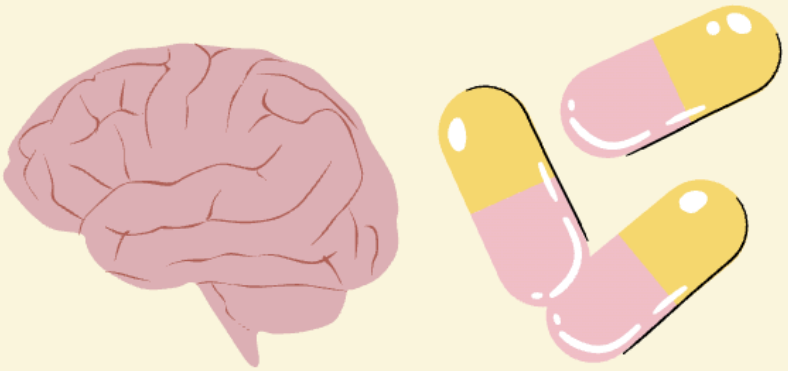
PHRM30002

Drugs Affecting the Nervous System



H1 Complete Subject Notes

Peripheral Nerves

LOs

- Discuss the role of presynaptic receptors
- Describe the implication of nerves being able to release more than one neurotransmitter

Key Drug Types

- Agonist - Activated receptor
- Full agonist - Produces maximal effect
- Partial agonist - Activates receptor, but weaker max effect
- Antagonist - binds with no effect; blocks receptor
- Allosteric modulator - Binds different site & enhances/inhibits receptor function (e.g. benzodiazepines)

- **Affinity** - measure of molecular attraction and relative selectivity for different molecular targets
- **Potency** - measure of drug needed to elicit a effect
- **Efficacy** - measure of how big an effect is

Autonomic Nervous System

- **Parasympathetic**
  - Neurotransmitter: **ACh**
  - Receptors: **N (ganglia), M (targets)**
  - Effects: ↓ HR, ↑ GIT, broncho-constriction, pupil constriction
- **Sympathetic**
  - Neurotransmitter: **ACh (ganglia) → NA (targets)**
  - Receptors: **α & β adrenoceptors**
  - Exception: **Sweat glands use ACh + M receptors** (sympathetic cholinergic)
  - Adrenal medulla = **ACh binds to N receptor and releases adrenaline**

Peripheral nervous system chemical transmission

Division	Primary neurotransmitter	Receptor class
Somatic	Acetylcholine	Cholinergic receptors
Parasympathetic	Acetylcholine	Cholinergic receptors
Sympathetic	Noradrenaline (except ACh at sweat glands)	Adrenoceptors (except Cholinoceptors at sweat glands)
Ganglionic transmission	Acetylcholine	Cholinergic receptors

Adrenoceptors

Receptor subtype	α 1	α 2	β 1	β 2
Major Effect	**Vasoconstriction**	**Decrease presynaptic NA release. Lowers BP in blood vessels.**	**Increase HR**	**Bronchodilation, vasodilation**
G-protein subunit	G-alpha q	G-alpha i	G-alpha s	G-alpha s
Effector	Stimulates phospholipase C (PLC)	Inhibits adenylate cyclase (AC)	Stimulates adenylate cyclase (AC)	Stimulates adenylate cyclase (AC)
Second messengers	Increased IP3 + DAG leads to an increase in [Ca2+]	SAMPLE	SAMPLE	SAMPLE
Responses	Smooth muscle contraction Vasoconstriction Increased BP	SAMPLE	SAMPLE	SAMPLE
Location	**Most sympathetic target tissue** Blood vessels in smooth muscle	SAMPLE	SAMPLE	SAMPLE
Activation	NA > A	SAMPLE	SAMPLE	SAMPLE
Overall Effect	Stimulation	SAMPLE	SAMPLE	SAMPLE
Agonist	Phenylephrine	SAMPLE	SAMPLE	SAMPLE
Antagonist	Prazosin	SAMPLE	SAMPLE	SAMPLE

Clonidine

- Clonidine (α_2 agonist) acts in the **brainstem**
- Stimulates **presynaptic α_2 receptors which inhibits release of noradrenaline**
- ↓ Sympathetic "fight-or-flight" output
- ↓ Heart rate + ↓ peripheral vascular resistance -> **BP falls**
- **MOA**
    - Inhibition of AC -> decreased cAMP -> decreased PKA activity -> less calcium influx into nerve terminal -> less neurotransmitter release! *Essentially anti-exocytotic*
    - Can also increase K+ efflux -> hyperpolarisation (secondary)
- Autoinhibition: Neurotransmitters can act on **their own nerve terminal** to regulate release.

