral nerve and lower motor neurones

➤ Imaging
- Computerised Tomography (CT)
  o Uses X-ray source; high concentration of ionising radiation
  o Shows hard tissues well, but not good for soft tissues
  o Relatively fast and inexpensive
- Magnetic Resonance Imaging (MRI)
  o Based on the behaviour of hydrogen protons in the tissues to a strong, externally applied magnetic field
  o Good for differentiating soft tissues
  o Does not use ionising radiation, non-invasive

E.g. 1: Multiple Sclerosis

- MRI shows degeneration of the white matter (white patches seen)

E.g. 2 Migraine

- ANGIOGRAPHY demonstrates cerebral vessels radiographically after injection of contrast medium
  • Increased brain activity → increased blood flow
  • Asymmetry of brain activity and dampening of activity seen during migraine
  • Recovery of symmetrical pattern seen after
Cells of the Nervous System

NMH 3 - Professor Richard Reynolds (r.reynolds@imperial.ac.uk)

1. Draw and label a diagram of a typical neuron, identifying soma, dendrites, axon and terminals.
2. Define the role of each cellular component in the specialised function of the neuron.
3. Outline the organisation and functions of intracellular transport in the neuron.
4. Define the functional subtypes of neurons and list the ways in which they are organised collectively in the nervous system.
5. Describe the organisation of synapses.
6. Name the main classes of neuroglia and explain their functions in the nervous system.

The main aims of this session are as follows:
7. To explore the diversity of the structure of cells in the nervous system and to relate this to the diversity in their function;
8. To relate the variety in structure and function of neurons to their organisation into ganglia, nuclei, laminae, fibre tracts and nerves;
9. To provide an appreciation of the dependence of neurons upon one another via the concept of integration of synaptic inputs;
10. To describe the role of glial cells and illustrate this by their response to different types of injury to the nervous system.

Introduction

The Neuron

- Basic structural and functional unit of the nervous system
- Information processing unit
- Responsible for the generation and conduction of electrical signals
- Communicate with one another via chemicals released at the synapse (NEUROTRANSMITTERS)
- Supported by NEUROGLIA
- Comprising several different cell types
- Neuroglia outnumber neurons by approx 9:1

Neuronal Structure

Cellular structure of all neurons is similar. Diversity is achieved by differences in the number and shape of their processes

Cell Body

- Known as the SOMA
- Metabolic centre of the cell
  - Highly organised metabolically active cell
- Has a large nucleus, and prominent nucleolus
- Abundant rough ER and free ribosomes
- Well developed Golgi
  - Secretory cell, therefore highly involved in the trafficking and packaging of proteins via the secretory pathway
- Large number of mitochondria
Numerous lysosomes
Highly organised cytoskeleton

**Dendrites**
- Input; major area of reception and incoming information
- Spread from soma and branch frequently
  - Diameter decreases further away from the cell body
- Greatly increase the surface area of the neurone
- Over covered in protrusions called DENDRITIC SPINES
  - Dendritic spines receive the majority of synapses
  - One of the most “plastic” elements of the nervous system; dynamic as can increase/decrease the number of spines present
  - Large PYRAMIDAL neurons may have as many as 30,000/40,000 spines, e.g. PURKINJE neurons have >80,000 spines per cell (present in the CEREBELLUM; control intricate movement)
  - Spines may have multiple synapses
  - E.g. Schizophrenia; loss of dendritic spines present

**Axon**
- Output; conducts impulses away from the cell body
- Emerge at the axon hillock, with a slight increase in diameter
  - Action potential generated at hillock
- Usually only one per cell, but may branch extensively after leaving cell body and at target cell
- Prominent microtubules and neurofilaments
- Can be myelinated or unmyelinated
  - In myelinated neurons, the axon membrane is only exposed at nodes of Ranvier, where the action potential is boosted
  - In unmyelinated neurons, the diameter < 1 micron
- The molecular composition of the axon is organised into domains:
  - NODE- consists of all Na+ channels
  - PARANODE- next to the node
  - JUXTAPARANODE- next to the paranode, and consists of all K+ channels

**Axon terminals**
- Close to the target the axon forms a number of terminal branches (TERMINAL ARBOR)
- Also forms specialised structures called synaptic terminals
  - BOUTON: large, bulb-like structure which forms at the end of the terminal branches
  - VARICOSITIES: swelling like structures that form along the axon

**Synapse**
- Synaptic vesicles are packaged in the Golgi and shipped by FAST ANTEROGRADE transport
- Have specialised mechanism for association of synaptic vesicles with the plasma membrane
- Abundant mitochondria
  - 40% of total energy consumption is required for ion pumping and synaptic transmission
  - Function of synaptic transmission highly sensitive to oxygen deprivation
Neuronal cytoskeleton

- Axons range in length from micrometers to up to a meter in the human adult
- Highly organised cytoskeleton is required
  - Consists of microfilaments, intermediate filaments and microtubules
  - Maintains axon tensile strength and allow transport of proteins
- NEUROFILAMENTS play a critical role in determining axon calibre
- Microtubules are very abundant in the nervous system

Intracellular Transport (functional polarization)

Fast Axonal Transport

- Transport of membrane
- Vesicles with associated motors are moved down the axon at 100-400 mm per day
- Different membrane structures targeted to different compartments
- Retrograde moving organelles are morphologically and biochemically distinct from anterograde vesicles

Anterograde Transport

- Definition: transport of materials needed for neurotransmission and survival away from cell body
- FAST anterograde:
  - E.g. Synaptic vesicles, transmitters, mitochondria
  - 400mm/day
  - Uses microtubular network and requires oxidative metabolism
  - Uses specific molecular motors
- SLOW anterograde:
  - Bulk of cytoplasmic flow of soluble constituents

Retrograde Transport

- FAST retrograde:
  - Return of organelles
  - Transport of substances from extracellular space
  - Uses different molecular motors
  - E.g. Trophic growth factors, neurotrophic viruses

Morphological Subtypes of Neurons

- Wide range of structural diversity
- Cell body varies from 5 micrometers from small INTERNEURONS to 135 micrometers for the largest motor neurons

Pseudounipolar

- Dorsal root ganglia (DRG) sensory neurons have two fused axonal processes
- DRG neurones have no dendrites and receive no synapses
- Have a soma
- Single axon acts as a continuous cable carrying action potentials from the peripheral receptor organ to the central terminal in the spinal cord

**Bipolar**
- E.g. in cerebral cortex, retina
- Two axonal processes with central soma

**Golgi Type I Multipolar**
- Highly branched dendritic trees
- Axons extend long distances
- E.g. Pyramidal cells of the cerebral cortex
  - All of the CORTICAL OUTPUT is mediated through pyramidal neurons which are the major excitatory neurons
  - Can be subdivided into numerous classes based on morphology, laminar location and connectivity
  - Triangular shaped soma
  - Single axon
  - Large apical dendrite which arises from the apex of the principle cell’s soma (single long thick, branches several times as the distance from the soma increases)
  - Multiple basal dendrites arise from the base of the soma. The basal dendritic tree consists of 3-5 primary dendrites. As distance from the soma increases, the basal dendrites branch profusely
  - Branches on the dendrites are known as secondary dendrites
  - Dendritic spines are also present
- E.g. 2. Purkinje cells of the cerebellum
- E.g. 3. Anterior horn cells of the spinal cord
- E.g. 4 retinal ganglion cells

**Golgi Type II Multipolar**
- Highly branched dendritic trees
- Short axons terminating quite close to the cell body of origin
- E.g. stellate cells of the cerebral cortex and cerebellum
  - Represent the major excitatory input to cortical pyramidal cells
- Small multipolar cells with local dendritic and axonal arborizations
- Use glutamate or aspartate as a neurotransmitter

**Functional Subtypes of Neurons**

- **Sensory neurones**
  - Commonly pseudounipolar with one major process which divides into two branches
    - One runs to CNS
    - One to sensory receptor
  - Conducts impulses from sensory receptors to CNS
  - E.g. dorsal root ganglia neurons
- **Motor neurons**
  - Conduct impulses from CNS to effectors; muscles and glands
  - Generally multipolar with large soma
  - E.g. spinal motor neurons

- **Interneurons**
  - Cell bodies and processes (axons etc) remain within CNS
  - Majority of neurons within the CNS
  - Can be large multipolar or small bipolar local circuit neurons
  - Responsible for the modification, coordination, integration facilitation and inhibition that must occur between sensory input and motor output

**Functional Organisation of Neurons**

Neurons in the CNS tend to be collected into groups often according to function (Diagrams on pp)

- **Nucleus**
  - Group of UNENCAPSULATED neuronal cell bodies within the CNS
  - Usually consist of functionally similar cells
  - E.g. brain stem nuclei (Raphe), deep cerebellar nuclei (Dentate)

- **Laminae**
  - Layers of neurons of similar type and function
  - E.g. cerebral cortex grey matter, cerebellar gray matter

- **Ganglion**
  - Group on ENCAPSULATED neuronal cell bodies in the peripheral nervous system
  - E.g. dorsal root ganglia, sympathetic ganglia

- **Fibre tracts**
  - Groups or bundles of axons in the CNS
  - Mixture of myelinated and unmyelinated
  - E.g. corpus callosum, internal capsule

- **Nerves**
  - Discrete bundles of axons
  - Bring information to the CNS from sensory receptors and bring axons to effector organs
  - Often mixed sensory and motor neurons
  - Usually part of the peripheral nervous system
    - Except e.g. optic and olfactory nerves

**Synaptic Organisation**

- Terminal portions of axons form synapses onto other neurons
- Communication through chemical transmitters
- Use a variety/diversity of transmitters
- Neurons receive multiple synaptic input
- Competing inputs are integrated in the postsynaptic neuron (NEURONAL INTEGRATION)
- Types of synapses:
  - AXO-DENDRITIC: often excitatory
  - AXO-SOMATIC: often inhibitory
  - AXO-AXONIC: often modulatory (hillock etc)
Neuroglia

- Support cells of the CNS:
  - Astroglia
  - Oligodendroglia
  - Microglia
  - Ependymal cells
- Support cells of the PNS:
  - Schwann cells
  - Satellite glia
- Perform many and varied support functions
- In close contact with neurons and are essential for their correct functioning

Astroglia (astrocytes)

- **Structure**
  - Star-shaped cells
  - Numerically the largest population of CNS cells
  - Intimate associations with blood vessels, ventricles, leptomeninges, neuronal soma, synapses, nodes of Ranvier (many other cell types)
  - Divided morphologically into different types:
    - FIBROUS astroglia (white matter)
    - PROTPLASMIC astroglia (grey matter)
    - RADIAL astroglia
  - Most prominent cytoplasmic component of fibrous astroglia is numerous intermediate filament bundles
  - Gap junctions: suggest astroglia-astroglia signalling

- **Function**
  - Scaffold for neuronal migration and axon growth during development
  - Formation of blood-brain barrier and brain-CSF barrier via ENDFEET
  - Transport of substances from blood to neurons
    - Ordered arrangement of astrocytes with minimal overlap
    - Each cell forms a specific territory that interfaces with MICROVASCULATURE
    - Might include thousands of synapses
  - Segregation of neuronal processes (synapses)
  - Removal and degradation of neurotransmitters
  - Synthesis and release of neurotrophic factors
  - Neuronal-glial and glial-neuronal signalling
  - K+ ion buffering
  - Glial scar formation:
    - Respond to injury by dividing and migrating to site of injury
  - Glioma formation

Oligodendroglia (oligodendrocytes)

- Myelin forming cells of the CNS
  - INTERFASICULAR oligodendroglia- found in rows along axon tracts
  - PERINEURONAL oligodendroglia- found in association with neuronal cell bodies
Structure
- Small spherical nuclei
- Few thin processes
- Prominent ER and Golgi
- No intermediate filaments
- Highly metabolically active

Function
- Production and maintenance of the myelin sheath
- Each cell is capable of producing up to 40 internodes
- MYELIN:
  - Lipid-rich insulating membrane
  - Up to 50 lamellae
  - Dark and light bands seen at electron microscope level
  - Highly susceptible to damage
    - Therefore oligodendroglia very susceptible to nutritional state, toxins, infection etc
- Myelin disease states: disastrous neurological consequences, e.g. multiple sclerosis, adrenoleucodystrophy

