Drug Action in CNS is different

- special significance to us as humans (some we use regularly for non-medical purposes: caffeine, alcohol, nicotine) and they affect the way we "feel" – not easy to measure scientifically
- CNS is complicated! The human brain ~1.4kg, contains 85 billion neurons
  - 15 in telencephalon (cerebral cortex)
  - 70 in cerebellum
  - <1 in brainstem / spinal cord
  - (these are roughly the same no. of glial cells)
- Each neuron receives (on average, but varies widely) 7000 synapses
- about 595,000 billion synapses in the brain (mostly chemical synapses, can have electrical too!)

Type	Eg	Target	Main role
Amino Acids	Glutamate (excitation)	ligand-gated ion channels	fast / slow excitation and inhibition
	GABA (inhibition)	GPCRs	
catecholamines	noradrenaline, Dopamine, Ach	GPCR	fast / slow transmission and modulation
peptides	Substance P, NPY, vasoactive intestinal polypeptide	GPCR	modulation
lipids / steroids	endocannabinoids, androgen / estrogen	GPCR and nuclear and membrane receptors	modulation and plasticity
small molecules	nitric oxide, [illegible] monoxide	multiple targets	modulation

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definitions

- EPSP: ~~excitation~~ post-synaptic excitatory potential (EPSP)
- IPSP: ~~inhibit~~ inhibitory
- modulator – used to be an effect which did not give rise to excitation / inhibition, but "affected their effectiveness" – amplification / reduction of other activity – but now includes up / down regulation of transmitter release, action outside synapses (NO and GABA) merges into long term neurotrophic effects
- constitutive receptor activation: some receptors are in an active state, even in the absence of a ligand, ~~peptide~~ proportion is highly variable, dependent upon receptor type, location and pathophysiology
  - ↓ can be induced in certain circumstances

Inhibitory amino acids: glycine

- high concentration in spinal cord
- as neurotransmitter, role is distinctly different from action on NMDA receptors
- transporter proteins for reuptake – Gly_{T1} (astrocytes throughout CNS)
  Gly_{T2} (spinal cord)
- synthesised in the body from serine, though also available in the diet
- 5-subunit pentameric receptors

Muscle contraction under voluntary control

↳ the Renshaw cell provides collateral / recurrent inhibition, driven by axon collaterals from the Ia motor neurons

↳ Renshaw cells prevent over-activity in contracting muscle and also over-relaxation in antagonist muscle

agonist – glycine
antagonist – strychnine
location – spinal cord (Renshaw cells)

Actions/uses: uptake inhibition – potential to treat pain, Parkinson's disease, epilepsy

Catecholamines { dopamine (Parkinson's, schizophrenia)
noradrenaline → depression
serotonin (5-hydroxytryptamine) (sleep management)

1,2 dihydroxybenzene

* dopamine can inhibit tyrosine hydroxylase (end-product inhibition)

general properties

- long projection systems
- modulatory role over multiple brain pathways and circuits
- but some specific eg: dopamine in motor systems works along Ach
- multiple receptor types and sub-types
- good site for drug therapy
- major serotonergic pathway arise in the Raphe nuclei

tyrosine
↓ tyrosine hydroxylase
DOPA (L-DOPA)
↓ DOPA decarboxylase
dopamine
↓ dopamine-β-hydroxylase
noradrenaline
↓ phenylethanolamine-N-methyltransferase
adrenaline

apple: good source of catecholamine

catecholamine oxidase → apple turn brown

* tyrosine restricted to enter the brain by blood brain barrier (BBB)
DOPA is taken up by transporter in BBB better compared to tyrosine, hence DOPA → Parkinson's disease treatment

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Acetylcholine Receptors

Type	Nicotinic (similar to AMPA, important in NMJ)	Muscarinic (important in CNS)
Signal	↑ Na^+	Influences K^+ permeability
Effect	excitatory	mixed
	"FAST"	"SLOW"

↳ Na^+ influx when channel open

* 2 Ach required for nAchR activation

Muscarinic

- 5 subtypes $mAchR_{1-5}$ (GPCR)
- M_1 M_3 M_5 are excitatory through non-linear action of "M current"
- M_2 M_4 are inhibitory through actions of K^+ (open) and Ca^{2+} (close) channels (hyperpolarisation)

Nicotinic

- nAchR → ligand-gated to Na^+, K^+ and Ca^{2+} channels
- pentameric structure, homo / heteromeric, usually presynaptic (CNS), facilitating Glu release though some specific postsynaptic sites also (NMJ)

↳ Muscarinic receptors probably most important ie mediate major [illegible], more widely spread

↳ nicotinic receptors have special role for [illegible] tobacco effects

↳ multiple drug actions on [illegible] synthesis and breakdown of transmitter, actions on receptors

