

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 sulphhydryl 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_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 PGE₁, 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 PGE₁) depletion – as stores become less, increased levels of ethanol are needed to give a given level of PGE₁

Neuroadaptation

- reduction in the number of GABA_ARs 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 Ca²⁺ channels (VOCC)