Microglia

Structure
- Derived from bone marrow during early development of blood monocytes that invade the brain
- Dense lysosomes, lipid droplets and residual bodies
  - Characteristic of phagocytosing cells
- Morphology (diagrams on pp): 3 categories
  - RESTING RAMIFIED
  - ROD-LIKE
  - ACTIVATED

Function
- Resident macrophage population of the CNS
- Involved in immune surveillance and antigen presentation
- First cells to react to infection/damage
- Role in tissue modelling and synaptic stripping

Ependymal cells
- Epithelial type cells which line the ventricles and central canal of the spinal cord
- Apical microvilli and cilia
- Prominent gap junctions between cells
- Not connected by tight junctions

Peripheral cells

Schwann cells
- Unmyelinated axons of motor and sensory neurones in the PNS are enveloped by Schwann cells
- Myelin producing - Produce only one myelin sheath per cell
- Also perform functions of astrocytes and promote axon regeneration

Satellite cells
- Each neuronal cell body in a spinal ganglia is surrounded by metabolically supportive satellite cells
- Perform the functions of astrocytes in the GREY matter of the CNS
Clinical Demonstration: Multiple Sclerosis
NMH 3 - Professor Richard Reynolds (r.reynolds@imperial.ac.uk)

“*A chronic inflammatory multifocal demyelinating disease of the CNS of unknown cause resulting in loss of myelin and oligodendroglial and axonal pathology typically affecting young-adults with exacerbating-remitting pattern or chronic progressive evolution*”

- Symptoms result from disruption of myelinated tracts in the CNS:
  - Visual
  - Motor
  - Sensory
  - Cognitive & psychiatric
  - Bowel, bladder
  - Sexual
- Onset: hours to days
- Recovery: days to months

**Diagnosis**

- MRI - Multiple areas of hyperintense signal (white spots seen)
- CEREBROSPINAL FLUID (CSF) analysis:
  - Increased production of immunoglobulin in CSF
  - Oligoclonal bands

**Clinical Subtypes**

- **Relapsing-remitting**
  - Complete recovery from relapses
  - Incomplete recovery from relapses
- **Secondary progressive**: relapses with increased worsening of disability and recovery
- **Primary progressive**: increased disability with no recovery

**Summary**

- **Onset and Symptoms:**
  - Usually presents between the ages of 20 and 40 years, more frequently in females
  - result from inflammation and disruption of myelin in the CNS
  - can involve any neurological function – most commonly sensory, motor and visual symptoms
- **Clinical Course:**
  - MS typically begins as exacerbating (relapsing) - remitting disorder
  - Less commonly starts with a progressive course
- **Diagnosis:**
  - Primarily based on clinical history
  - Supported by magnetic resonance imaging (MRI) and cerebrospinal fluid (CSF) analysis showing inflammatory abnormalities
- **Therapy:**
  - Immuno-modulatory and immuno-suppressive treatments are aimed at reducing relapses
  - Treatments are also available to attenuate symptoms (pain, spasticity, bladder dysfunction)
1. Define the following:
   - Diffusion of an ion
   - Permeability of a cell membrane
   - Electrochemical gradient of an ion.
2. Describe how a resting membrane potential can arise from a difference in concentration of an ion across a selectively permeable membrane (use diagrams).
3. Define electrochemical equilibrium for an ion.
4. What is the equilibrium potential for an ion?
5. The Nernst equation is $E_{x^+} = (RT/ZF) \ln \left( \frac{C_o}{C_i} \right)$. You should know that $E_{x^+}$ is the equilibrium potential of ion $X^+$, $R$ is the gas constant, $T$ is absolute temperature, $Z$ is the charge on the ion, and $F$ is Faraday’s number 96,500 coulombs of charge/mol of a singly charged ion.
6. Substituting the values of the constants and $T=37$°C, and converting to $\log_{10}$, gives (for an ion with charge +1)
   $$E_{x^+} = 61 \log \left( \frac{C_o}{C_i} \right)$$
7. You need not memorize the Nernst equation, but you are expected to be able to use it (and get the signs right!). For example, given this equation and $C_o$ and $C_i$, you should be able to calculate the equilibrium potential for the ion, or given the equilibrium potential and one of the concentrations, you should be able to calculate the other concentration.
8. What are typical values for the concentration of $K^+$ and for $Na^+$ inside and outside a normal neuron?
9. What is a typical value for the resting potential of a neuron?
10. $K^+$ concentration has a much stronger effect on the resting potential than $Na^+$ concentration does. Explain the basis of this difference.

The Nervous System

- Transmits information reliably and quickly over long distances
  - Reliably- signals always work
  - Quickly- when compared to other physiological systems e.g. the endocrine system
- Mechanisms: the resting and action potential

Diffusion in solution

- Useful for transport over short distances
- Down concentration gradient eventually leading to the reach of a DIFFUSION EQUILIBRIUM
- Spontaneous- no extra energy required
- FLUX: the number of ions that cross a unit area per unit time
  - Decreases as solutions reach diffusion equilibrium
  - At equilibrium, the net flux is zero

Electrical Concepts

- Electrical forces
  - Ions that have different charges attract, and move closer together
  - Ions that have the same charges repel, and move further apart
  - The more ions involved, the stronger the forces and the greater the resulting movement
Membrane potentials
- Potential/ E.m.f: electrical force between ions that repels like charges and attracts opposite charges (mV)
- Current: movement of ions due to the influence of potential (A)
  - The may be transmembrane, or within intracellular or extracellular solutions
- Resistance: of a material- a measure of how hard it is for current to flow through it
  - Resistance of current flow across a membrane > resistance within intracellular/extracellular solutions

The Resting Potential

- ZERO REFERENCE POINT is outside the cell
- Inside of the cell is negative compared to the reference
- Measured using voltmeter
- All cells have a membrane potential - In excitable cells, this is particularly important to cell function e.g. neurones, muscle cells

Ionic basis

- Membrane separates charge if:
  - The membrane is selectively permeable
  - The concentration of at least one permeant ion is different on the two sides of the membrane
- PERMEABILITY: The flux of the ion through the membrane per unit of concentration gradient
  - Number indicating how easy it is for the ion to cross the membrane
  - Depends on the type and number of specific ion channels in the membrane
  - The more open channels/protein pores, the greater the permeability
- Protein channels:
  - Ungated K+ and Na+ channels are always open
  - Voltage-gated K+ and Na+ channels are open/closed depending on their conformation as a result of changing membrane potential

Generation of a membrane potential

- Is due to diffusion of ions through a selectively permeable membrane
- CASE 1: impermeant membrane
  - No open protein channels, so not diffusion across membrane despite concentration gradient
  - No separation of charge
  - Membrane potential = 0
- CASE 2: selectively permeable to K+ only
  - K+ crosses membrane down concentration gradient
  - This leads to a charge separation as one side accumulates positive charge
  - As more K+ ions cross the membrane, the charge separation continues. However the like positive charges of all the positive ions create an ELECTRICAL gradient, which pushes some of the K+ ions back across the membrane
  - Eventually, ELECTROCHEMICAL EQUILIBRIUM is reached, when the electrical gradient and concentration gradient are equal so there is no net movement of K+ ions
- CASE 3: selectively permeable to Na+ only
  - Same as case 2, except with Na+ ions
  - The sign of the membrane potential will therefore be OPPOSITE to case 2
• NB: only a very small number of ions cross the membrane, so the change in concentration is very small. However this has a bigger impact on the membrane potential.

**Electrochemical equilibrium:** for an ion is reached when its concentration gradient is balanced by the electrical gradient across the membrane

**Equilibrium potential:** of an ion is the electrical potential that prevents diffusion down the ion’s concentration gradient

**Size**

• The Nernst Equation can be used to calculate the size of an equilibrium potential of an ion, and relates it to the size of its concentration gradient. This is provided that two conditions are met:
  o The membrane is selectively permeable to one ion
  o The concentration of two ions are not equal on either side of the membrane

$$E_{X^+} = (RT/ZF) \ln \left( \frac{C_o}{C_i} \right)$$

- $C_o$ = concentration of ion outside cell
- $C_i$ = concentration of ion inside cell
- $R$ = Gas constant
- $T$ = temperature (K)
- $Z$ = charge on ion
- $F$ = faraday’s number (96500 C of charge per mol of ion with single charge)

Substituting constants gives:

$$E_{X^+} = (61/Z) \log_{10} \left( \frac{C_o}{C_i} \right)$$

• To check the sign of the equilibrium potential, consider what sign does it need to be in order to keep the concentration as is?
  o If the intracellular fluid is **negative** compared to the extracellular fluid, the equilibrium potential needs to be **positive** to prevent the movement of **positive ions into** the cell
  o If the intracellular fluid is **positive** compared to the extracellular fluid, the equilibrium potential needs to be **negative** to prevent the movement of **positive ions out of** the cell

**In practice:**

• Na+ and K+ are the most important ions for the resting potential
• [Na+]: intracellular fluid < extracellular fluid
  o $C_o = 150$ mmol/l
  o $C_i = 10$ mmol/l
• [K+]: intracellular fluid > extracellular fluid
  o $C_o = 5$ mmol/l
  o $C_i = 150$ mmol/l
• Using the Nernst equation:
  o Equilibrium potential for Na+ = +72mV
  o Equilibrium potential for K+ = -90mV
• REAL MEMBRANE POTENTIAL for a typical neuron is -70mV
  o This is closer to the equilibrium potential for K+
  o This is because the membrane is more permeable to K+
K+ diffuses out of the cell down its concentration gradient through permanently open channels, so the inside of the cell becomes negative.

The membrane is slightly permeable to Na+, so some ions diffused into the cell cancelling out the effect of an equivalent number of K+ ions.

This means the real membrane potential will be more positive than the equilibrium potential for K+.

- **GOLDMAN EQUATION** describes the real resting membrane potential.
  - Influenced by Na+, K+ AND Cl-
  - The size of each ions concentration is proportional to how permeable the membrane is to the ion.

Goldman Equation describes the resting membrane potential.

\[
V_m = \frac{RT}{F} \ln \left( \frac{P_K [K_o] + P_{Na} [Na_o] + P_{Cl} [Cl^{-}]}{P_K [K] + P_{Na} [Na] + P_{Cl} [Cl^{-}]} \right)
\]

Changes in Membrane Potential

**Depolarising**: changes away from the resting potential, towards zero

**Overshoot**: changes away from the resting potential, above zero towards the Na+ equilibrium potential (positive)

**Repolarising**: changes towards the resting potential

**Hyperpolarisation**: changes away from the resting potential, but in the same direction as repolarisation and results in a membrane potential that is closer to the K+ equilibrium potential (more negative)

Graded Potentials

Change in membrane potential in response to stimulation, and occur at synapses and sensory receptors. Their function is to contribute/initiate or prevent action potentials.

Have specific defining characteristics:

- May be in depolarising (positive) or hyperpolarising (negative) direction depending on stimulus
- The magnitude of the membrane potential change is dependent on strength of stimulus
- The magnitude of the membrane potential change decreases with time, and with the distance measured from stimulus site. This is known as DECREMENTAL SPREAD
1. You should be able to explain in general terms what the function of the action is.
2. Give some examples of other types of excitable cells (in addition to neurons) in which action potentials occur.
3. Define the following terms as they apply to action potentials:
   a. Threshold
   b. Refractory period
   c. “All or nothing” behaviour
   d. Depolarization
   e. Repolarization
   f. Hyperpolarization
   g. Saltatory conduction
4. Define the following terms as they apply to the membrane channels involved in producing the action potential:
   a. Voltage-gated channel
   b. Channel inactivation
   c. Positive feedback
5. Outline the sequence of events during a typical action potential in the neuron. Include: changes in membrane potential, changes in membrane permeability, and fluxes of ions across the membrane (a diagram will help).
6. State the size and duration (including units) of a typical action potential in a neuron.
7. Define the term “regenerative” as applied to action potentials, and its significance for spread of the action potential along an axon.
8. Explain how conduction of the action potential occurs (conduction here means spread along the axon, alternatively this process may be called transmission or propagation).
9. List two structural features that affect the conduction velocity along normal axons. Briefly explain why they affect velocity as they do.
10. Be able to list at least one pathological condition that affects conduction velocity.