↳ wide profile of drug actions resulting from side-effects of other drugs

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Structure of nAchR

ε - foetal form
δ - adult form

- Heteropentamer of 4 related subunits (α, β, γ or ε, δ) — always 2 α, 2Ach needed for activation
- each subunit has a TM α-helix (the M2 helix)
- 5 M2 helices combine to form the pore
- each α-subunit contains a Ach binding site
- binding of Ach opens the receptor
- most ligand-gated ion channels have similar structure
- Ach induces a conformational change in the receptor, large hydrophobic residues are replaced by small polar residues (+ve charged)

Pharmacological treatments

- L-DOPA (levodopa), substrate for DOPA decarboxylase, can ↑ CNS dopamine levels
- can cause peripheral effects so given with carbidopa / benserazide to block peripheral DOPA decarboxylase (doesn't cross BBB)
- can also be combined w entacapone / tolcapone - COMT inhibitors, working both peripherally to prevent L-DOPA metabolism, centrally to prevent dopamine metabolism

Unwanted side effects

- L-DOPA can cause "involuntary writhing movements" or dyskinesia - seen in majority of patients within 2 years of initiation
- rapid changes in clinical status - the "on-off" effect, when symptoms like hypokinesia suddenly reappear for short periods - possibly due to short $t_{1/2}$ of DOPA and the loss of dopamine stores
- nausea, can be treated w domperidone - itself a dopamine antagonist, but works via chemo-trigger zone at the BBB interface and does NOT cross into the
- postural hypotension
- psychological effects - schizophrenia-like symptoms (delusions and hallucinations) more commonly confusion, insomnia, nightmares (~20% of patients)

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Dopamine agonists

- Bromocriptine and pergolide - orally active ergot derivatives
- use limited by side effects (mainly nausea / vomiting)
- pramipexole and ropinirole - more active at D2 / D3 receptors, don't have the levodopa "on-off" effect
- use limited by side-effects which include "compulsive behaviour" such as gambling and hyper-sexuality, through actions on dopamine-mediated reward circuits

New Avenue

- 6-OHDA : relatively selective catecholaminergic neurotoxin
- taken up by the dopamine & NA transporters
- selectivity for dopamine is achieved by pre-treating the subjects w desimipramine, a NA transporter blocker
- bilateral 6-OHDA lesion causes symmetrical bradykinesia (slow movement)
- In mice expressing channelrhodopsin in direct pathway neurons, these effects can be counteracted by bilateral illumination of the striatum

Huntingtons disease

- inherited (autosomal dominant) disorder, results in progressive brain degeneration
  5-10 per 10,000 become obvious only in middle life
- results in dementia, but also severe motor symptoms - chorea : involuntary writhing movements which can be extremely debilitating. Death occurs 15-20 years after onset
- probably due to ↓ local inhibition, resulting in ↑ dopaminergic activity
- results in early neural degeneration in the striatum, affecting cells in the indirect pathway
- removes an inhibitory influence on GPe and STN (reduces its excitatory drive to GPi)
- result is ↓ inhibitory drive to the thalamus
- thalamo-cortical drive to motor areas ↑ (opposite of Parkinsons disease)

Pharmacological Treatments

- limited, at best
- tetrabenazine, an inhibitor of vesicular monoamine uptake (VMAT), ↓ DA levels
- chlorpromazine, a dopamine antagonist, usually used as an anti-psychotic
- haloperidol, olanzapine, risperidone and quetiapine can be used to suppress chorea in Huntington's disease. All are used labelled "unlicensed indication"

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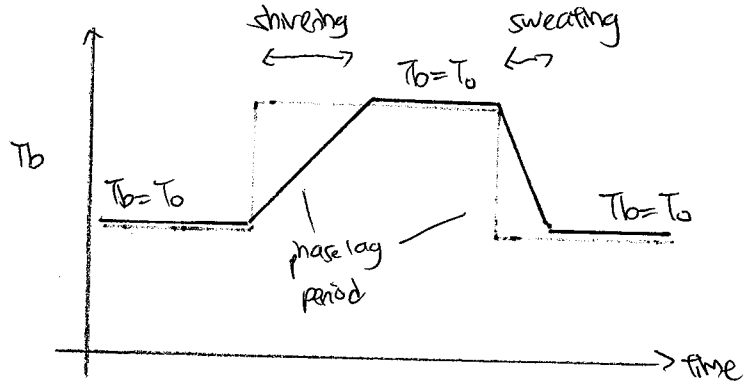
PGE_2

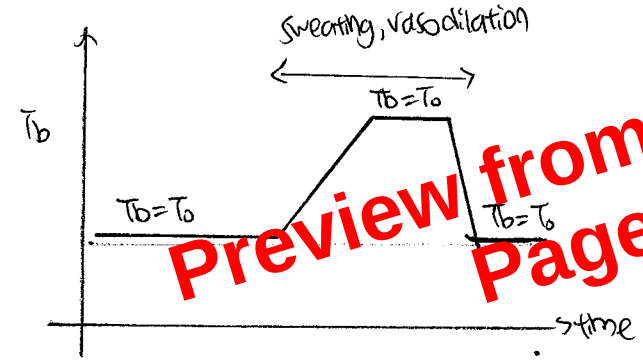
Receptors	Presence in POA	Effect of knock-out
EP 1	Yes	attenuated pyresis
EP 2	NO	-
EP 3	Yes	no pyretic response
EP 4	Yes	??

