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Module 1 – Principles of Drugs Action in the Nervous System

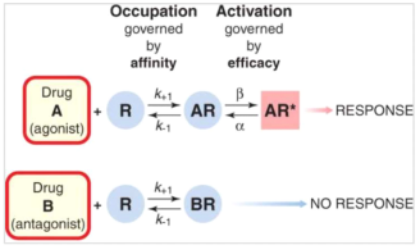
Lecture 2: Principles of Drug Action

Lecture Summary

- Rang and Dale CHP 2, 3; Neal CHP 1, 2;
- What is pharmacology, pharmacodynamics; how do drugs produce their effects, drug targets versus drug receptors, receptor-effector linkages; drug concentration-response relationships and bioassays;

Learning Outcomes

Four primary steps of analgesia = (1) administration (dosage, absorption), (2) distribution, (3) interaction of drug with 'target', (4) metabolism and elimination



Pharmacology: the study of drugs and how they work

- Pharmacodynamics, describing the effects of a drug on the body
- Pharmacokinetics, describing the effects of the body on a drug
  - (Both covered in PCOL2011 + autonomic pharmacology and drug design)

→Importance = safe, effective use of medicines; right patient, drug, dose, route and time;

1.1 Define drug specificity/ selectivity, agonist, antagonist, substrate, product, inhibitor, blocker

Drugs alter protein function by, activation/ agonism (+); modulation (+/-); inhibition/ antagonism/ block (-)

- Nucleosides, and proteins can be affected
- Drug targets refers to drug binding sites: receptors are a special category of drug target for pharmacologists
- Some examples,
  - Activating receptors are agonist e.g. salbutamol β-receptor agonist = bronchodilation
  - Antagonising receptors are antagonists e.g. atenolol β-adrenoceptor antagonist = ↓HR, ↓BP
  - Blocking ion channels e.g. lignocaine Na+ channel blocker = precents AP and sensory sensation causing local anaesthesia but NOT pharmacological receptor
  - Inhibiting enzymes e.g. aspirin inhibits COX and PG production = analgesia and reduce inflamm.
  - Inhibiting transporters e.g. fluoxetine inhibits serotonin/ 5HT uptake in CNS = increase synaptic concentration = treatment against depression

1.2 Outline how drugs produce their effects and list the four main molecular targets of drugs;

Most drugs (typically small molecules) bind to proteins (large molecules, i.e. drug targets), with few drugs binding to nucleic acids, the main four are:

1	Receptors	- Protein molecules that enable E/C molecules to alter I/C events - Agonists bind to (occupy) and activate the receptor to produce a response directly or indirectly (i.e. transduction), whether it be enzyme activation/ inhibition, ion channel modulation, DNA transcription, etc. - Antagonists, bind to (occupy) but do not activate the receptor (no effect, endogenous mediators blocked)
2	Enzymes [Biochemistry]	- Metabolises substrates to products - Inhibitors prevent metabolism/ product formation; false substrates produce abnormal metabolites - Enzymes can convert inactive pro-drugs to active drugs
3	Carrier molecules/ transporters	- Transporters 'carry' or transport substrates across membranes - Inhibitors prevent transport/ false substrates cause abnormal compounds to accumulate in the cell
4	Ion channels [Physiology]	- Allows ions (e.g. Na+, Ca2+, K+) to cross membranes and are often voltage-gated, *distinguished from receptor/ ligand operated channels* - Blockers prevent ions from passing the channel, i.e. permeation blocked - Modulators increase/ decrease the opening probability of the channel

Drug specificity: no drug is completely specific but most drugs are selective i.e. show a high degree of binding site specificity. The higher the dose, the more likely non-specific effects will occur = unwanted side effects

Lecture 4: Anticholinesterases (Pesticides) Poisoning

Lecture Summary

- The use of AChEs as pesticides, the impact on communities and current research in this area

Learning Outcomes: uncertain.