Key concepts

Mechanisms Responsible:

1. Time-course voltage vs. Time
2. Voltage-gated channels and ion fluxes
3. Permeability changes vs. Time

Ionic basis

- Permeability depends on channel state (open/closed)
- When permeability to an ion increases, it crosses the membrane down its electrochemical gradient
- This moves the membrane potential towards the equilibrium potential for that ion
- Changes in membrane potential during the action potential are NOT due to ion pumps (e.g. Na/K pump), but are due to the diffusion of ions through a semi-permeable membrane through protein channels

1. Time-course voltage vs. Time
2. Voltage-gated channels and ion fluxes
Overview of action potentials

- Occur in the axon
- Amplitude: full change in membrane potential during the action potential (approx 100mV)
- Duration: depends on excitable cell involved
  - Neurones: approx 2ms
  - Dendritic cells: approx 100ms
  - Skeletal muscle fibres: approx 2ms
- 5 stages:
  - Resting potential
  - Stimulus
  - Upstroke/Depolarisation phase
  - Repolarisation phase
  - After hyperpolarisation phase

1) Resting Potential

- Membrane potential is -70mV. This is closer to the equilibrium potential for K+ than Na+
- Permeability of membrane for K+ > Na+
- Ungated channels are responsible for the resting potential. Ions diffuse through the membrane down their concentration gradient.

Voltage-Gated channels

- Responsible for action potential
- Both Na+ and K+ channels are TRANSMEMBRANE channels
- K+ channel:
  - Gate is within hydrophobic core of the membrane, and is closed during the resting potential
- Na+ channel:
  - Gate within hydrophobic core of the membrane is known as the ACTIVATION GATE, and is closed during the resting potential
  - Gate on the cytosolic face of the membrane is known as the INACTIVATION GATE, and is open during the resting potential

2) Stimulus

- Depolarizes the membrane potential (moves it in the positive direction)
- Also known as the “FOOT”
- Foot also present in graded potentials
- Only if the stimulus/foot reaches the threshold membrane potential is an action potential generated

3) Upstroke/Depolarisation phase

- CHANNELS:
  - K+ channel closed, but opens slowly
  - Na+ channel activation gate open
  - Na+ channel inactivation gate closed
- The permeability of the membrane to Na+ increases rapidly as the voltage-gated Na channels
- Starts at THRESHOLD POTENTIAL
- Na ions enter the cell down the electrochemical gradient
- Voltage-gated K channels start to open, but slowly, so the permeability to K+ increases slowly. K+ ions then leave the cell down their electrochemical gradient, but fewer than Na+.
- The membrane potential moves towards the Na equilibrium potential
4) **Repolarisation Phase**
   - **INITIAL CHANNELS:**
     - K+ Channel open
     - Na+ channel activation gate open
     - Na+ channel inactivation gate CLOSED
   - **LATER CHANNELS:**
     - Na+ channel activation gate CLOSED
     - Permeability to Na+ decreases, and Na entry to the cell stops
     - Permeability to K+ increases as more voltage-gated K+ channels open and remain open
     - K+ leave the cell down their electrochemical gradient
     - Membrane potential moves towards the K+ equilibrium potential
   - **ABSOLUTE REFRACTORY PERIOD:**
     - New action potential cannot be triggered as the inactivation gate is closed
     - The strength of the stimulus will have no effect

5) **After hyperpolarisation phase**
   - **CHANNELS:**
     - K+ channel open
     - Na+ channel activation gate closed
     - Na+ channel inactivation gate OPEN
     - Permeability to K+ is greater than at rest because the voltage-gated channels are still open
     - K+ ions continue leaving the cell down their electrochemical gradient
     - Membrane potential moves closer to the K+ equilibrium potential (more negative) until the voltage-gates K+ channels close
     - Then the membrane potential returns to the resting potential
   - **RELATIVE REFRACTORY PERIOD:**
     - Inactivation gate is open
     - Stronger than normal stimulus can trigger a new action potential

3. **Permeability Changes vs. Time**

   ![Permeability Changes vs. Time Diagram]

   **The Regenerative Nature of the Action Potential**

   **Threshold Potential:** membrane potential once reached triggers an action potential

   **“All-or-nothing” nature:** once an action potential is triggers, it is full-size

   **Refractory state:** time period whereby the membrane potential is unresponsive to threshold depolarization

   **Permeability to Na+ and Membrane Potential**

   - Depolarization < Threshold potential → graded potential
   - Depolarization >/= threshold potential → action potential

   NB: Action potential cycle then has a positive feedback mechanism
**Positive Feedback**

- Depolarisation $\rightarrow$ opening of voltage-gated Na channels $\rightarrow$ increased Na permeability $\rightarrow$ increased Na entry into cell $\rightarrow$ increased depolarization
- Cycle continues until inactivation gate of voltage-gated sodium channels CLOSE
- These then become voltage insensitive, and Na+ entry stops
- The membrane remains in a **refractory** (unresponsive) state until the Voltage-gated Na channels recover from inactivation and become Voltage-sensitive again

**Ion movements**

- Na+ enters cell
- K+ leaves cell
- Only a very small number cross the membrane, but have a large effect on the membrane potential
- Between action potentials, the Na/K pump returns ions that moved during the action potential
  - Pumps 3 Na+ out of the cell, and 2 K+ into the cell
  - This maintains the negative resting potential

**Propagation of Action Potential**

- Stimulus $\rightarrow$ Depolarization
- Site of stimulus = active area at peak of action potential
- The adjacent area, and the remainder of the axon is at resting potential
- The depolarisation of the active area $\rightarrow$ local current flow which depolarises the adjacent region towards the threshold potential
- This creates a new active area at peak of action potential
- The initial stimulus site returns to resting potential
- Local current flow depolarises a NEW adjacent region towards the threshold
- In this way, the action potential is propagated along the axon

**Conduction Velocity**

- In mammalian axons:
  - Large diameter, myelinated axons = 120ms
  - Small diameter, non-myelinated axons = 1ms
- Increases with diameter because of the electrical properties (less resistance to current flowing inside the large diameter)
- Higher in myelinated neurones because of SALTATORY CONDUCTION where action potentials can “jump” between adjacent nodes of Ranvier
- Multiple sclerosis and diphtheria are examples of demyelinating diseases
- Conduction velocity also reduced by cold, anorexia, compression and drugs (some anaesthetics)
1. Define the essential components required for neurotransmitter release
2. Understand the differences between excitatory and inhibitory transmission
3. Define at least two mechanisms for the termination of neurotransmitter action at the synapse
4. Describe how modulation of the synaptic properties of GABA can be used pharmacologically to treat epilepsy

**Neurotransmission**

- Information transfer across a synapse requires the release of neurotransmitters and their interaction with postsynaptic receptors.
  1) **Transmitter released from 1st cell** (action potential – nerve terminal – release of neurotransmitter)
  2) **Synaptic activation of 2nd cell** (neurotransmitter binds to receptor)
  3) **Signal integration and signal conduction by 2nd cell**
- Responsible for cognitive function, behaviour, learning – highly complex functions
- Forms basis for a number of neurological and psychiatric disorders e.g. Parkinson’s

**The Synapse**

Consists of:
- **Presynaptic nerve ending/terminal**
- **Synaptic GAP** (20-100nm) – large electrical resistance
- **Post synaptic region** – responsible for information of reception (dendrites/dendritic spines) and integration of input (cell body/soma)

The synapse is asymmetric: the post-synaptic membrane is very dense, and known as the POST-SYNAPTIC DENSITY.

**The Nerve Terminal**

- Specialised
- Packed full of synaptic vesicles – each contain approx 5000 molecules of neurotransmitter
- Also contain mitochondria – area of high metabolic activity; synthesis and release of neurotransmitter requires high oxidative metabolism

**Synaptic Transmission**

Consists of 3 stages:
- **Biosynthesis, packaging and release of the neurotransmitter**
- **Receptor action**
- **Inactivation**

I: **Biosynthesis, packaging and release of the Neurotransmitter**

**Neurotransmitters**

- Wide diversity in transmitters and genes that encode receptors
- Types of molecules:
  - **AMINO ACIDS**, e.g. glutamate and GABA
- AMINES, e.g. noradrenaline and dopamine
- NEUROPEPTIDES, e.g. opioid peptides

- Function: May mediate rapid (µs- ms) or slower effects (ms-s)
- Vary in abundance from mM to nM CNS tissue concentrations
- Neurones receive multiple transmitter influences which are then integrated to produce diverse functional responses

**Activation of a CNS synapse**

- Action potential passes down axon – depolarisation of nerve terminal, Na+ influx into nerve terminal and K+ efflux
- Depolarisation leads to opening of Voltage-gated Ca2+ channels, causing an influx of Ca2+ into presynaptic terminal
- Influx of Ca2+ causes neurotransmitters to be released from synaptic vesicles into synaptic cleft – neurotransmitter then binds to receptors on post-synaptic membrane
- This neurotransmitter binding causes the influx of Na+ into the post-synaptic region, depolarising the post-synaptic terminal
- The neurotransmitter is then broken down and taken back up into the pre-synaptic terminal using active transport

**Synaptic transmission**

- Fast (200 microseconds)
- Ca2+ dependent – release of neurotransmitter requires an increase in intracellular Ca+ concentration by 200 micromoles
- Synaptic vesicles provide source and storage system for neurotransmitters

**Activation/Release of Neurotransmitter**

- Ca2+ dependent
- Requires RAPID transduction- known as ELECTROMECHANICAL TRANSDUCTION (200 microseconds)
  1) Membrane depolarisation
  2) Ca2+ channels open
  3) Ca2+ influx
  4) Vesicle fusion
  5) Vesicle exocytosis
  6) Transmitter release
- Vesicles are PRIMED and filled with neurotransmitter at active zone
- Docked in the synaptic zone – close to Ca2+ channels in microdomain on pre-synaptic membrane
- Ca2+ entry – rapid protein complex formation between vesicle, presynaptic membrane and cytoplasmic proteins – enable rapid response to Ca2+ with fusion and exocytosis
- Vesicle recycling occurs – after synaptic transmission, neurotransmitters are taken back up into the presynaptic cytoplasm using ATP and repackaged in the synaptic vesicles
- Vesicle proteins therefore target for NEUROTOXINS:
  - Zn2+ dependent ENDOPEPTIDES degrade the vesicle proteins and therefore inhibit neurotransmitter release
  - ALPHA LATROTOXIN stimulates neurotransmitter release leading to depletion of source (black widow spider)
II: Receptor Action

*Chemical Neurotransmission*

- **FAST excitatory and inhibitory transmission** – mediated by ION CHANNEL receptors
  - milliseconds
  - Typically pentameric complex

- **SLOW transmission** – mediated by G-protein coupled receptors
  - Seconds- mins
  - Transmitter binds with transmembrane receptor, G-protein on cytoplasmic domain activates 2nd messenger e.g. cyclic AMP cascade
  - 2nd messenger then greatly amplifies the effect
  - E.g. ACh at muscarinic receptors, dopamine (DA), noradrenaline (NA), 5-hydroxytryptamine (5HT)and neuropeptides

*Ion channel-linked receptors*

- Nicotinic cholinergic receptors (nAChR) – Na+ influx (excitatory)
- **Glutamate (GLUR)** – Na+ influx (excitatory).
- **GABA: Gamma amino butyric acid (GABAR)** – Cl- influx (inhibitory)
- Glycine (GlyR) – Cl- influx (inhibitory)
- **SHT3**: 5-hydroxytryptamino receptor – K+ efflux (inhibitory)

*Glutamate Receptors (GLUR)*

- **AMPA receptors**
  - Alpha amino-3-hydroxy-5-methyl-4-isoxole propanoic acid
  - Majority of FAST excitatory synapses
  - Rapid onset, offset and desensitisation
  - Leads to Na+ influx

- **NMDA receptors**
  - N-methyl-D aspartate
  - SLOW component of excitatory transmission
  - Serves as coincidence detectors which underlies learning mechanisms – only activated if cell is ALREADY depolarised, i.e. it is a Voltage-gated channel
  - Leads to Na+ and Ca2+ influx- Ca2+ acts as 2nd messenger activating other pathways

