B4 - Pain

(a) To define pain

= an unpleasant sensory or emotional experience associated with actual or potential tissue damage.

(b) To describe pain pathways & mediators involved in nociception. To describe peripheral & central sensitization, gate control theory, preemptive & preventative analgesia.

Pain Pathways

Sensors

- naked nerve endings -> two fiber systems to CNS (1) A zeta fibers ('fast', myelinated, 20m/s) (2) C fibers ('slow', non-myelinated, 1m/s) -> dorsal horn ->

Central processor

(1) brainstem
(2) spinothalamic tract (contralateral side)

-> ventral posterior nuclei -> thalamus -> cortex

Effectors

Reflexes:

- somatic response to visceral pain (muscle spinting & guarding)
- visceral response to somatic pain (vasodilation)

Mediators

-> all either cause pain or decrease threshold for transmission of pain.

A zeta fibers ->

C fiber stimulation -> release of vasoactive mediators to surrounding tissues by impulses moving from sensory nerve to periphery (substance P)

Neurokinins

(1) Substance P - causes pain, oedema, vasodilation
(2) Calcitonin gene related peptide - acts @ NK1 receptor

(3) Capsaicin - in chillis - depletes substance P from nociceptor after transport up C fibers to nerve cell bodies -> causes pain and then reduces it.

Kinins

(1) Bradykinin - releases prostanoids, cytokines & degranulates mast cells.
(2) Kallidin - similar action to bradykinin

Other mediators

(1) Histamine - from mast cells -> stimulates substance P release -> causes pain
(2) Adenosine - reduces K+ ion permeability -> hyperexcitability
(3) Serotonin - acts on 5HT3 receptors -> increases Na+ permeability, decreases K+ permeability
(4) Prostaglandins & leukotrienes - lower threshold to activation of sensory neurons -> increased pain
(5) Cytokines
(6) Interleukins
(7) Excitatory amino acids - glutamate
(8) Nerve growth factors

Peripheral sensitization

- neuropathic pain of a peripheral origin = a distinct type of chronic pain that occurs in the complete absence of an inflammatory reaction.
- continual ectopic spontaneous discharge of pain signals
- area becomes sensitive to stimulation (mechanical, thermal) -> severe chronic pain, hyperalgesia & allodynia (non-painful stimuli produces pain)
- this can contribute to secondary hyperalgesia & central sensitization

Central sensitization

- increased number of action potentials by C fibers -> -> increased excitability of secondary afferent neurons evoked by neurochemical changes resulting from activation of the NMDA receptors -> secondary afferent neurons (gate-keepers) compromised -> excitatory pain transmission unopposed -> spontaneous generation of pain signals & exaggerated nervous system responses .

- higher levels of brain cannot discern the origin of the pain signals -> patient in continual state of pain.
- emotional or physical stress exacerbates
- gapapentin can help.

Gate control theory

- proposed by Melzack & Wall (1965)
- 'interneurones of the dorsal horn act as gates controlling transmission of nociceptive information'
- whether the gate is open (pain) or closed (analgesia) depends of inputs from the interneurons from C fibers & A beta fibers

- these are under control of GABA (GABAr) & glutamate & glycine (NMDAr)
- this junction show considerable plasticity

- ie. stimulation of large-diameter afferent fibers from an area from which pain is being initiated reduces the pain
- collateral branches from the touch fibers in the dorsal columns enter the substantia gelatinosa -> impulses in these collaterals or interneurons inhibit transmission from the dorsal root pain fibers to the spinothalamic neurons.

Preemptive analgesia

- designed to prevent the establishment of altered central processing that amplifies postoperative pain
- smaller dose required to treat preemptively as compared to once it has occurred.
- central sensitisation can be reduced

Preventative analgesia

- preemptive analgesis must be started pre-incision and then carried out throughout the entire whole post operative period.

(c) To describe the pharmacology as pertaining to pain management of:

- opioids
- tramadol
- LA
- NSAIDs
- paracetamol
- NMDA antagonists
- anticonvulsants
- antidepressants
- corticosteroids
- inhalational analgesics - N2O, methoxyflurane

Opioids

- act as agonists at opioid receptors at presynaptic & post-synaptic sites in the CNS (brainstem & spinal cord) and in peripheral tissues.
- opioid receptors are activated by 3 endogenous peptide ligands - enkephalins, endorphins, dynorphins.
- opioids mimic their action by binding to the receptors -> activate pain-modulating systems.
- primary effect of receptor activation = decrease in neurotransmission via inhibition of transmitters (Ach, dopamine, norephinephrine, substance P)
- this si from (1) increase in K+ conductance -> hyperpolarisation (2) Ca2+ inactivation
- both -> decrease in neurotransmitter release.

Tramadol

- opioid receptor agonist
- centrally acting:

(1) moderate affinity for mu receptors, weak kappa & delta.
(2) in spinal descending inhibitory pathways by inhibition of neuronal reuptake of norephinephrine & serotonin.
(3) also via presynaptic stimulation of seritonin release.

- x 10 less potent than morphine
- racemic mixture of two enantiomers
- provide analgesia without respiratory depression.