History of Ops

- Organophosphorous (OP) and Tabun (GA): developed in Germany, WWII, as pesticide due to shortage of nicotine;
- Increasing OP pesticide use across world; less stable in environment than organochlorines
- Ongoing use as 'nerve agents' e.g. Iran-Iraq war, Tokyo terrist attack 1995; Syria 2013;

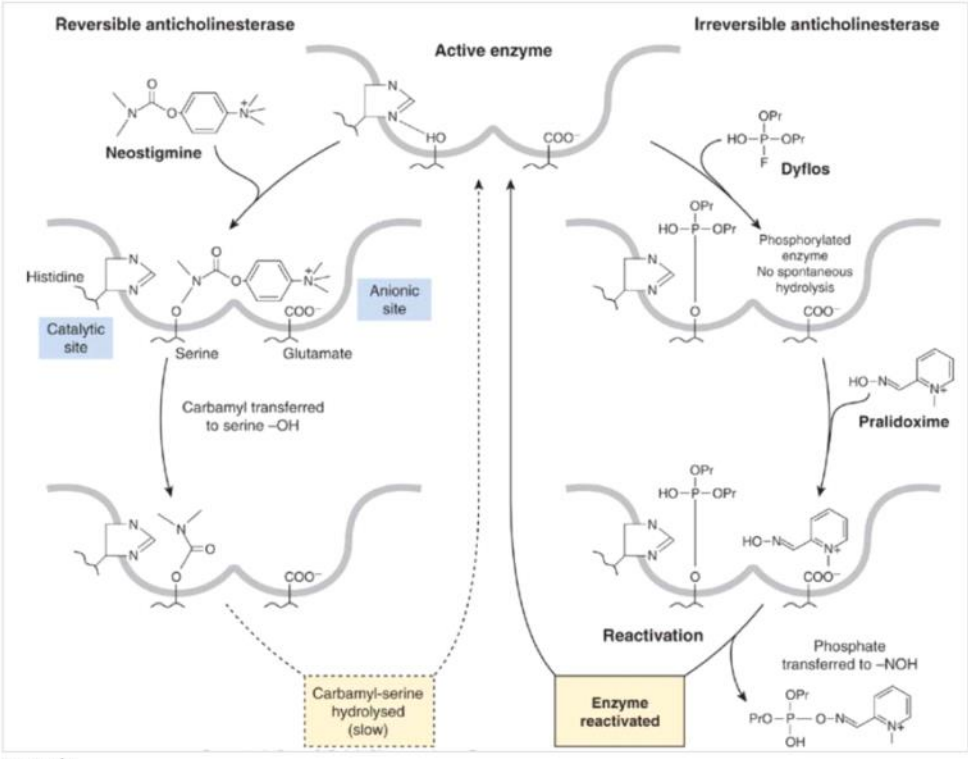
Toxicology

- OPs inhibit various 'esterase' enzymes in the body: AChE inhibition is the most important in inducing acute effects as AChE is important for normal communication between nerves and other nerves, glands, muscles, etc.
  - Examples – PSNS glands; SNS adrenal, sweat, BVs; Somatic skeletal muscle, etc.
- Chemical warfare 'nerve agents' are OP anticholinesterase agents

Cholinergic Syndrome

- (wet, weak, slow), symptoms include diarrhoea, urination, miosis, bradycardia, bronchorrhea, bronchoconstriction, emesis, lacrimation, salivation, sweating (muscarinic → atropine)
- Muscle weakness with fasciculations
- CNS effects = ↓LOC and seizures

Differences between reversible and irreversible anticholinesterases:



OP compounds

- Pro-poison or active (thion, or oxon); they have different kinetics e.g. fat solubility and clearance, affecting half-life; as well as different propensity to age.
- There are reversible vs. non-reversible binding to acetylcholinesterase
  -Neuopathic? (PNS and CNS, multiple mechanism)

Tolerance/ tachyphylaxis

- Neuronal M2 receptor function tested using pilocarpine; increasing dosage inhibited vagally induced bronchosconstriction in dose-related manner;