III: Transmitter Inactivation

*Excitatory CNS Synapse (Glutamate mediated)*

- Glutamate synthesised from ALPHA-KETOGLUTARATE (in TCA cycle)
- After binding with GLUR on post-synaptic membrane, Glutamate must be removed from the synaptic cleft to prevent excess excitation
- Removed by EAAT (EXCITATORY AMINO ACID TRANSPORTER) on the pre-synaptic nerve terminal and GLIAL cells
- Once taken up into the nerve terminal, it is repacked in synaptic vesicles
In the Glial cell, Glutamate is converted to GLUTAMINE by GLUTAMINE SYNTHETASE

- Abnormal cell firing, e.g. epilepsy – leads to seizures associated with excess glutamate in the synapse

**EPILEPSY**

- One of the commonest neurological conditions – affect 50 mil
- Characterised by recurrent seizures due to abnormal neuronal excitability
- 30% of cases are REFRACTORY (unresponsive) to treatment

**Inhibitory CNS Synapse (GABA mediated)**

- Glutamate precursor to GABA – converted to GABA in a single enzyme reaction involving the loss of a carboxyl group by GLUTAMIC ACID DECARBOXYLASE (GAD B6)
- After GABA binding with receptors, GABA transporter (GAT) takes GABA back into nerve terminal and glial cells
- In the glial cells, GABA TRANSMAMINASE (GABA-T) converts the GABA to SUCCINATE SEMI-ALDEHYDE (SSA)
- In the nerve terminal, GABA can be repackaged into synaptic vesicles, or converted to SSA and enter the TCA cycle – this is known as the GABA SHUNT

**PENTAMERIC ORGANISATION OF GABAR**

- 5 binding domains
- Pharmacologically important
- Targeted by barbituates, steroids, benzodiazepines, ethanol, zinc, convulsants
- Drug examples: antiepileptic, anxiolytic, sedatives, muscle relaxants – all dampen excitatory activity by facilitating GABA transmission by either increasing the diameter of the Cl- channel or increasing the time the channel is open

**EPILEPSY TREATMENT**

- Focused on dampening excitatory activity – look at tutorial

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**Tutorial 1: Epilepsy**

NMH 6 - Dr Martin Croucher (m.croucher@imperial.ac.uk)

**Study Guide Notes**

**Epilepsy: terminology.**

The term **epilepsy** refers to a disorder of brain function characterized by the periodic and unpredictable occurrence of seizures. The term **seizure** refers to a transient alteration of behaviour due to the disordered, synchronous, and rhythmic firing of populations of brain neurones. The pharmacological agents in current clinical use for inhibition of seizures are referred to as anticonvulsant or antiepileptic drugs.

Seizures are thought to arise from the cerebral cortex and they can be classified into **partial seizures**, those beginning focally at a cortical site, and **generalized seizures**, those that involve both hemispheres widely from the outset. The behavioural manifestations of a seizure are determined by the functions normally served by the cortical site at which the seizure arises. Thus, for example, a seizure involving the motor cortex is associated with clonic jerking of the body part controlled by this region of the cortex. A **simple** partial seizure is associated with preservation of consciousness, whilst a **complex** partial seizure is associated with impairment of consciousness. Examples of generalized seizures include absence, myoclonic and tonic-clonic seizures. You will be shown examples of the principal seizure types, by video presentation, during this teaching session.
Neurotransmitters in epilepsy.

Epilepsy is a neurological disorder associated with abnormal neurotransmitter function in the brain. A decrease in GABA-mediated inhibition or an increase in glutamate-mediated excitation in the brain may result in seizure activity. Indeed, both glutamate and GABA are thought to play key roles in the brain mechanisms causing epilepsy in man.

Pharmacological evidence for a role of neurotransmitters in epilepsy

Impairment of GABA-mediated inhibition causes seizures in animals e.g. impairment of synthesis, release (tetanus toxin) or postsynaptic action (bicuculline, picrotoxin).

Enhancement of GABA-mediated inhibition leads to seizure suppression e.g. central (i.c.v.) administration of GABA or inhibition of the GABA metabolizing enzyme GABA-T (vigabatrin).

Many clinically useful anticonvulsant drugs are known to act, at least in part, by potentiating central GABA-mediated inhibition e.g. benzodiazepines, phenobarbital (see Section 3).

Central (i.c.v.; focal) administration of glutamate or glutamate receptor agonists causes seizure-like activity in animals.

Glutamate receptor antagonists are anticonvulsant in experimental models of epilepsy.

Some therapeutically effective anticonvulsant drugs act partly by blocking glutamate-mediated excitation in the brain e.g. phenobarbital.

Biochemical evidence for a role of neurotransmitters in epilepsy

Cobalt-induced seizures in rodents are associated with ↑ glutamate release and with ↓ GABA concentration, ↓ GAD activity and ↓ GABA uptake (probably reflecting GABA neurone loss) at the seizure focus.

Audiogenic seizures in mice (DBA/2 mice) are associated with ↑ glutamate receptor binding in the brain and with ↓ GABA release from depolarized brain slices.

The baboon Papio papio, which is highly sensitive to photically-induced seizures, has a lower than normal CSF GABA concentration.

Some examples of antiepileptic drugs.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cellular Mechanisms</th>
<th>Main Uses</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valproate</td>
<td>Weak effect on GABA transaminase and on Na+ channels</td>
<td>Most types, especially absence seizures</td>
</tr>
<tr>
<td>Phenobarbital</td>
<td>Enhanced GABA action inhibition of synaptic excitation</td>
<td>All types EXCEPT absence seizures</td>
</tr>
<tr>
<td>Benzodiazepines</td>
<td>Enhanced GABA action</td>
<td>All types</td>
</tr>
<tr>
<td>e.g. Clonazepam, clobazam, diazepam</td>
<td></td>
<td>Diazepam used intravenously to control status epilepticus</td>
</tr>
<tr>
<td>Vigabatrin</td>
<td>Inhibits GABA transaminase</td>
<td>All types</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Appears to be effective in patients resistant to other drugs</td>
</tr>
</tbody>
</table>
Questions to be addressed.

1. **Review** the process of neurotransmission occurring at central synapses utilising the inhibitory neurotransmitter GABA

2. **Present** a convincing case for a role of neurotransmitter (glutamate or GABA) malfunction in the aetiology of epilepsy

3. **Draw a diagram** to illustrate the principal steps in GABAergic neurotransmission (synthesis, storage, release etc).

   Indicate on your diagram i) established and ii) potential new target sites for drugs acting to enhance GABA-mediated neurotransmission in the brain.

**Tutorial Notes**

- **Generalized Seizures** - simultaneous firing leading to engulfing of both hemispheres of brain
  - TONIC-CLONIC (old Grand-mal) – most common; loss of consciousness and convulsions
  - ABSENCE (old petit-mal) – common in children; loss of awareness, i.e. “zoning-out”
  - MYOCLONIC – sudden stiffening of muscles
  - ATONIC – sudden loss of all muscle tone

- **Partial Seizures** - also focal seizures, can identify origin of abnormality
  - SIMPLE
  - COMPLEX – impairment of consciousness; repeated stereotype behaviors e.g. lip-smacking; usually in temporal lobe
  - SECONDARY GENERALISED – begin as partial, lead to full generalized

- **Cause**: synchronous firing of motor neurons

- **Symptoms**: depends on locus and spread
  - If originates in motor cortex, will spread to both hemispheres and lead to a generalized seizure

- **Neurotransmitters**:
  - Glutamate: excitatory, therefore excess or agonists can trigger seizures
  - GABA: inhibitory

*Look at Handwritten Diagram of GABA synapse below (from notes made in tutorial)*

- Depolarisation of pre-synaptic membrane $\rightarrow$ Na$^+$ influx $\rightarrow$ Ca$^{2+}$ influx $\rightarrow$ SNARE proteins trigger vesicle fusion and exocytosis $\rightarrow$ GABA release
- Storage vesicles allow the coordinated and rapid release of GABA involving snare proteins
- GABA receptor: ligand-gated Cl- ion channel $\rightarrow$ hyperpolarisation of the post-synaptic membrane therefore is inhibitory
- Uptake 1: acts to control GABA concentration by reuptake -- deactivation process different to that of acetyl choline whereby Ach is broken down by acetyl cholinesterase
- Uptake 2: after uptake, GABA can be:
  - Recycled and repacked into secretory vesicles
  - Converted into SUCCINATE SEMI-ALDEHYDE (which then enters TCA cycle) by GABA TRANSAMINASE

**Treatment**

Effectively want to increase GABA concentration, therefore increasing inhibition and reducing seizures.

- **Reduce reuptake** (on diagram- uptake 1) e.g. TIAGADINE
- **Prevent conversion to SSA** (on diagram- uptake 2) by inhibiting GABA-T e.g. VIGABATRIN
- **Enhance receptor function** – ALLOSTERIC binding sites on GABA receptor (next to GABA binding site) can be used to modulate function, increasing the number of Cl- molecules that are transported for each GABA molecule, i.e. HYPPERPOLARISATION = inhibition
- **GABA agonist**- binds to GABA receptor; not yet proven effective

Basic actions can applied to different illnesses:

- E.g. depression – serotonin
  - Increase selective serotonin reuptake inhibitors e.g. PROZAC

**The Central Nervous System**

NMH 7 - Dr Maggie Lowrie (m.lowrie@imperial.ac.uk)

1. **Draw a diagram to explain the relationship between the following major divisions of the CNS: spinal cord, brainstem, cerebellum, diencephalon, cerebral hemispheres.**
2. **Define the functions of the dorsal and ventral horns of the spinal cord and explain how the dorsal and ventral roots and spinal nerves relate to them.**
3. **Define the 3 components of the brainstem and state the main functions of the brainstem.**
4. **Describe the functions of the 2 main structures in the diencephalon.**
5. **State the functions of the basal ganglia and the cerebellum.**
6. **Draw on a diagram of the cerebral hemisphere, the cortical lobes and primary cortical areas.**
7. **Recognise the main structures of the brain in a diagram or MRI.**
8. **Describe the 3 layers of the meninges and explain their role in protecting the brain.**
9. **Explain how the major divisions of the brain relate to the cranial fossae in the base of the skull.**
10. **Explain the relationship between the spinal segments, spinal nerves and vertebrae and state at what level a lumbar puncture can be performed safely.**
11. **Identify the components of the ventricular system and relate them to the divisions of the CNS.**
12. **Explain the composition, circulation and functions of CSF.**
13. **State the average total volume and flow rate of CSF.**
14. **Define hydrocephalus and outline how it may be treated.**
15. **Distinguish between an epidural (extradural) and subdural haemorrhage.**
Overview

Structure

- The CNS consists of:
  - Brain
  - Spinal Cord
- The brain developed from the neural tube - then has three main divisions, each consisting of different separate structures (shown in diagram below):
  - Forebrain
  - Midbrain
  - Hindbrain
- The brainstem consists of Midbrain, Pons and the medulla – these lay between the two hemispheres and share a lot of similar functions.
  - THE BRAINSTEM IS ALSO THE PART OF THE BRAIN WHICH MERGES WITH THE SPINAL CORD
- The two hemispheres are divided by the MID-SAGGITAL LINE, with the diencephalon sitting between the two hemispheres
  - Each hemisphere is covered in a folded cortex consisting of folds/elevations (GYRI) and grooves/depressions (SULCI)
  - The groove that runs between the two hemispheres is called a DEEP LONGITUDINAL FISSURE
Specific Structures and related Functions

Each of the main divisions is large and consists of different structures with different functions:

FOREBRAIN

- **Cerebral hemispheres**
  - **CEREBRAL CORTEX** – involved in a wide range of functions: consist of functional cortical areas known as PRIMARY CORTICAL AREAS and ASSOCIATED AREAS
    - **Primary cortical areas** - discrete areas with specific functions, therefore a deficit as a result of any damage to these areas can be predicted:
      - **Primary motor cortex** – involved in effector/motor functions
      - **Primary somatosensory cortex** – receives sensory input from the body
      - **Primary visual cortex** – first location to receive input from the retina
      - **Primary auditory cortex** – first location to receive input from the inner ear
    - **Associated cortical areas** – areas primarily involved in the higher functions of the brain but much more unpredictable
      - **Broca’s area** – involved in producing intelligible speech
      - **Wernicke’s area** – involved in comprehension of language
      - These areas are much better represented in the LEFT hemisphere (as shown in diagram below)

