Dermatology - Chemistry

Describe factors affecting drug absorption across the skin.

- Drugs cross the skin as a result of passive diffusion across the stratum corneum. Very little gets across hair follicles and sweat glands. *(to be continued)*

Pain (Opioid) - Chemistry

Mu-opioid pharmacophore should include:

1. A 3-OH group
2. A phenyl group
3. A basic nitrogen
4. Extra phenyl group – binds at additional lipophilic receptor site and increase affinity
5. Unsubstituted position 15, 16

Types of bonds involved:

1. Hydrogen bond (between 3-OH and phenolic site) *(to be continued)*

… more in between …

Advantages of tramadol:

- Misuse potential is lower (due to weak agonist activity on opioid receptor in limbic system, hence low amount of dopamine released)
- Can be used where respiratory depression is problematic (due to weak agonist activity on opioid receptor in brainstem)
- Less problem with constipation (due to weak agonist activity on opioid receptor in gut)

Drug classes	Adverse effects
NSAID drugs	Gastrointestinal effects (upper abdominal pain, gastric erosions, peptic ulcers, gastrointestinal bleeding), cardiovascular effects (rise in BP, fluid retention, MI, stroke, cardiovascular death), renal (renal impairment)
Selective μ-opioid receptor agonist (e.g. morphine)	Bradycardia, hypotension, respiratory depression, nausea, vomiting, constipation, dependence, tolerance, addiction; sedation (kappa), dysphoria (kappa)

Describe the mechanism of action of opioid drugs.

- Opioid drug molecules bind to an opioid receptor in the presynaptic membrane of afferent pain neurons
- This results in the closure of Ca^{2+} channels, hence blocking Ca^{2+} ion influx into the cell.
- In addition, cAMP levels within the neurone decrease and potassium channels open, allowing positive ions to exit the cell.
- These events hyperpolarize the cell, hence making the pain neurone less likely to fire an action potential by releasing substance P.
- Opioid acts to quiet neurons along the pain pathway to dampen the transmission of pain signals and result in analgesia.

What are the structural modifications for enkephalins (i.e. a peptide) to reduce their metabolism?
Hint: enkephalin is Tyr-Gly-Gly-Phe-Leu

- Modify the terminal COOH (of leucine) to CH_2OH (structure below)
- Change glycine (2nd from left of enkephalin) to D-alanine (structure below)
- Add methyl group to NH of amide
- Cyclize peptide

[IMPORTANT] What is the SAR of morphine?

- Aromatic ring A for potency
    - Substitution at C1 and C2 decreases activity → no substitution at C1 and C2
    - Changes from 3-OH to $3\text{-}OCH_3$ (in codeine) decreases activity → 3-OH (in oxymorphone, hydromorphone, morphine) is essential for activity
        - **GOOD:** 3-methoxy group in codeine provides a potent antitussive activity
        - **GOOD:** 3-methoxy group in codeine increases lipophilicity of the compound and increases gut absorption or has reasonable oral pharmacokinetics
        - **BAD:** 3-methoxy group of codeine is required to be metabolized by O-demethylation into 3-OH (i.e. morphine) to give mu opioid activity. Thus, those who lack CYP2D6 have a reduced effect to codeine.

- Ring C
    - 6-OH (in morphine) for good activity; but 6-ketone (in hydromorphone) for better activity (albeit ketone is polar, it is easier to get through membrane compared to -OH group) ……

(to be continued)

Pain (NSAID) – Chemistry

Describe the pharmacological actions of prostaglandins.

1. Mediation of pain and inflammation due to PGs produced by COX-2
    - PGG_2, PGH_2 – mediation of pain responses and vasoconstriction
    - PGG_2 – mediation of the inflammation response

2. Major cytoprotective role – maintain the integrity of GIT mucosa due to PGs produced by COX-1
    - PGEs and PGI_2 inhibit gastric secretion
    - PGE_1 stimulates secretion of an alkaline mucus and HCO_3^-
    - PGE_1 maintains or increase mucosal blood flow

Describe the COX isozymes.

- The size, substrate and active sites of COX-1 and 2 are remarkably similar, however two key amino acids were found to be different.

- COX-1 Ile 434 and Ile 523 (isoleucine) are replaced with the smaller amino acid, valine, in COX-2. The COX-2 binding site is therefore larger in size.

- COX-1 located in GI tract (cytoprotective role), kidneys and platelets; whilst COX-2 is located at sites of inflammation which can be induced by inflammatory cytokines (e.g. interleukins, TNFα)

Mechanisms of action of aspirin:

- Aspirin is one of the salicylates (precisely called "acetylsalicylic acid")
    - Potency / toxicity is modified by substitution on OH or COOH

(to be continued)

PAC4451: Pain Pathways (Dan)

Compare and contrast between nociceptive and neuropathic pain.

Nociceptive pain	**Differences**	**Neuropathic pain**
Acute or chronic	Severity	Normally chronic
• Somatic (involving superficial structures such as skin or muscle) • Visceral (involving deeper organs such as liver or pancreas) • Referred pain (e.g. cardiac ischaemia) – i.e. nociceptors from several locations converge on a single ascending tract in the spinal cord	Origin of stimulus	Damage to nociceptive pathways (i.e. damage to neurons that carry pain signals either to or from brain) 3 types: • Peripheral – phantom limb pain or diabetic neuropathy • Central – trigeminal neuralgia (facial pain) or spinal cord injury • Both peripheral and central – post-herpatic neuralgia (shingles)

etc… etc…. (all are IMPORTANT for understanding and answering exam-type Questions!!!)