8.2 Cocaine (Psychostimulant)

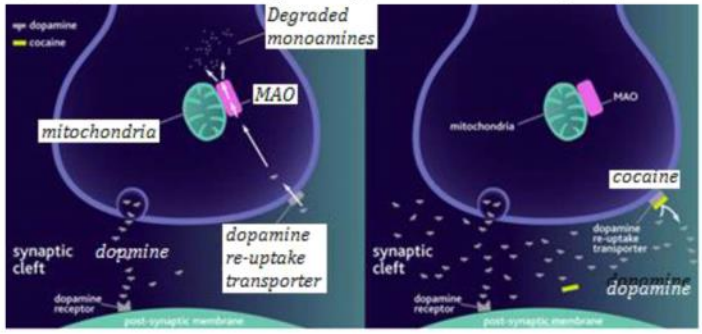
History

- Derived from the Erythroxylum coca plant; South American Indians have chewed coca leaves for thousands of years
- Cocaine first isolated by Alvert Niemann, (1855); Used as local anaesthetic, in coca wine in the 19th century; in coca-cola until 1906 when addictive properties were found; 1% Australian population used in the last 12 months

Pharmacological effects

- [Cocaine/ cocaine hydrochloride is a stimulant with similar effect to amphetamines like speed and ice, but more intense effect and shorter "high" depending on dosage]
- Acute effects: euphoria, appetite suppressant, ↑ alertness/ self-confidence/ sense of well-being/ energy/ motor activity/ sexuality, ↓anxiety and social inhibition, ↑HR, ↑BP, local anaesthetic actions
- Side effects, repeated use; eating and sleeping disorders, impaired sexual performance, respiratory problems, convulsions, kidney failure, ↑risk of stroke; binge use followed by severe "crash" with experiences of depression, lethargy, hunger.
  - 5-50% purity only with unknown component potentially toxic adulterants
  - Damage to nasal membranes and septum if snorted, tissue damage due to vasoconstriction when injected
  - Chronic use can lead to (1) psychotic episodes, (2) damage to the heart → heart failure
  - Excessive dosages – tremors and convulsions, followed by respiratory depression and cardiac arrhythmias

Mechanism of action – it increases the levels of DA, NA, and 5-HT in the brain by blocking the catecholamine transporter (blocks dopamine and serotonin transporter); the anaesthetic effect is via another MOA.



8.3 Methamphetamine (Psychostimulant)

History

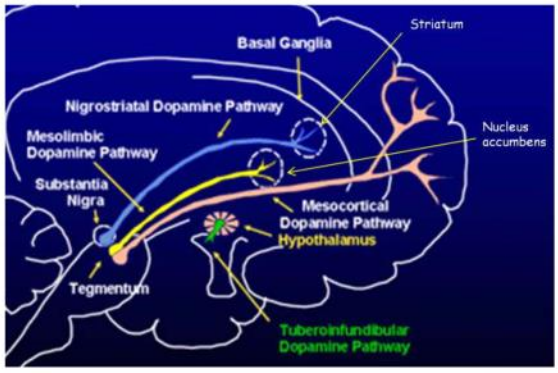
- Methamphetamine is a synthetic homologue of amphetamine first synthesised [from ephedrine] in Japan (1893)
- Most-widely abused illicit drug worldwide after cannabis (35 million people); highly addictive

Pharmacological effects

- Initial effects: euphoria, ↑alertness/ concentration/ energy/ libido, appetite suppressant
- Side effects: ↑HR ↑breathing rates, hypertension, irregular body temperature, blurred vision, dizziness, vasoconstriction
- Long-lasting cognitive and emotional changes: paranoia, anxiety, depression, irritability, hallucinations, mood swings, violent behaviours, loss of ability to make decisions, ↑risk of stroke, chronic sleep disorder, memory loss, blood-borne infections [e.g. Hep C, HIV], anorexia, malnutrition, etc. [itching, picking, scratching at skin]; neurotoxicity = neurodegenerative damage to DA and 5-HT neurons and transporters, loss of gray matter, alteration of the integrity of the BBB → long-term emotional and cognitive impairments