- **CORTICAL LOBES** – each hemisphere consists of a series of folds (GYRI) and grooves (SULCI), which come together to form 4 lobes, which then in turn contain the functional cortical areas:
  - **Frontal Lobe** – most anterior lobe
  - **Parietal Lobe**
  - **Occipital Lobe** – most posterior lobe
  - **Temporal Lobe**
    - The two hemispheres are separated by a groove known as the deep longitudinal fissure, but then 3 main grooves can be thought to divide each cerebral hemisphere:
      - **Central sulcus** – can be thought to run medially through the lateral aspect of the hemisphere, with the frontal lobe just anterior and the parietal lobe just posterior to the sulcus
      - **Lateral fissure** – anterior to and below the central sulcus, the lateral fissure separates the frontal and temporal lobe (the frontal lobe being anterior, and the temporal lobe posterior)
      - **Parietal-occipital sulcus** – posterior to the central sulcus, the parietal-occipital sulcus runs posterior to the parietal lobe and anterior to the occipital lobe, separating the two lobes.
- **CORPUS CALLOSUM** – interconnects corresponding parts of the 2 hemispheres across the midline (C shaped structure seen if the brain is cut in the MID-SAGITTAL PLANE)
- **BASAL GANGLIA** – groups of neurones referred to as nuclei within each hemisphere that are responsible for the control of movement, as well nerve signalling within the brain

> **Diencephalon**
> - Lies between the two hemispheres
> - Consists of two main structures:
>   - **THALAMUS** – involved in the relax of information between the brain stem/lower structures and cerebral cortex
>   - **HYPOTHALAMUS** – below and anterior to the thalamus – involved in the coordination of homeostatic mechanisms
>     - Interface between CNS, autonomic nervous system (ANS) and the endocrine system
> - There are also other related structures which lie within the diencephalon:
>   - **OPTIC CHIASMA/NERVE** – (anterior) passes through the optic canal to the retina
>   - **INFUNDIBULUM** – the stalk of the pituitary gland, which lies just below the hypothalamus

**BRAIN STEM**
- Ascending and descending tracts connect the spinal cord to the brain
- Controls **vital functions** e.g. respiration, consciousness, sleep cycle, blood pressure
  - Also controls **cranial nerve functions** – as most cranial nerves are attached to the brain stem and innervate the head region
- Consists of the:
  - **MIDBRAIN** – tubular structure which is the first part of the brain stem
  - **PONS** – tubular structure with a bulbous form and a convex anterior surface
  - **MEDULLA** – base of brainstem, which lies just above the spinal cord; again has a short tubular structure

**HINDBRAIN**
> **Cerebellum**
> - Most basal posterior structure
> - Has folded surface similar to that of the hemispheres
> - Again similarly to the hemispheres, consists of two lateral hemispheres and a midline
> - Function is to coordinate movement

**OTHER COMPONENTS**
> **Cranial Nerves**
> - Form part of the PNS (basal ganglia and optic nerve form CNS)
> - Functional components less regularly organised than for spinal nerves
> - Supply sensory and motor innervations to the head
  - Also autonomic (parasympathetic) innervations to the head, thoracic and abdominal organs
> - Also involved in special sense e.g. vision, hearing, balance

> **Meninges**
> - Three membranes enclosing the brain and spinal cord for protection:
- **DURA MATER** – touch membrane attached to bone or forming partitions between the hemispheres (dural folds) with venous sinuses in their margins
- **ARACHNOID MEMBRANE** – thin membrane attached to the underside of the dura
- **PIA MATER** – delicate membrane closely adherent to the surface of the brain and spinal cord

- Clinical significance – CSF flows in the subarachnoid space
  - Obstruction e.g. by meningitis may cause hydrocephalus
  - Bleeding between the layers may cause a type of stroke

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**Spinal Cord**
- Supplies motor, sensory and autonomic (parasympathetic) innervations to spinal nerves
- Mediates reflexes

**Ventricular System**

- Structure of interlocking spaces filled with CEREBROSPINAL FLUID (CSF) within the brain
- **LATERAL VENTRICLE** – 2 C-shaped spaces (with posterior protruding “spurs”) lie on either side of the corpus callosum. The structure of the ventricle consists of: Anterior horn and main body
  - The anterior horn then connects to a single ventricle called the third ventricle
- **THIRD VENTRICLE** – single ventricle which bisects the diencephalon along the mid-saggital line between the two hemispheres.
  - The lower end of the third ventricle then forms a narrow channel called the aqueduct
- **AQUEDUCT** – narrow channel goes through the midbrain, and then forms the fourth ventricle
- **FOURTH VENTRICLE** – forms posterior to the brain stem anterior to the cerebellum
  - The fourth ventricle then again forms a narrow channel called the central canal
- **CENTRAL CANAL** – narrow channel goes down into the spinal cord
- Each aspect of the ventricular system is associated with a specific area of the brain

**CSF and the Meninges**

- CSF continuously secreted by CHOROID PLEXUS (glands) within each ventricle
  - Formed by the filtration and modification of blood, and differs bothcellularly and in its ionic concentrations (see practical notes)
- **FUNCTION** – important in the protection of the soft-tissue of the brain from both gravity and trauma
  - Also has metabolic functions, as important in removing waste and delivery of substrates to the brain tissue
- Circulates through the ventricular system and the SUB-ARACHNOID SPACE within the meninges
- Most of the CSF leaves via the fourth ventricle and spreads into the sub-arachnoid space
  - A little goes into the central canal to the spinal cord
- The meninges consist of three membrane layers:
  - **DURA MATER** – tough connective tissue inside skull, which forms folds within the groove between the cerebral hemispheres known as DURAL FOLD
  - **ARACHNOID MEMBRANE** – fine membrane just below the dura
  - **PIA MATER** – delicate membrane surrounding the brain
The sub-arachnoid space is the space between the arachnoid membrane and the pia mater
- The CSF must be returned to the venous circulation to prevent an increase in intracranial pressure (ICP)
  - This is via pockets of the arachnoid membrane known as ARACHNOID VILLI, which drain the CSF into a VENOUS SINUS
  - HYDROCEPHALUS is a build up of CSF in the brain

Below is a diagram of the layers of the meninges (shown in the CORONAL section of the head and is a posterior aspect)

**The Spinal Cord**
- Has a segmented structure seen by the regular arrangement of roots and nerves
- Ascending and descending tract of brain stem connects the spinal cord to the brain
- Sensory input – via dorsal root ganglia and dorsal roots into the dorsal horn of the grey matter within the spinal cord
- Motor output/effector function – via ventral horn of the grey matter within the spinal cord through ventral roots
- Spinal nerves consist of two nerve roots: the dorsal and ventral therefore carry both sensory and motor information
- The spinal cord is protected by another segmented structure which surrounded it known as the vertical column

(Transverse section through the spinal cord shown in the diagram opposite)

**The vertebral column**
• Consists of vertebrae which surround the spinal cord and a separated by cartilage rings which act as shock absorbers (diagram of vertebra opposite)
  o Gaps between the arches laterally (known as INTERVERTEBRAL FORAMINA) allow spinal nerves to emerge horizontally
  o There are 31 vertebrae with associated spinal nerves (if coccyx is included)
• Consists of 5 types of vertebrae:
  o CERVICAL – 7 vertebrae, 8 nerves which lie above and below each vertebra
  o THORACIC – 12 vertebrae, 12 nerves which lie below each vertebra
  o LUMBAR – 5 vertebrae, 5 nerves which lie below each vertebra
  o SACRAL – 5 vertebrae, 5 nerves which lie below each vertebra
  o COCCYX – 2 vertebrae (but this is variable, may be fused to form one bone), with 1 COCCYGEAL nerve associated
• The length of the spinal cord is shorter than the vertebral column
  o This is because the spinal cord develops early during embryonic development, but its development stops much earlier than the end of the vertebral column growth
  o This means the spinal and vertebral levels are not level – the lumbar and sacral spinal segments are higher than their corresponding vertebrae therefore nerves have to travel downwards to get to associated region of body
  o Therefore when performing a lumbar puncture (for CSF analysis), to protect the spinal cord you would complete the cistern below L2 (preferably between L3 and L4)

Aspects of the Brain and Skull

*Brain cut in mid-saggital plane*(Lateral Aspect: Anterior-Posterior Axis)
The Skull – relating it to structures within the brain
- Frontal lobe – lies in the anterior cranial fossa
- Temporal lobe – lies in the middle cranial fossa
- Cerebellum – lies in the posterior cranial fossa
- Midbrain – lies at junction between middle and posterior cranial fossa
- Hypothalamus (part of diencephalon) – lies directly above the body of the sphenoid bone
- Optic nerve/chiasma (related structure to the diencephalon) – passes through the optic canal
- Medulla (part of the brain stem) – passes through the foramen magnum
The Ventricular System – relating it to structures within the brain

- Lateral ventricle – the cerebral hemispheres
- Third ventricle – the diencephalon
- Aqueduct – midbrain
- 4th ventricle – pons and medulla
- Central canal - brainstem

The brain in different planes – identifying the numbered structures

Axial Plane (looking from above)

Coronal Plane (posterior view)
### Mid-saggital plane (lateral view: anterior – posterior)

<table>
<thead>
<tr>
<th>Number</th>
<th>Structure</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Lateral ventricle</td>
<td>[may be cut through twice in horizontal or coronal plane]</td>
</tr>
<tr>
<td>2</td>
<td>Third ventricle</td>
<td>[may look like a hole or a slit in coronal and horizontal plane, depending on angle of section]</td>
</tr>
<tr>
<td>3</td>
<td>Fourth ventricle</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Aqueduct</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Corpus callosum</td>
<td>[may be cut through twice in horizontal plane]</td>
</tr>
<tr>
<td>6</td>
<td>Frontal lobe</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Occipital lobe</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>Parietal lobe</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>Temporal lobe</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Basal ganglia</td>
<td>[may be more than one part]</td>
</tr>
<tr>
<td>11</td>
<td>Thalamus</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>Internal capsule</td>
<td>[both anterior and posterior limbs seen in horizontal plane]</td>
</tr>
<tr>
<td>13</td>
<td>Optic chiasma</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Midbrain</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>Pons</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Medulla</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td>Cerebellum</td>
<td></td>
</tr>
</tbody>
</table>
Difference between the composition of CSF and blood

- Few cells
- Less protein
- Reduced concentration of potassium and calcium ions
- Higher concentration of magnesium and chloride ions

Volume and Flow rate of CSF

- Volume 150ml
- Flow rate approx 500ml/day

Hydrocephalus

Main types and causes:

- COMMUNICATING (all 4 ventricles affected)
  - Causes: Block in CSF absorption or CSF flow over brain surface caused by:
    - Meningitis
    - Head injury
    - Congenital
    - Haemorrhage (sub-arachnoid)
- **NON-COMMUNICATING** (not all ventricles enlarged)
  - Causes: Block in ventricular system caused by:
    - Aqueduct stenosis
    - Ventricular tumours
    - Paraventricular tumours

*Signs and symptoms*

- Headache
- Drowsiness
- Blackouts
- Raised intracranial pressure
- Increased head circumference (in child)

*Treatment*

- Remove cause, e.g. papilloma
- Divert CSF, e.g. shunt
- Open alternate pathway, e.g. ventriculostomy

**The Meninges**

*Haemorrhages*

- **Epidural/ extradural haemorrhage** – usually due to a damaged meningeal artery between the skull and the dura after head trauma.
- **Subdural haemorrhage** – usually due to a damaged vein between the dura and arachnoid membrane.
- Both can cause a space-occupying lesion in the confined space of the cranium and hence neurological deficits.
- Distinguishing between haemorrhages - The first symptoms (which may be headache, drowsiness, vomiting or seizure) are likely to arise promptly after arterial bleeding in an epidural haemorrhage whereas symptoms may be delayed by hours or days after venous bleeding in a subdural haemorrhage

**Meningitis**

- Structures infected - Pia mater and subarachnoid space, with some spread to the upper layers of the cortex in severe cases
- CSF Analysis – used to distinguish between bacterial and viral meningitis
  - With bacterial infection there will be a high white cell count, with neutrophils predominating.
    - Protein concentration is increased and glucose concentration is decreased.
    - Bacteria may be identifiable – cloudy CSF
  - With viral infection any increase in white cells is predominantly lymphocytes.
    - Protein and glucose level of the CSF are usually normal
    - Viral identification is unlikely
1. Describe the structural and functional components of a normal peripheral nerve.
2. List the factors that affect conduction velocity of peripheral axons.
3. Define the terms: dermatome, myotome, ramus, plexus, and explain their significance with regard to innervation of the body.
4. State the spinal levels which contribute to the nerves of the upper and lower limb.
5. Compare and contrast the effects of injury and disease on peripheral nerve function.
6. Outline the main diagnostic techniques for peripheral nerve disorders.