Termination of catecholamines

- **Reuptake inhibitors**
    - NET -> blocked by TCAs, SNRIs, cocaine -> increase NA in synapse
    - DAT -> cocaine, amphetamine -> increase DA -> euphoria/addiction
    - SERT -> SSRIs -> increase serotonin

- Cocaine inactivates NA reuptake via NET; DA>NA>5HT

Tricyclic Antidepressants (TCAs)

- Block reuptake of NA & 5-HT (also block muscarinic, H1, alpha 1)
- **TCAs** inhibit reuptake of NA to amplify response
- TCAs inhibit NET thus inhibiting reuptake of NA -> leads to greater concentration of NA in junction and longer presence in junction -> more NA to bind and activate post-junctional receptors -> amplification and prolongation of response
- **Desipramine:** blocks NET -> increase NA

- **Monoamine metabolism**
    - **MAO inhibitors** inhibit metabolism of NA
        - **MAO A** (tyramine, 5-HT, NA, DA); Inhibitor: **moclobemide** -> antidepressant
        - **MAO B** (DA selectivity); inhibitor: **selegiline** -> prevents DA breakdown centrally, used in early PD
    - **COMT inhibitor**: **Entacapone**
        - Prevents breakdown of levodopa in periphery so more reaches the brain; used in PD given with levodopa

Dopamine receptors

- **D1 like (D1,D5):** excitatory; increase cAMP (postsynaptic excitation)
- **D2 like (D2-D4):** inhibitory; decrease cAMP (presynaptic auto receptor, and postsynaptic inhibition)
    - **Agonists**: **bromocriptine, apomorphine** -> PD
    - **Antagonists**: **haloperidol, chlorpromazine** -> anti-psychotics, anti-emetics

Summary!

Mechanism	Drug	Clinical point
Replaces lost DA	L-DOPA	PD
Blocks peripheral conversion	Carbidopa	Decrease peripheral DA side effects
False transmitter	Alpha-methyl-DOPA	Decrease BP
Displaces NA	amphetamine	Stimulant

GABA

- Major inhibitory neurotransmitter
- Balances excitatory glutamate
- Widespread in the brain: cortex, basal ganglia, spinal cord
- Critical for movement, anxiety, sleep, breathing, cardiovascular control
- Target for: alcohol, benzos, barbiturates, anaesthetics, hypnotics, anticonvulsants

Synthesis and astrocyte cycle

- Synthesised from glutamate
- Glu + astrocyte metabolism = GABA (via GAD enzyme)

1. Glucose -> α-ketoglutarate (Krebs cycle)
2. α-ketoglutarate -> glutamate via glutamate dehydrogenase (GHD)
3. glutamate -> GABA via GAD65/67 + PLP
    - Note: Vitamin B6 is a cofactor. Low B6 -> decreases GABA -> seizures
    - PLP is the active form of B6
4. Glucose ⟶ α-ketoglutarate ⟶ Glutamate ⟶ (GAD + B6) ⟶ GABA

- **Astrocytes**
- Convert Glutamate ⟶ Glutamine ⟶ back to neurons ⟶ Glutamate ⟶ GABA
- Are essential for GABA function; they produce the α-ketoglutarate and transports everything (tripartite synapse)
- *GABA is synthesised in neurons, but requires astrocytes for precursor supply and transport*

GABA receptors

- **GABA-A**
    - Ionotropic
    - Pentameric: **α subunit essential** for chloride channel
    - Cl- influx -> fast inhibition
    - *Mostly presynaptic*
- *Potentiators*
- **Benzodiazepines**
    - Positive allosteric modulators (require GABA to be present)
    - Increase frequency of Cl- channel opening -> greater inhibition
    - **Use:** anxiolytic, sedative, anti-convulsant, muscle relaxant
    - Diazepam, lorazepam
    - **Side effects:** tolerance, dependence, withdrawal
    - **Antagonist**: flumazenil -> reverses benzos
- **Barbiturates**
    - Positive allosteric modulators (at high doses, DON'T need GABA -> high overdose risk)

Alzheimer's Disease

Learning Objectives

- Describe the key neuropathological changes in AD.
- Explain the cholinergic hypothesis and current symptomatic therapies.
- Discuss amyloid and tau hypotheses and their evidence.
- Explain why most disease-modifying trials failed.
- Outline new and emerging therapeutic strategies.

Alzheimer's Disease

- Progressive neurodegenerative disorder that causes memory loss, cognitive decline, and personality changes. Accounts for 60% of dementia cases.
- **Risk factors**
    - Age (Strongest)
    - APO-e4 allele (3-12x risk)
    - Family history/genetic mutations (APP,PSEN1/2)
    - Lifestyle: hypertension, diabetes, obesity, low cognitive reserve

Pathological hallmarks

- **Amyloid-β (Aβ) plaques**
    - Aggregation of **Aβ42** peptide from APP cleavage -> triggers microglial activation and synaptic toxicity
    - Located extracellularly
- **Neurofibrillary tangles (NFTs)**
    - Hyper-phosphorylated tau -> microtubule disassembly -> axonal transport failure + neuronal death
    - Intracellular
- **Cholinergic loss**
    - Basal forebrain (nucleus basalis of Meynert)
    - Decreased ACh synthesis -> decreases choline acetyltransferase -> memory + attention deficits
- **Neuroinflammation**
    - Glial activation (microglia, astrocytes) -> chronic cytokine + ROS release -> neuronal dysfunction
- **Atrophy**
    - Hippocampus and cortex
    - Neuron & synapse loss -> cognitive decline
- *Amyloid appears first, tau correlates best with symptoms.*