Mechanism of action – release of [monoamine, especially:] dopamine and blockade of monoamine transporters = hyperstimulation of postsynaptic neurons, including DA, NA, 5-HT; effects can last for several hours due to long half-life, "binge-and-crash" pattern of euphoric effects

- [The amphetamine-induced release of dopamine and inhibition of monoamine oxidase increases both cytosolic and synaptic levels of dopamine leading to the acute manifestation of stereotypic and self-injurious behaviour. In turn, the enhanced extravesicular levels of dopamine lead to oxidative stress through the generation of reactive oxygen species and dopamine quinones, and cause the long-lasting neuronal damage.]
- Dopaminergic pathways:
  - The mesocortical dopamine system connects the ventral tegmental area and prefrontal cortex and is implicated in anxiety, working memory and schizophrenia.
  - The nigrostriatal daopmine system connects the substantia nigra with the striatum and is implicated in the control of movement and Parkinson's disease
  - The mesolimbic dopamine system connects the VTA and nucleus accumbens and is implicated in reinforcement and addiction as well as stress and attention



Sensing temperature

- (best understood) Transient Receptor Potential, TRP, channels
  - 6 channels sense over range between 0-60*C (<17 TRPA1, M8, V4, V3, V1, V2 >52)
- Noxious heat & TRPV1
  - Image of free nerve ending : when channel heats, conformational change = opens ion channel; cation channel letting through Na+, Ca+; causes depolarisation → activate sodium channels → action potential → Na_v 1.8/1.9 is somewhat selective to noxious effects (p.13)
  - Spinal cord → releases glutamate + substance P (excitatory), activates spinal cord neurons → threshold reached → AP → releasing glutamate into various brain regions; e.g. into thalamus, then to somatosensory cortex.
  - (Pathways to cingulate/ insular cortex much less understood; do not worry about the specific brain regions like the amygdala etc.; focus on where the information needs to be at the end, rather than the intermediatr stance)

Distinguish between nociception and pain:

- Nociception: encoding or processing of noxious stimuli
- Pain: conscious subjective experience of pain in a sentient being
- Noxious cold: effectively same pathway but using different receptor, TRPM8
- Acid: acid sensing ion channel, ASIC, binds protons for conformational change, etc.
- Ischaemia: increase protons, increased lactic acid (change of Ca+ around channel), chelates Ca → activated ASIC

These are all ion channels; so some transducers GPCR receptors e.g. bradykinin, prostaglandins (PG)

- Inflammation changes sensory neuron function
  - Primary afferent release both ends; ATP, CGRP, Substance P, etc. released
  - Promotes increased blood flow and PG production (inflammation); how does PG produce sensitisation? → main cause of allodynia and hyperalgesia; **peripheral sensitisation**, release of PG signals via intracellular PKA and PKC:

1. PKA activation = more sodium channels in terminals
2. PKC = change sensitivity of TRP channels (phosphorylates) to heat i.e. responds to lower levels of heat

Therefore, stronger activation = stronger nociception = stronger pain perception (e.g. happens in ongoing pain like back pain, arthritis)

(II) Neuropathic Pain

- People experience allodynia, hyperalgesia, burning sensation
- Nerve damage in pain circuitry (may be firing when there is no stimulus) → aberrant neuron firing → PAIN
  - Periphery: post-herpatic neuralgia (after shingles, shingle lesion in that particular nerve zones for some unknown reason, may go on for years after), MS (loss of myelin sheath around neurons = damage), phantom-limb pain (still in brain, cutting of nerves originally direct to the limb), cancer (changes nerve), chemotherapy (kills nerves)
  - CNS: thalamic stroke
- Neuropathic pain is a different mechanism → different drug therapy
- Analgesia for neuropathic pain: (Does not have to learn all these drugs, but know that they try to treat the aberrant firing of neurons; most successful drugs like gabapentin that changes activity of neuron channels, dereases aberrant firing used in epilepsy; amitriptyline not well known either, not a great drug in terms of side effects but strong clinical support; capsaicin from chilli peppers, activates TRPV1, overacts neurons and quieten down, i.e. hard for blinded studies, cannot get good placebo, burning discomfort; some evidence for THC binding to CB1 receptors all over brain)

Refer also to: Chapter 42 of Rang and Dale Pharmacology 8th ed.