Introduction

- The PNS consists of:
  o Peripheral nerves (axons)
  o Ganglia (soma)
- Peripheral nerves may be subdivided into:
  o Spinal
  o Cranial
- Ganglia may be anywhere in the body, including the brain – these are known as basal ganglia
- The PNS receives input from and sends output to the CNS, i.e. is involved in sensory and motor function
- Motor neurones are either:
  o Somatic – innervating muscle
  o Autonomic – innervating smooth muscle, glands, blood vessels, viscera
- Sensory neurones are present in the skin, joints, viscera etc

Microscopic Organisation of the PNS

**Ganglia**

- Sensory neurone cell bodies (both somatic and autonomic) lie in ganglia associated with spinal dorsal roots (DORSAL ROOT GANGLIA) or some cranial nerves
  o Dorsal root ganglia have no dendrites, and are PSEUDOUNIPOLAR cells
- Postganglionic neurone cell bodies lie in AUTONOMIC ganglia, which are either arranged in rows PARAVERTEBRALLY (sympathetic) or closer to internal organs (parasympathetic)
- The supporting cells of ganglia are SATELLITE cells – a type of glial cell

**Peripheral Nerves**

- Bundles of axons – sensory & motor; somatic and autonomic
  o Bundles of individual axons are known as FASCICLES
  o Fascicles are bundled into NERVES
- Blood vessels then lie in between nerves
- Axons are carefully packaged so they aren’t damaged by movement:
  o ENDONEURIUM - Individual axons and their associated Schwann cells are surrounded by delicate loose connective tissue. This is important for the regeneration of axons
  o PERNEURIUM - Groups of axons (fascicle) surrounded by dense connective tissue
  o EPINEURIUM - Whole nerve surrounded by loose connective tissue
Axons

- **Unmyelinated axons**
  - Usually small diameter (about 1um)
  - Clothed in cytoplasm of Schwann cells (NEUROLEMMA) which can accommodate several axons per Schwann cell
  - Slow conduction speed (CONTINUOUS conduction) – approx 1ms

- **Myelinated axons**
  - Axon diameter: 1.5 – 20um
  - Clothed in a succession of Schwann cells, each wrapping tightly around the axon in up to 100 layers – this wrapping forces the Schwann cells to lose their cytoplasm forming a sheath of cell membranes
  - Myelin sheath separated by nodes of Ranvier in which there is a gap in the cell membrane sheath
  - Myelin sheath increases velocity of conduction via SALTATORY conduction (the depolarisation of the axon membrane of adjacent nodes of Ranvier involving localised electrical currents)
    - There are no Na+ channels in the membrane of the Schwann cells, therefore depolarisation cannot occur – i.e. the cells act as electrical insulators
    - Repolarisation of the membrane requires energy using the Na/K ATP pump – therefore myelinated axons are more energy efficient as repolarisation only occurs at adjacent nodes, not the entire axon membrane
    - This allows the range of conduction speeds to be extended
  - Rapid conduction speed (SALTATORY conduction) – approx 120ms
  - Functional groups of axons have characteristic sizes/conduction velocities, eg: the fastest axon is the muscle spindle primary afferent (120m/sec); the slowest axon is the C-pain fibre (1m/sec)

Macroscopic Organisation of the PNS

NB: Not all the components of the PNS are arranged in the same way

**Neurones**

- **Sensory neurones**
  - Autonomic and somatic neurones are the same
  - Receptors on skin, joints, viscera – when stimulated trigger action potential
    - Impulses travel via dorsal root ganglion to the CNS

- **Motor neurones**
  - **SOMATIC**
    - Soma in CNS
    - Impulses pass along ventral root through spinal nerve to appropriate skeletal muscle and trigger contraction
  - **AUTONOMIC**
    - PREGANGLIONIC neurone in CNS
    - Impulse passes along axon, where it synapses at the AUTONOMIC GANGLION with the POSTGANGLIONIC neurone
    - Postganglionic neurone then carries impulse to appropriate target e.g. blood vessels, smooth muscle, glands, viscera
Relationship with CNS

- Spinal cord – develops from neural tube, surrounded by grey matter and white matter
- Grey matter divided into dorsal (POSTERIOR) horn and ventral (ANTERIOR) horn
- Dorsal and ventral roots of the somatic nervous system come together to form a spinal nerve, which emerges horizontally from the vertebral column

The autonomic nervous system

- Sensory neurones – impulses travel from periphery of body via dorsal root ganglion into the dorsal horn of grey matter within the spinal cord
- Motor neurones – preganglionic neurone forms ventral root from the ventral horn of grey matter and synapses with the postganglionic neurone at the autonomic ganglion
  - This synapse may be close to or far away from the spinal cord

The somatic nervous system

- Sensory neurones – impulses travel from periphery of body via dorsal root ganglion into the dorsal horn of grey matter within the spinal cord
- Motor neurones – impulses travel from the ventral horn of grey matter via the ventral root
- The location where the dorsal and ventral roots meet the white matter of the spinal cord is the interface between the PNS and CNS
- SPINAL NERVE formed at INTERVERTEBRAL FORAMEN by junction of dorsal and ventral roots
- A typical spinal nerve innervates a specific band of skin (DERMATOME) and muscle (MYOTOME) in a particular part of the body
- Each spinal nerve then divides into RAMI (sing. ramus):
  - DORSAL RAMI innervate muscle and skin of back
  - VENTRAL RAMI innervate muscles and skin of rest of body, including limbs
- The RAMI COMMUNICANTES (white and gray) provide interconnections between some spinal nerves and ganglia of the sympathetic nervous system
- DERMATOMES: the specific band of skin innervated by a particular spinal nerve
  - There is a specific distribution of spinal and peripheral nerves to the skin
- It has a striped appearance correlating to the horizontal emergence of spinal nerves from the vertebral column
- The spinal nerves are coded by a letter and number
- This is useful for diagnosis of spinal nerve injury as a loss of sensation in a particular dermatome will correlate to a particular spinal nerve – however there is some degree of overlap of innervation of spinal nerves, therefore injury to a particular spinal nerve may not have any observable effects as other nerves compensate for the sensory loss

**LIMB INNERVATION**
- In the main trunk of the body, the spinal nerves are in parallel, but in order to innervate the limbs, they combine to form peripheral nerves.
- The location in which the axons of different spinal nerves are recombined to form peripheral nerves is called a PLEXUS
- Ventral rami of spinal nerves C5-T1 innervate the upper limb through the BRACHIAL plexus
- Ventral rami of spinal nerves L2-S2 innervate the lower limb through the LUMBOSACRAL plexus

**DERMATOME CHART**

Diagram of the distribution of spinal and peripheral nerves to the skin: the coloured map shows the spinal nerves, whereas the black and white map shows peripheral nerves.
• Sensory loss can be charted by the area of loss of sensation corresponding to a particular dermatome on the chart, which will correspond to a particular spinal nerve.
• If the area of sensory loss is NOT confined to a particular dermatome, the damage must be POST-PLEXUS therefore damage to a peripheral nerve (and hence many spinal nerve axons) has occurred.

Disorders of the PNS

Peripheral nerve injury

When a peripheral nerve is damaged:
• A – The normal axon is contained by the endoneurium; a compression injury occurs which breaks the continuity of the AXOPLASM, therefore action potentials cannot be propagated.
• B – The distal part of the nerve degenerates, but the PROXIMAL STUMP remains intact (unless injury is close to soma) and macrophages phagocytose the axonal and myelin debris (WALLERIAN DEGENERATION).
• C – The proximal part of the axon and cell body usually survive but undergo metabolic changes (CHROMATOLYSIS) – outgrowth of AXONAL SPROUTS from the proximal stump occurs; these are guided down by a scaffold of proliferating Schwann cells.
• D – When the first axonal sprout makes contact with target organ, growth and myelination occurs; the other axonal sprouts then draw back into the proximal stump.
  o Successful regeneration mainly depends on how badly the axons and connective tissue sheaths are damaged and the distance from the target organ.
  o Failure to reconnect leads to formation of a NEUROMA containing trapped axons.
• E – the nodes of Ranvier in the regenerated axon will be closer together than initially.

Peripheral neuropathies

• Progressive degeneration of peripheral nerves.
• May be a consequence of a metabolic disorder (diabetes), infection, or be hereditary.
• Usually begins in distal parts of limbs (glove and stocking distribution) and is in the distal – proximal direction.
• May affect sensory and/or motor axons.
• May initially affect myelin or axon.
• SEGMENTAL DEMYELINATION – Schwann cells eventually die therefore continuous conduction replaces saltatory which affects the conduction speed.
• AXONAL DEGERATION – leads to a complete conduction block; may be the result of prolonged and increase segmental demyelination.
Diagnostic techniques for peripheral nerve disorders

- **Conduction velocity** can determine whether a peripheral neuropathy is present, and if so, whether it is demyelinating or axonal
- **Nerve biopsy** (e.g. sural nerve) can be used to study pathogenesis of the disease

NMH 8 - PNS Practical Notes

**MDL-1 Dr Paul Strutton (p.strutton@imperial.ac.uk)**

**Learning Objectives**

1. To understand the procedures by which nerve conduction velocity can be measured and its clinical relevance  
2. To understand the factors that affect the measurement of nerve conduction velocity

**Practical Notes**

Action potentials in muscle fibres are of larger amplitude than those in peripheral nerve axons; this makes them easy to record through the skin using surface electrodes. Because of their large amplitude it is easy to record their precise time of occurrence and any changes in amplitude as stimulus intensity is varied. We will record the electromyographic (EMG) activity of the adductor pollicis muscle in the thenar eminence of the hand in order to monitor the activity of some of the motor axons in the ulnar nerve.

![Diagram of EMG recording setup](image)

We will use brief pulses (approx 0.5 ms) of negative electrical current applied to pre-determined locations over the ulnar nerve using a hand-held monopolar stimulating electrode (cathode). The positive stimulating electrode (anode) will be sited at a location on the arm proximal to the cathode. We will apply the stimulating cathode over the ulnar nerve at the following locations:

- **S1**: the medial aspect of the forearm at the wrist
- **S2**: the ulnar groove at the elbow

We will apply recording electrodes over the thenar muscle group to an amplifier and computer
Practical Method

- Each stimulating electrode location will be marked with a felt-tipped pen.
- The absolute distances between (S1 and S2) will be measured using a tape measure.
- Six stimuli will be delivered at each location and latency of each response measured in milli-seconds. Remember that the latency time (T_1 and T_2) for each of the responses includes:
  - Activation time.
  - Conduction delay from the cathode to the neuromuscular junction.
  - Delay at the neuromuscular junction.
  - Conduction delay along the muscle fibres to the EMG recording electrodes.
- We will adjust the stimulation intensity at each site so as to evoke compound action potentials in the muscle of similar intensities.
- Time delays at stages A, C and D will be the identical whatever the position of the stimulating electrode.
- The delay at stage B will increase when the stimulating electrode is further from the recording electrodes, therefore the delay at stage B at S2 > S1.
- In order to measure conduction velocity of the activated nerve axons we must measure the distance between (S_1) and (S_2) and divide this by the conduction delay from the two stimulating cathodes (1) to (2).
- We can calculate the conduction delay from (1) to (2) by subtracting the response latency from stimulating at (S_1) from the response latency from stimulating at (S_2), i.e. T_2 – T_1.

