Neurophysiology

Growth hormone
- release is stimulated by:
  - exercise
  - sleep
  - insulin hypoglycaemia
  - CLONIDINE
  - arginine
  - GLUCAGON
  - DESIPRAMINE

Prolactin
- causes of elevated prolactin include:
  1. Normal states:
     - stress
     - pregnancy
     - lactation
  2. Drugs:
     - D₂ antagonists
     - oestrogens
     - TRH
     - dopamine depleting drugs, e.g. RESERPINE, METHYLDOPA
  3. Other:
     - pituitary tumour (prolactinoma) -- prolactin usually > 4000 mU/L
     - renal failure
     - post-herpes zoster
     - chest wall reflex (e.g. nipple stimulation)
     - epileptic seizure
     - ECT

Neurophysiological measures

Event-related potentials
- occur on the EEG in response to specific events
- each peak reflects the firing of large groups of neurones, within different regions of the brain, at different times during the information processing sequence
- evoked potentials are averaged to eliminate random variations in the EEG tracings
- may utilise the ‘oddball paradigm’ – when an array of similar stimuli contains an unexpected one
• ‘early potentials’ occur within the first 40 ms – they are termed ‘exogenous potentials’ and are not affected by subject factors significantly (e.g. attention, anaesthesia)
• the N100 is followed by the P300 which occurs 300-500 ms after a stimulus is presented
• the P300 corresponds to the cognitive processes required for the recognition, retrieval from memory, and evaluation of a specific stimulus
• in schizophrenia, there is reduced amplitude of the P300 Response

Galvanic skin response
• is a measure of autonomic arousal
• shows increased arousal in chronic schizophrenia – it has been suggested that some negative symptoms are secondary strategies to reduce this hyper-arousal
• is slow to habituate in some schizophrenics
• may be controlled by the ipsilateral limbic system

Cerebral metabolism

Oxygen consumption
• highest in the cortex and cerebellum
• the brain has a respiratory quotient of 1.0, meaning that it uses carbohydrate exclusively

Glucose utilisation
• low blood glucose slows brain metabolism
• glucose utilisation decreases with age

Cerebral blood flow (CBF)
• investigated using xenon-133 (Ingvar, 1960s) or nitrous oxide (Kety and Schmidt, 1940s)
• xenon-133 can be injected or inhaled
• in normal people, there is more blood flow to the frontal lobes
• in schizophrenics, there is increased blood flow to the posterior lobes
• CBF is increased by:
  • carotid sinus massage (increases vagal tone)
  • stellate ganglion blockade (causes a decrease in sympathetic stimulation)
  • increased CO₂ concentration (hyperventilation can be used to reduce intracranial pressure)
  • decreased intracranial pressure (reduced resistance to blood flow)

The GABA Shunt
• the metabolism of certain glucose metabolites is closely related to that of the ‘glutamate group’ of amino acids (GABA, glutamate, aspartate)
• the GABA shunt is a bypass around the Krebs cycle from α-oxoglutarate to succinate, and accounts for 10% of total glucose turnover
• the importance of this pathway can be seen in Vitamin B₆ deficiency:
• pyridoxal phosphate is a cofactor in the enzymes glutamate decarboxylase and glutamate transaminase, which are involved in GABA production from glutamate
• dysfunction of the decarboxylase enzyme may result in low levels of GABA and resulting seizures
Neurotoxicology

Lead

Properties
• has a strong affinity for sulphydryl groups, and it is able to alter the tertiary structure of proteins, resulting in enzyme inhibition
• the lead ion has the ability to mimic the ions of Calcium, Zinc, Magnesium, and Copper, enabling it to disrupt many metabolic processes

Lead poisoning
• presents with multiple seizures, mania, delirium, blindness, aphasia, and dementia
• causes a peripheral neuropathy, predominantly motor

Alcohol

Acute intoxication
• one theory proposes that alcohol acts as a non-specific membrane perturbant, changing membrane fluidity
  • accounts for anaesthesia and sedation, but does not account for euphoria and anxiety reduction at low doses
• it is more likely that ethanol exerts its intoxicating effects via an action on Cl fluxes associated with GABA\textsubscript{A} receptor activation – it effectively potentiates GABA inhibition
• it also inhibits the excitatory actions of glutamate by interacting with the NMDA receptor
• intoxication may be due to increased production of PGE\textsubscript{1}, a prostaglandin which has similar effects to those of ethanol

Tolerance and dependence
• tolerance is partly due to an increased rate of ethanol metabolism by alcohol dehydrogenase
• theories of dependence include:
  1. *decremental tolerance* – the cell adapts in such a way to lessen the effects of the drug
  2. *oppositional tolerance* – the response is achieved by active opposition to the drug, and withdrawal represents the consequence of opposition in absence of ethanol
    • one possibility is that TIQ derivatives (metabolites of ethanol) act as agonists at the binding sites for enkephalins and endorphins
    • tolerance may be due to DGLA (a fatty acid needed for the production of PGE\textsubscript{1}) depletion – as stores become less, increased levels of ethanol are needed to give a given level of PGE\textsubscript{1}
Neuroadaptation

- reduction in the number of GABA$_A$Rs or a reduction in the effects of GABA on Cl$^-$ flux would explain dependence
- chronic ingestion leads to an upregulation of the NMDA receptor – an action that would resist ethanol-induced inhibition
- the prolonged presence of ethanol in the vicinity of neurones evokes, as an adaptive response, an increased sensitivity to agonists of L-type of voltage-operated Ca$^{2+}$ channels (VOCC)