DRUG	MECHANISM OF ACTION	CLINICAL SUIPPORT	SIDE EFFECTS
gabapentin	•Activate α2δ calcium channels reducing glutamate release •Inhibits sodium channels •Increases [5-HT]	Strong	Well tolerated - sedation, confusion, tremor, headache, peripheral oedema.
amitriptyline	• Block 5-HT and NAd transporters (need both) •Inhibits sodium channels	Strong	Many - dry mouth, sedation, urinary retention, cardiac arrythmias and hypotension.
capsaicin	• acts at TRPV1 receptors • depletes nerve endings of substance P	Contentious - inadequate placebo group	Burning discomfort
Cannabis/THC	• acts at CB1 receptors	Good animal Data, human?	Psycho-active

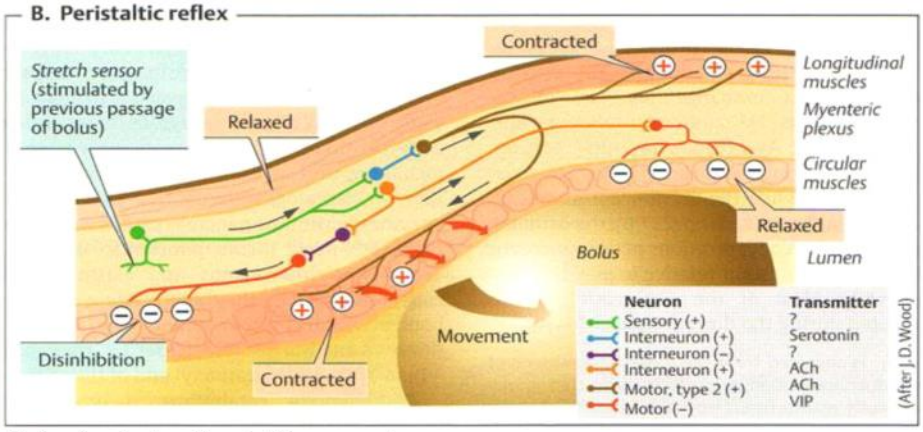
Lecture 17: Theory and Experimental Design of Laboratory 2

Lecture Summary

- How our understanding of peristalsis is unmasked using a pharmacological approach is reviewed in this lecture along with the experimental design and data analysis of the second practical class.

Lecture Notes

- Basic anatomy of the gut
  - The outer covering of the small intestine consists of the peritoneum and serosa, followed by a longitudinal layer of muscle & a circular layer of muscle between which lies the myenteric plexus
  - The nerves in the myenteric plexus are crucial for the peristaltic reflex. [intrinsic neural network of the gut]
    - [The organ bath is set-up so that the Guinea Pig ileum is vertical in the bath → we are to record the activity of the longitudinal muscle (length), NOT the circular muscle (diameter). Of course, we want to measure the circular muscle but these two muscles work together so just measuring longitudinal is good enough.]
- What is peristalsis and why is it important
  - The main function of the small intestine is the completion of digestion and absorption of breakdown products, water and electrolytes
  - Intestinal motility is important to move chyme through the intestine by propagating rhythmic contractions of smooth muscle
  - Any propulsion of intestinal contents that involves propagating rhythm is referred to as peristalsis
  - Peristalsis is brought about through activation of the peristaltic reflex
    - [Migrating wave – there will be a constriction that moves along the gut; quite a lot of variability in the guts; if the "ring" of constriction is not well demonstrated in your gut, have a look at someone else's'.
    - We are using ACh to bring this about.]
- About the peristaltic reflex
  - In vivo, the reflex is elicited by the food bolus stretching the intestinal wall resulting in stimulation of stretch receptors (sensory neurons, interneurons and motor neurons)
  - Depolarisation of sensory neurons (intrinsic primary afferent neurons – IPANs) cause the release of an excitatory NTs, which stimulate interneurons
  - Many interneurons release ACh which stimulates neuronal nicotinic receptors (ligand-gated) located on cell bodies of motor neurons
  - Excitatory motor neurons release ACh, stimulating muscarinic ACh receptors on the smooth muscle, resulting in contraction
  - Inhibitory motor neurons release NO, ATP or VIP (vasoactive intestinal polypeptide), resulting in relaxation → However, we will not be looking at this