Calculations

speed = distance/time
Therefore speed = distance between S1 and S2 / conduction delay between S1 and S2, T2 – T1
Remember: distance needs to be in metres, and time in seconds, as speed is always measured in m/s

Summary

- Both sensory and motor nerve axons are activated by the electrical stimulus.
- We have assessed the conduction velocity of motor nerve axons.
- The nerve axons activated at lowest electrical stimulus intensities are large diameter (sensory > motor) therefore we feel stimulus before response is seen.
- Slowed conduction velocity might indicate demyelination, hypothermia or increased pressure to the nerve bundle.
- The motor axons activated by the stimulus send action potentials towards the hand.
- The sensory axons activated by the stimulus send action potentials towards the spinal cord.
- The ulnar nerve supplies the adductor pollicis muscle as well as other muscles.
- Absence of EMG action potentials in response to the stimulus could indicate that the ulnar nerve is blocked or the device is broken.
- Nerve compression in the forearm can result in slowing of ulnar nerve conduction at the wrist: this would just be seen as longer conduction delays in both S1 and S2.
- 3 factors which can influence conduction velocity of peripheral nerve axons in vivo are myelination, axon diameter and ambient temperature.
Peripheral Nerve Lesions

A – Dorsal Root
B – Dorsal root ganglion
C – Spinal nerve
D – Ventral Root

V – Damage to dorsal root leads to loss of sensation in dermatome supplied by the corresponding spinal nerve. (Probably not detectable if only one root affected as there is considerable overlap of dermatome innervation by adjacent spinal nerves)

W – Damage to ventral root leads to weakness of muscles supplied by the corresponding spinal nerve. (Most limb muscles are innervated by 2 or more spinal nerves therefore paralysis is unlikely unless all spinal roots are damaged)

X – Damage to spinal nerve leads to combined effects of V and W above

Y – Damage to a sensory nerve (eg. in the skin) leads to loss of sensation in the area of distribution of that peripheral nerve

Z – Damage to a muscle nerve leads to weakness/paralysis of muscle supplied by that peripheral nerve

Causes of lesions:
- Spinal root and spinal nerve damage is most often a consequence of strain injuries to the spine, eg. prolapsed disc.
- Peripheral nerves may be affected by trauma or disease (peripheral neuropathy)
- The brachial plexus may be affected by trauma to the shoulder joint. The lumbosacral plexus is much better protected and therefore unlikely to be injured.
The Autonomic Nervous System

NMH 9 - Professor John Laycock (j.laycock@imperial.ac.uk)

1. Describe the sympathetic and parasympathetic pathways and their central/spinal connections.
2. Identify the neurotransmitter substances released at different levels within the autonomic nervous system and describe the principal steps involved in their biosynthesis and metabolism.
3. Describe the influence of the sympathetic and parasympathetic nervous system on the principal systems/organs of the body (e.g. cardiovascular system, lung, gut, exocrine glands) and understand the concept of dual innervation and autonomic tone (giving examples).
4. Give an example of an autonomic reflex and describe the principal pathways involved.
5. Classify the cholinoreceptors found within the autonomic nervous system and identify the principal loci of (a) the nicotinic cholinoreceptors and (b) the muscarinic cholinoreceptors. Note that the nicotinic receptors are ion-gated and the muscarinic receptors are G-protein coupled.
6. Identify the principal loci of adrenoceptors in the autonomic nervous system. Classify these receptors and sub-classes and note that they are G-protein coupled.
7. Describe how autonomic activity can be estimated with physiological and biochemical examples.
8. Describe the main abnormalities in autonomic failure differentiating between localised and generalised disorders.

Basic Structure

- The ANS is one of the principle efferent paths of communication between the CNS and PNS
- It targets the exocrine glands, smooth muscle, cardiac muscle, metabolism and host defence
- Consists of two components, which are anatomically, functionally and neurochemically distinct:
  - SYMPATHETIC - fight or flight response
  - PARASYMPATHETIC – rest and digest

<table>
<thead>
<tr>
<th>Target</th>
<th>Function of Sympathetic</th>
<th>Function of Parasympathetic</th>
</tr>
</thead>
<tbody>
<tr>
<td>EYE</td>
<td>Dilation of pupil</td>
<td>Constriction of pupil</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Contraction of ciliary muscle</td>
</tr>
<tr>
<td>TRACHEA &amp; BRONCHIOLES</td>
<td>Dilation</td>
<td>constriction</td>
</tr>
<tr>
<td>LIVER</td>
<td>Glycogenolysis</td>
<td>-</td>
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<tr>
<td></td>
<td>Gluconeogenesis</td>
<td>-</td>
</tr>
<tr>
<td>ADIPOSE</td>
<td>Lipolysis</td>
<td>-</td>
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<tr>
<td>KIDNEY</td>
<td>Increased renin secretion</td>
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<tr>
<td>URETERS &amp; BLADDER</td>
<td>Relaxes detrusor muscle</td>
<td>Contraction of detrusor</td>
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<tr>
<td></td>
<td>Constriction of internal sphincter</td>
<td>Relaxation of internal sphincter</td>
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<tr>
<td>SALIVARY GLANDS</td>
<td>Thick viscous secretion</td>
<td>Copious watery secretion</td>
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<tr>
<td>SKIN</td>
<td>Piloerection</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>Increased sweating</td>
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<td>HEART</td>
<td>Increase rate and contractility</td>
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<td>GASTROINTESTINAL</td>
<td>Decrease motility and tone</td>
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<td>---------------------------</td>
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<tr>
<td>Contraction of sphincter</td>
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<td>Increase secretions</td>
</tr>
<tr>
<td>BLOOD VESSELS</td>
<td>Dilation of skeletal muscle</td>
<td>-</td>
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<tr>
<td>Contraction of skin, mucous membranes and splanchnic area</td>
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</table>

The sympathetic nervous system (SNS)

- Fight or flight response
- Prepares the body for responses to stressful situations
- Key role in regulation of
  - blood pressure
  - body temperature
  - metabolism

The parasympathetic nervous system (PSNS)

- Controls a number of functions in non-stressful conditions e.g. GI motility and secretions
- Rest and digest
- Opposes the actions of the SNS on e.g. heart rate

Autonomic Nerves

- Nerves consist of two nerve fibres/neurones, which arise from different regions of the spinal cord:
  - PRE-GANGLIONIC NEURONE
  - POST-GANGLIONIC NEURONE

Parasympathetic Nerves

- Arise in cranial and sacral regions off spinal cord
- Pre-ganglionic neurone LONG
- Post-ganglionic neurone SHORT
- Ganglia are located in or very close to the effector cell/target tissue

Sympathetic Nerves

- Arise in the thoracic and lumbar regions of the spinal cord
- Pre-ganglionic fibre SHORT
- Post-ganglionic fibre LONG
- Ganglia located in a chain close to the vertebral column (PARAVERTEBRAL GANGLIA) or closer to the target tissue (e.g. COELIAC GANGLION)
  - The connections between these ganglia allow MASS ACTIVATION
• The ADRENAL MEDULLA also acts as a modified ganglion
  o Made up of secretory cells (CHROMAFFIN CELLS) innervated by pre-ganglionic fibres
  o Its products (CATECHOLAMINES) are released directly into the bloodstream and reach their target cells via circulation
  o This leads to a more generalised effect

Physiology

➢ Control of the CVS
  - Cardiac output is proportional to the mean arterial blood pressure / total peripheral resistance
  - The total peripheral resistance is inversely proportional to radius^4 therefore an increase in the radius by 2 will result in a decrease in the total peripheral resistance by 16

➢ Control of Cardiac Output (CO)
  - Cardiac output = stroke volume x heart rate
    o i.e. the amount of blood pumped per unit time
  - Sympathetic stimulation of the heart:
    o INOTROPIC EFFECT – increased force of contraction → increased stroke volume
    o CHRONOTROPIC EFFECT – increased heart rate
    o This leads to an increased cardiac output

➢ Control of total peripheral resistance (TPR)
  - Achieved by controlling the SYMPATHETIC TONE of arteries, veins and particularly arterioles
  - Therefore increased activity leads to generalised VASOCONSTRICTION and increased TPR
    o Reduced sympathetic activity leads to generalised VASODILATION and reduced TPR – i.e. there is a degree of control
  - Control of mean arterial blood pressure (MABP)
  - Increased sympathetic activity results in:
    o Increased cardiac output
    o Increased total peripheral resistance
  - MABP is proportional to CO X TPR
    o Therefore increases mean arterial blood pressure

➢ Vasodilation
  - Mainly due to decreased SYMPATHETIC TONE
  - Exceptions:
    o Increased sympathetic activity to some blood vessels in skeletal muscle (either cholinergic fibres of adrenergic beta-receptors)
    o Localised VASODILATORS – products of metabolism e.g. CO₂, increased H+ conc, nitric oxide, histamine etc
    o Increased PARASYMPATHETIC stimulation to certain blood vessels to discrete glands, organs e.g. penis
- **Innervation of the GI Tract**
  - Sympathetic activity – inhibits PERISTALSIS
    - Generally decreases motility and tone
    - Stimulates contraction of sphincters
    - Inhibits secretory activity
  - Parasympathetic activity – stimulates PERISTALSIS
    - Opposite effects

- **Control of the lungs**
  - Increased sympathetic activity
    - Dilates bronchi and bronchioles
    - Increases oxygen delivery to the lungs

- **Innervation of the Penis**
  - Parasympathetic activity essential for ERECTION
  - Sympathetic activity involved in:
    - Penis FLACCIDITY
    - EJACULATION
  - Therefore both components are necessary for reproduction

- **Innervation of the eye muscles**
  - Sympathetic activity:
    - Contracts radial muscles
    - Pupil dilation
  - Parasympathetic activity:
    - Contracts papillary sphincter → pupil contraction
    - Contracts ciliary muscle → lens bulges for near vision

- **Regulation of the bladder**
  - Smooth muscle – DETRUSOR – surrounds bladder
  - Parasympathetic control is main influence
    - Ganglion in muscle and post-ganglionic fibre innervates muscle
  - Sympathetic control
    - Internal sphincter control
  - Motor nerves/voluntary control
    - External sphincter
    - Determines end result
  - Increased pressure in the bladder increases the AFFERENT activity to the spinal cord, the MICTURITION REFLEX to the sacral spinal cord occurs
    - INCREASED Parasympathetic activity via the PELVIC NERVE leads to contraction of detrusor muscle
    - DECREASED Sympathetic activity via the HYPOGASTRIC NERVE relaxes the internal sphincter
    - CENTRAL INHIBITION of Voluntary control via the PUDENDAL NERVE relaxes the external sphincter → decreased pressure in bladder
Neurochemistry and Signal Transduction

Neurotransmitters

- Neurotransmitters used by the ANS:
  - ACTEYLCHOLINE
  - NORADRENALINE
  - ADRENALINE

- Actetylcholine – acetic acid and choline
- Noradrenaline & adrenaline – catecholamines from precursor dopamine
- Parasympathetic NS
  - The pre- and post-ganglionic fibres are cholinergic, i.e. they release acetylcholine

- Sympathetic NS
  - The pre-ganglionic fibres in the sympathetic system are also cholinergic.
  - The vast majority of post-ganglionic fibres are noradrenergic (sometimes called adrenergic), i.e. the transmitter they release is noradrenaline.
  - The adrenal medulla forms part of the sympathetic system; it is innervated by pre-ganglionic cholinergic fibres which, trigger the release of neurohormones (mainly adrenaline but also some noradrenaline) into the circulation.
  - In some instances (e.g. sweat glands) the neurotransmitter used by post-ganglionic sympathetic fibres is acetylcholine.

- Transmission in the PSNS
  - Transmission at all autonomic ganglia is fast. The receptor used by acetylcholine in the ganglia (termed NICOTINIC receptor) is a ligand gated ion channel.
  - Transmission at the effector organs is relatively slow and is mediated by G-protein coupled receptors. The acetylcholine receptors are termed MUSCARINIC receptors.

