

Pharmacology

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Pharmacology

Study of how drugs interact with organisms to produce a change in function

Drug = medicinal substance

- organic or inorganic
- natural or synthetic

- some truth in old wives tales/witches brews
- herbal remedies still being used
- bioscreening for novel compounds
- synthetic analogues created in labs
- problems with supply and demand
- problems with drug resistance
- problems with certification (FDA, TGA)



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Pharmacology

Pharmacodynamics (PD)
study of what drug does to body

- mimic/inhibit normal processes
- inhibit pathological processes
- stimulants, depressants, toxins

Pharmacokinetics (PK)
study of what body does to drug

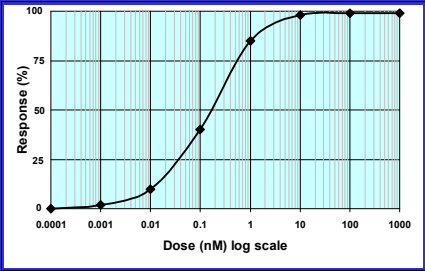
- Absorption
- Distribution
- Metabolism
- Excretion

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Pharmacodynamics (PD)

DOSE – RESPONSE CURVE

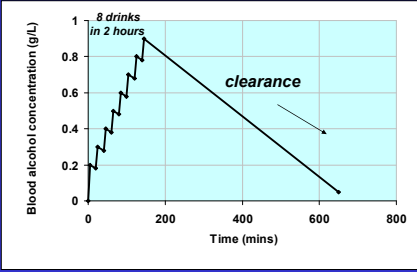


Sigmoidal (S-shaped) curve reminiscent of logistic growth curve

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Pharmacokinetics (PK)

CONCENTRATION-TIME CURVE




Linear functions
Surge functions (power + exponential)

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Tobacco

- cigarettes, cigars, pipes, snuff
- widely used stimulants (inhaled, chewed)
- mainstream cigarette smoke
 - 1-3 billion particles/mL
 - 4,000 substances (43 carcinogens)
 - metals (arsenic, cadmium...), promoters (phenols...)
 - irritants (formaldehyde...), toxins (cyanide)
 - carbon monoxide (200x affinity for Hb than O₂)
- causative agents for many diseases, incl.
 - lung cancer
 - chronic respiratory diseases
 - cardiovascular diseases

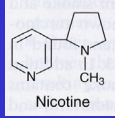
Why smoke? nicotine addiction



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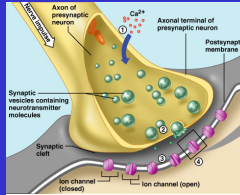
Nicotine

- alkaloid substance (insecticide)
- readily crosses blood-brain barrier
- stimulates receptors in neural synapses (nicotinic acetyl choline)



Three main effects

- enhanced dopamine release (reward circuit, ↑ pleasure)
- addictive behaviours (physical dependence) (psychologic dependence)
- enhanced neurotransmission (↑ cardiovascular responses, ↑HR, ↑BP, ↑CO) (hypertension, arteriosclerosis, MI, stroke) (COPD – chronic obstructive pulmonary disease)



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Nicotine

Pharmacokinetics (PK):

~ 1mg/cigarette, LD₅₀ ~ 1 mg/Kg

Absorption

- through lungs, within seconds

Distribution

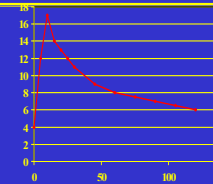
- throughout body via circulation
- effect on brain within 7 seconds

Metabolism (t_{1/2} ~ 2 hours)

- oxidation in liver (cytochrome P450 system, CYP2A6, CYP2B6) (FMO system, flavin-containing monooxygenase)

Excretion

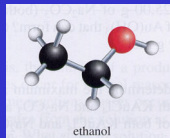
- must be metabolized



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Alcohol

- colourless volatile fluid(s)
- general formula: C_nH_{2n+1}OH
e.g. ethanol C₂H₅OH



- obtained by fermentation of sugars
- ingredient of beer, wine, distilled spirits
- most commonly used drug throughout the world



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Pharmacodynamics: ethanol

- central nervous system (CNS) depressant (similar to anaesthetics)

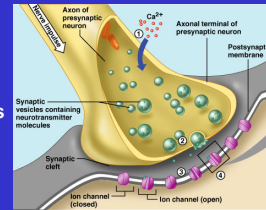
- mode of action (unknown)

- ↓ signal transduction in brain

- inhibits:

- GABA transmitters
- voltage-gated Ca⁺⁺ channels
- NMDA receptors

- paradoxically, no specific receptor has been identified
- but chronic use leads to:
 - psychological dependence
 - physical dependence



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Pharmacodynamics: ethanol

EFFECTS:

- acute intoxication
 - slurred speech, motor incoordination
 - increased self-confidence, altered behaviour
 - impaired judgement, reflexes
- chronic use
 - liver disease (fat deposits, hepatitis, cirrhosis)
 - neuropathy (central and peripheral)
 - cardiovascular (myopathy, hypertension)
 - gastro-intestinal (gastritis, pancreatitis)
 - reproductive (testicular atrophy, abortion) (foetal alcohol syndrome)



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Pharmacokinetics: ethanol

ADME: - variable (age, sex, weight, race, history) (type, amount, activity, diet, etc)

Absorption

- 25% stomach, 75% duodenum
- peaks 0.5-2.0 hours after ingestion

Distribution

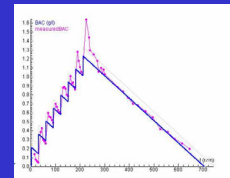
- rapidly throughout body via bloodstream

Metabolism

- 90% in liver

Excretion

- 1-5% in breath
- 1-3% in urine
- 0.5% in sweat



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Ethanol metabolism

Three enzyme systems in hepatocytes

- ADH (alcohol dehydrogenase), cytosolic
- MEOS (microsomal ethanol-oxidizing system), ER
- catalase, peroxisomes

All produce acetaldehyde

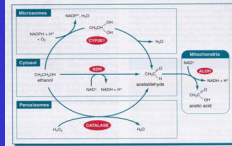
- toxic metabolite (flushing, ↑HR, nausea)
- broken down to acetic acid by ALDH (acetaldehyde DH)

All enzymes require co-factor

NAD (nicotinamide adenine dinucleotide)

robs other pathways, resulting in:

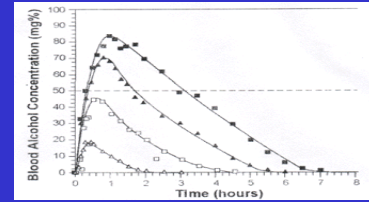
- ↓ pH ⇒ acidosis
- ↓ glycolysis ⇒ anorexia
- ↑ lipid synthesis ⇒ fatty liver
- ↑ inflammation ⇒ hepatitis
- ↑ fibrogenesis ⇒ cirrhosis



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Ethanol clearance

Alcohol saturates enzymes' capacities, so removed at constant rate (~ linear)



BAC: legal limit = 0.05% = 0.5‰ = 0.5 g/L = 50 mg/dL
 0.20% - acute intoxication (novices unconscious)
 0.35% - fatal poisoning (LD₅₀ ~ 0.4%)
 [habitual drinkers can survive 2 x LD₅₀]

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