- Review from Lecture 16: peristaltic movement

(1) Experimental aims

- To initiate a peristaltic reflex on a piece of guinea-pig ileum (small intestine) by distending the ileum and causing stimulation of stretch receptors
- To demonstrate that the peristaltic reflex is neuronal in origin and not just a property of the muscle itself using selected drugs

- [We are stimulating bolus movement by putting in fluid to stretch; reflex response; demonstrate

Lecture 25: Herbal Medicines – Safety and Efficacy

Lecture Summary

- Herbal medicines in Australia; TGA Office of Complementary Medicines; ARTG; why, how effective, quality control; drug-herbal interactions;

Lecture Notes

Complementary and Alternative Medicines (CAM)

- Also known as 'traditional'
- Include vitamin, mineral, plant, herbal, naturopathic, homeopathic preparation, aroma therapy products
- CAM use in Australia ~69% at least once in last year → even greater international 70-90%

Herbal Medicines

- Finished labelled medicinal products that contain as active ingredients, parts of plants, either crude or as extracts
- A medicinal product is one recommended or described as having prophylactic or therapeutic properties
- Comparison with pharmaceuticals
  - Contain many components, often the active ones unknown with a number of factors that can affect quality
  - Difficulties in producing herbal medicines of high quality, safety and efficacy

(Whereas, pharmaceutical agents = purity, other physicochemical characteristics of pure components)

- Regulated by the TGA – complementary and OTC medicine branch (+Australian Regulatory Guidelines for Complementary Medicines, ARGCM)

Regulation of Complementary Medicines

- Any product regarded as a therapeutic good must be entered on the ARTG
- All such products are required to meet standards of GMP
- Complementary medicines are generally regarded as "low-risk"
  - Listed
    - Low risk ingredients; only for minor, self-limiting conditions
    - Claims limited by therapeutic goods advertising code
    - Sponsors must hold appropriate evidence to support claims about products
    - Bear an L code number
  - Registered
    - Higher risk ingredients; for more serious claims
    - Registration applications undergo scientific evaluation for quality, safety, efficacy
    - Complementary Medicines Evaluation Committee (CMEC) provides advice on claims to be included on the ARTG as a registered product
    - Bears an R code number

- Why do individuals use herbal medicine?:
  - Disaffection with "western medicines" // Belief that natural medicines are inherently safe // Ethnic, cultural
- Why should you use them?
  - Good scientific evidence for some
  - Many traditional medicine used for 100+ years, appear to be safe and effective
  - Considered safer than many synthetic drugs
  - Generally broader spectrum of action; generally involve ingestion of multiple acting components of lower potency

Commonly used –

- St John's Wort (depression), Ginko biloba (mental function), Echinacea (cold), Valerian (relaxation and sleep)

Effectiveness

- Problems in substantiating efficacy; large placebo effect; many conditions resolve themselves
- Well-designed clinical trials rarely carried out due to lack of commercial incentives/ lack of strong patent protection for herbal products

Quality control

- Correct identification of herbal components; purity, no adulterants, no toxic compounds
- Standardised content of active principle/s or pharmaceutically relevant compounds
- Post-marketing surveillance
- Quality Considerations: need to differentiate between inherent difficulties due to the nature of herbal medicines VS breakdown in quality control or deliberate adulteration (fraud)