- Transmission in the SNS
  - Receptors for acetylcholine are nicotinic/muscarinic
  - Receptors for noradrenaline/adrenaline are called ADRENOCEPTORS; there are two main types of adrenoceptor, termed α and β.
    - These in turn have different sub-forms
    - Subgroups have different affinities to adrenaline and noradrenaline

Synthesis, release and metabolism of amine transmitters

- General processes
  - Precursor → neurotransmitter
  - Transmitter → vesicle
  - Action potential → increase in intracellular calcium → vesicle fusion and exocytosis
  - Transmitter binding with receptor on effector cell
  - Removal by uptake or local enzyme system
- **Acetylcholine**
  - Choline + Acetyl coenzyme A $\rightarrow$ acetyl choline + coenzyme A (Enzyme - CHOLINE ACTEYL TRANSFERASE)
  - General processes
  - Removal: acetyl choline $\rightarrow$ choline + acetate (Enzyme – ACETYLCHOLINESTERASE)

- **Noradrenaline**
  - Tyrosine enters cell
  - Tyrosine $\rightarrow$ DOPA (enzyme – TYROSINE HYDROXYLASE)
  - DOPA $\rightarrow$ Dopamine (enzyme – DOPA DECARBOXYLASE)
  - Dopamine stored in vesicle $\rightarrow$ noradrenaline (enzyme – DOPAMINE β-HYDROXYLASE)
  - General processes
  - Removal:
    - Uptake 1- reuptake into neurone
    - Metabolites (enzyme – MONOAMINE OXIDASE A ; MAO-A)
    - Uptake 2- uptake into effector cell, degradation by COMT

- **Adrenaline**
  - In adrenal chromaffin cells
  - Same as noradrenaline, but then $\rightarrow$ adrenaline (enzyme – PHENYLETHANOLAMINE METHYL TRANSFERASE)
  - General process, but the adrenaline binds to receptor and enters general circulation

**Fig. C4: SYNTHESIS, RELEASE AND METABOLISM OF ACETYLCHOLINE**

**Fig. C5: SYNTHESIS, RELEASE, REUPTAKE AND METABOLISM OF NORADRENALINE**

**Fig. C6: Synthesis, storage and release of adrenaline**
The ANS in General

- **Sympathetic activity**
  - Diffuse system which allows it to stimulate multiple parts of the body at once (MASS DISCHARGE)
  - Can also have more discrete effects

- **Parasympathetic activity**
  - Is a relatively discrete system innervating individual target tissues via specific nerves

- **Adrenal medulla**
  - Chromaffin cells synapse with pre-ganglionic fibres (Ach neurotransmitter)
  - Release catecholamines (80% adrenaline) directly into the blood - HORMONES

**Fight or Flight response**

- Mass sympathetic discharge in response to alarm or stress which results in:
  - increased arterial blood pressure
  - increased blood flow to active muscles (and decreased blood flow to other areas such as splanchnic bed)
  - increased blood glucose concentration
  - increased respiration
  - increased awareness, etc.
Acute stress response

- Stress acts on the hypothalamus and brain stem, which leads to the release of catecholamines from the adrenal medulla via the sympathetic nervous system. Results in:
  - Tachycardia
  - Splanchnic bed vasoconstriction
  - Increased metabolic rate
  - Sweating
  - Pupil dilation
  - Increased blood [glucose]
  - Increased mental alertness
  - etc.

Autonomic Reflexes
NMH 10 - Dr Chris John (c.john@imperial.ac.uk)

Baroreceptor Reflex

- Baroreceptors in carotid sinus and aortic arch
  - Modified nerve endngds that respond predominantly to the stretch of blood vessels as a result of blood pressure
  - When stimulated, signal Medulla in brain which then passes down to the sympathetic ganglia of the ANS
- Increased arterial blood pressure $\rightarrow$ increased stretch of the baroreceptors
  - Increased stretch $\rightarrow$ increased AFFERENT nerve activity to brain
  - Increased nerve activity $\rightarrow$ increased INHIBITION of sympathetic nervous system (i.e. reduced sympathetic activity)
  - Inhibition of SNS:
    - Decreased vasomotor tone $\rightarrow$ decreased total peripheral resistance
    - Decreased heart rate and force of contraction $\rightarrow$ decreased cardiac output
    - Decreased circulating catecholamines from adrenal medulla
  - Therefore blood pressure is reduced
- Decreased arterial blood pressure $\rightarrow$ reduced stretch of the baroreceptors
  - reduced stretch $\rightarrow$ reduced AFFERENT nerve activity to brain
  - reduced nerve activity $\rightarrow$ reduced INHIBITION of sympathetic nervous system (i.e. increased sympathetic activity)
  - Increased activation of SNS:
    - increased vasomotor tone $\rightarrow$ increased total peripheral resistance
    - increased heart rate and force of contraction $\rightarrow$ increased cardiac output
    - increased circulating catecholamines from adrenal medulla
  - Therefore blood pressure is increased

Normal CVS Responses

- Postural changes, e.g. gaining an upright position, require blood pressure changes
- Standing upright has a number of effects:
  - Increased pooling of blood in lower limbs
  - Reduced venous return $\rightarrow$ reduced contractility $\rightarrow$ reduced cardiac output
- Reduced blood pressure
  - Therefore reduced stimulation or baroreceptors and CARDIOPULMONARY RECEPTORS
    - Decreased vagal tone to heart
    - Increased sympathetic nerve activity
    - Increased cardiac output
    - Increased total peripheral resistance
  - This then increases the blood pressure

**Postural Hypotension**

- Impaired sympathetic nerve response leads to:
  - Little change in cardiac output
  - NO increase in total peripheral resistance
- Arterial blood pressure is therefore not maintained on standing
- There is then decreased cerebral blood flow → FAINT
- One body is SUPINE
  - Blood flow to brain restored
  - Consciousness usually regained

**Light Reflex**

- Consider the IRIS (coloured bit)
  - Increased parasympathetic activity → elongation of iris → contraction of pupil
    - PILOCARPINE is Ach analogue so stimulates parasympathetic activity (MIOSES)
  - Increase sympathetic activity → iris contracts → dilates
    - E.g. ATROPINE stimulates the sympathetic nervous system (MYDRIASIS)
  - In response to light, the iris elongates and the pupil constricts – the CONSENSUAL REFLEX
- Light is detected by PHOTORECEPTIVE PHOTORECEPTOR cells
  - This sensory input is then carried by the OPTIC NERVE (cranial II) to the PRETECTAL NUCLEUS in the brain (bypassing the visual cortex)
  - Pretectal nucleus activity then sends impulses to EDINGER-WESTPHAL NUCLEI
- The edinger-westphal nuclei act as the parasympathetic activity origin
  - Parasympathetic activity via the OCCULOMOTOR NERVE (cranial III- preganglionic fibre) to the CLIARY GANGLION
  - The post-ganglionic fibre then carries the activity to the SPHINCTER PUPILLUS, which constricts the pupil
- The CONSENSUAL nature of this reflex means that if you shine light in one eye, both eyes will constrict
  - If this does not occur, you know there is a problem with the motor function after the edinger-westphal nuclei
1. Describe the basic anatomy of ANS innervation in terms of pre-ganglionic neurons, ganglia and post-ganglionic fibres. Contrast the anatomical location of sympathetic and parasympathetic ganglia.

2. Describe the thoracolumbar (sympathetic) and craniosacral (parasympathetic) central origins of the ANS.

3. Understand the terms sympathetic trunk, plexus and subsidiary ganglia.

4. Identify the rich sympathetic plexuses that surround the major organs and blood vessels.

5. Understand the pre-ganglionic nature of the thoracic and lumbar splanchnic nerves and their synapses in subsidiary ganglia e.g. coeliac ganglion.

6. Understand the importance of the sacral parasympathetic outflow for innervation of structures within the pelvis e.g. the bladder.

7. Identify which of the cranial nerves contain parasympathetic pre-ganglionic fibres.

The ANS

- Responsible for involuntary control of the viscera
- 3 divisions:
  - Sympathetic
    - Mass responses
    - Mobilises body energies for increased activity
  - Parasympathetic
    - Localised physiological actions
    - Conserves body energy
  - Enteric
- Central control
  - Homeostatic changes and influence from higher brain centres e.g. memory act on the hypothalamus
  - The hypothalamus influences the medulla, which acts as the centre for control of the sympathetic and parasympathetic nervous system
- Pathways
  - Consist of a pre-ganglionic neurone, a post-ganglionic fibre and a ganglion
- Ganglia
  - Sympathetic - Found in the sympathetic trunk which is closer to the spinal cord than the organ/viscera being innervated
  - Parasympathetic - Found close to or even in the organ/viscera they innervate
- Nerves
  - AFFERENT – carry sensory impulses from all parts of the body to the CNS
  - EFFERENT – through which “messages” are conducted from the brain to the muscles and all of the organs of the body
Sympathetic Nervous System

- Preganglionic efferent fibres arise from:
  - THORACIC nerves
  - Upper LUMBAR nerves (L1-3)
- This is known as THORACOLUMBAR OUTFLOW
- Largest division of the ANS
- Consists of:
  - Sympathetic trunks (x2)
  - Nerve plexuses
  - Subsidiary ganglia
- Innervates:
  - Sweat glands in the skin
  - arrector muscles of hair
  - muscular walls of blood vessels
  - heart, lungs, abdominal and pelvic viscera
- Preganglionic neurons in the lateral column grey matter of spinal cord T1 to L3
  - Emerge from the spinal cord via the ventral root of the spinal nerve
  - Pass through ventral ramus to white rami communicantes to ganglion
- Synapse within ganglion or send fibres up and down to other ganglia
  - Postganglionic fibres distributed to effector organ via grey rami communicantes
  - Travel in dorsal or ventral rami

Sympathetic Trunk

- A chain of ganglia and connecting fibres which lie next to the vertebrae for the entire length of the vertebral column. This arrangement allows dispersion of the sympathetic outflow from a small region of the spinal cord (T1-L2) to peripheral regions via all spinal nerves
  - Base of skull to coccyx
  - 3 ganglia in cervical region
  - 11 or 12 ganglia in thoracic region
  - 4 or 5 ganglia in lumbar region
  - 4 or 5 ganglia in pelvis

Plexus

- A network of nerve fibres originating from different levels associated with an organ e.g. the cardiac plexus
  - Cervical
    - Plexus around pharynx
    - Cardiac plexus
    - Thyroid plexus
    - Pulmonary plexus
  - Thoracic
    - Plexus around thoracic aorta
    - Splanchnic nerves
Splanchnic Nerves

- **Greater**
  - Thoracic aorta supply
  - Pierces diaphragm – enters abdomen plexus around great blood vessels supplying gut
- **Lesser**
  - Pierces diaphragm – enters abdomen plexus around aorta
- **Least**
  - Pierces diaphragm – enters abdomen plexus around gut
- **Lumbar**
  - 4 lumbar ganglia
  - Lumbar splanchnic nerves take part in all plexi of sympathetic nerves in abdominal and pelvic regions

Sympathetic Actions

- Blood vessels (vasoconstrictor)
- Sweat glands (secretomotor)
- Hairs (motor)
- Accompany motor nerves to voluntary muscles but only distributed to blood vessels supplying the muscles
- Viscera – dilation of pupils, dilation of arterioles, movement of alimentary tract and urinary bladder (i.e. relaxes walls, constricts sphincters)

The Parasympathetic Nervous System

- Preganglionic efferent fibres arise from:
  - CRANIAL nerves
  - SACRAL nerves
- This is known as CRANIO-SACRAL OUTFLOW

- Sacral outflow
  - Anterior rami of S2-4
  - Visceral branches passing directly to pelvic viscera i.e. pelvic splanchnic nerves
  - Minute ganglia in wall of viscera giving rise to postganglionic fibres

Pelvic Splanchnic Nerves

- Motor fibres to rectum
- Motor fibres to bladder wall
- Inhibitory fibres to bladder sphincter
- Erection of penis/clitoris via vasodilator fibres
- Fibres also pass superiorly to supply large part of the gut with visceromotor innervation
Cranial Outflow

- **Oculomotor nerve (CN III)**
  - ciliary ganglion
  - postganglionic fibres to sphincter pupillae and ciliary muscle inside eye

- **Facial nerve (CN VII)**
  - Submandibular ganglion
  - postganglionic fibres to submandibular and sublingual salivary glands
  - Pterygopalatine ganglion
  - postganglionic fibres to paranasal sinuses and lacrimal glands

- **Glossopharyngeal nerve (CN IX)**
  - Otic ganglion
  - postganglionic fibres to parotid gland

- **Vagus nerve (CN X)**
  - enters neck and thorax via carotid sheath
  - branches to lungs, heart, oesophagus, stomach, intestines

The Enteric System

- In walls of alimentary tract
  - Myenteric (Auerbach’s) plexus
  - Submucous (Meissner’s) plexus

- **Sensory** – monitoring mechanical, chemical and hormonal activity of gut
- **Motor** – gut motility, secretion, vessel tone
- Can be overridden by sympathetic and parasympathetic systems

MORE DIAGRAMS ON PP