LA

- inhibit passage of Na+ ions through ion-selective Na+ channels in nerve membranes
- this slows the rate of depolarisation -> threshold potential is not reached -> action potential not propagated.

NSAIDs

- cyclooxygenase (COX) is an enzyme that catalyses the synthesis of prostaglandins from arachidonic acid.
- prostaglandins mediate a large number of body processes including:

(1) inflammation
(2) pain
(3) secretion of a protective gastri layer
(4) maintenance of renal perfusion
(5) platelet aggregation

- NSAIDs block the action of COX -> reducing production -> results:

(1) analgesia
(2) antinflammation
(3) decreased gastric mucosa -> ulceration
(4) decreased renal perfusion
(5) bleeding

Paracetamol

- acetaminophen
- widely used analgesic & antipyretic
- not true NSAID as it lacks significant antinflammatory effects.
- weak COX 1 & 2 inhibitor in peripheral tissues
- reduces prostaglandin production in the CNS

NMDA antagonists

- Mg2+
- Ketamine (see B2 (c))

Anticonvulsants

- ie. sodium valproate, phenytoin, clonazepam)
- not completely understood
- decrease neuronal excitability or enhance inhibition of neurotransmission by altering intrinsic membrane ion currents (Na+, K+ & Ca2+) OR by affecting activity of inhibitory neurotransmitters (GABA).

Antidepressants

SSRI's

- block the reuptake of serotonin -> enhance serotinergic activity.
- potent inhibitor of CYP450

TCA's

- anticholinergic, antiadrenergic & antihistaminergic properties.
- useful in low dose for chronic pain ?produce anti-inflammatory effects similar to LA
- sites of action:

(1) block re-uptake of serotonin
(2) block re-uptake of norephinephrine

MAOI's

- form stable, irreversible complex with the Monoamine Oxidase ezyme -> increased norephinephrine available for release from CNS neurons.
- not limited to the brain (increases in sympathetic nervous system)

Corticosteroids

- classifed according to the potency of these compounds to:

(a) evoke distal renal tubular reabsorption of Na+ in exchange for K+ (mineralocorticoid effect)
(b) produce an anti-inflammatory response (glucocorticoid effect)

- ie. hydrocortisone, cortisone, corticosterone, desoxycorticosterone, ALD.
- glucocorticoids attach to cytoplasmic receptors to stimulate changes in the transcription of defined on 456 DNA and thus synthesis of proteins.
- at high plasma concentrations -> extert antiinflammatory & immunosuppressive effects.
- prevents host-defense mechanisms that are activated during stress from overshooting & damaging the organism.

- inhibit phopholipase enzyme that is necessary for the inflammation chain reaction along both the cyclooxygenase & lipoxygenase pathways.

Inhalational analgesics

- certain volatiles may contribute to analgesia by release of endogenous opioids (encephalins, dymorphines, endorphines), but do not act directly on opioid receptors.

N2O

- decrease excitatory neurotransmission (block glutaminergic & muscarinic excitatory function) & increase inhibitory neurotransmission (enhance GABA function) -> dose dependent decrease in MAC

(d) To describe the different modes of administration of analgesic agents & evaluate their clinical applications.

IV

Benefits

- administrated straight into the blood stream -> absorption & bioavailability inconsequential
- easily titrate to response as effect-site equilbration time shortest

Weakesses

- must achieve venous access (traumatic for children)
- inadvertent intra-arterial injection
- tempting to give large amounts of medication
- catheter associated complications: infection - thrombophlebitis

IM

Strengths

- easy to administer
- reasonable absorption as muscle has good blood supply
- by passes first-pass hepatic metabolism

Weaknesses

- painful
- don't have access to blood supply in situation of anaphylaxis
- sequestration of medication (can be dangerous -> sedatives)

- haematoma formation
- can have variable absorption -> variable time of onset

SC

- see IM -> but even slower onset

PO

Strengths

- no needles
- patients compliant
- can be self adminstered

Weaknesses

- patients compliance
- variable absorption (dependent on med, and patient eaten...)
- medication subject to hepatic first pass metabolism
- oral formulation may be difficult to manufacter

Transdermally

Strengths

- well tolerated by patients
- often once daily dosing (nicotine) or even once every 3 days (clonidine/fentanyl)

Weaknesses

- variable absorption
- slow build up to theraputic plasma concentration
- allergy to patch

Topically

Strengths

- great in paediatric patients (EMLA)

Weaknesses

- duration of time until onset

- expensive

Epidural

Strengths

- less systemic side-effects than IV (but still present)

Weaknesses

- onset of side-effects many hours post administration (ie. hypoventilation post epidural morphine @ 12 -18hrs)

Intrathecal

- see epidural

Add on:

(e) The assessment of pain

History

- symptoms
- treatment modalities
- type of pain (peripheral/central, neuropathic or visceral)
- severity

- pain scales

-> children - happy to sad faces
-> adults - visual analogue scale, verbal numberical, verbal descriptor (mild, mod, severe)

Examination

- vitals
- area & system involved
- other possible pathology

Investigation

- as guided by clinical findings
- blood concentrations of measurable medications