Pyrexia, fever



Tb = body temp
To = set point

Hyperthermia



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Anti-pyretic Actions

- thermostat raised by IL and PGs - core temp. ↑
- Aspirin inhibit cox enzymes : ↓ PG production
  - : thermostat back to normal
  - : sweat } vasodilate to lose heat
  - : reduce core temp.
- will not decrease temperature in hyperthermia (not due to ↑ thermostat)
  - ↳ have to be treated using ice bath, cold pack...

Sensory (afferent) inputs

- Acute 'sharp' pain : Aδ - fibres (myelinated, 5-30m/s)
- Aching dull pain : C-fibres (non-myelinated, 1m/s)

} from dorsal horn
Rexed's laminar pattern in spinal cord
Continues into ventral horn

Ascending pathways involved in pain

3 pathways - spinothalamic : affective sensation - immediate reaction to "pain" (connections to cingulate cortex) + pain localisation
- spinoreticular : emotional aspects & anxiety
- spinomesencephalic : direct to PAG, initiating pain modulation system
- cervicothalamic
- spinohypothalamic

Descending pathways involved in pain

Body's own pain management system

- periaqueductal grey matter = PAG
- locus coeruleus = LC / A6 (arousal centre of brain)
- nucleus raphe magnus = NRM

Pain circuits

ascending pathways ↑ | ↓ descending inhibition

)) Damage to tissue → nociceptor activity

Activators of pain:
- NO
- bradykinin, PG
- nerve growth factor (NGF)
- substance P, calcitonin-gene related peptide (CGRP)

Cortex : amygdala, insular cortex, hypothalamus
↓
Midbrain : PAG → Medulla : rostroventral medulla

Opioids (not just opiates)

- compounds / drugs w morphine like actions
- these actions blocked by naloxone, an opioid antagonist

Includes : Morphine (naturally occurring - opium extract)
Semisynthetic derivatives
Synthetic compounds
Endogenous neuropeptides

Opioid

eg: endorphins, enkephalins, dynorphins (contains Tyr residue which fit onto the μ receptor)

- role in response to pain, released in response to pain, acupuncture / sport

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Opioid Receptors

- family of GPCRs, 3 subtypes have been cloned
- show 65% homology
- negatively linked to adenylate cyclase (↓ cAMP)
- thereby regulate ion channels — open K^+ channels (hyperpolarisation)

Traditional	New
Mu (M)	MOPr
Delta (δ)	DOPr
Kappa (κ)	KOPr
others (ORL1)	NOPr

* Actually an anti-opioid receptor, Nociceptin-orphanin FQ receptor

subtypes exist for each receptor class

Mu opioid receptors (MOPr)

- subtypes 1,2,3 exist
- Act to open K^+ channels (hyperpolarisation)
- ↓ neuronal activity
- inhibit neurotransmitter release eg: Ach, GLU, substance P
- responsible for most analgesic effect
- major side effects: respiratory depression, constipation, euphoria, sedation, dependence

(GIRK)

- G-protein-activated inwardly rectifying potassium channels

subunit, GIRK2

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(when taken in nasally / IV)

↑ not always seen

Delta opioid receptors

- subtypes 1 & 2 exist,
- act similarly to Mu receptors
- produces analgesia
- can be proconvulsant

Kappa opioid receptors

- subtypes 1,2,3 exist
- ↓ Ca^{2+} channel activity
- inhibit neurotransmitter release
- analgesia at the spinal level

↑ opposite of euphoria

- may elicit sedation, dysphoria / hallucinations. KOPr activity can be coupled to Mu antagonism

Pharmacokinetics of General Anaesthesia

- we would like rapid induction and rapid recovery
- prefer to avoid stage 2
- prefer patient NOT to die in stage 4
- prefer to avoid side effects

Inhalation Anaesthetics

- Enter and leave body via the lungs
- metabolism generally unimportant for recovery
- pass from gas phase to blood, then to tissues

Blood-gas partition coefficient

- A measure of how well drug dissolves in blood
- determines rate of induction and recovery
- a low blood-gas partition coefficient gives rapid induction and recovery

Oil-gas partition coefficient

- High oil-partition coefficient confers high potency
- BUT lots of anaesthetics will dissolve in blood
- fat is poorly vascularised
- anaesthetics will take a long time to leave fat tissue
- patient will have a slowly resolving "hangover"
- this will be worse the fatter the patient (and the more fat-soluble the drug)

GABA$_A$ – halothane

NMPA – halothane

Twin-pore K^+ channels – halothane

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Which is the best anti-psychotic?

- such drug do not exist
- patients respond individually
- Some patients ~~don't~~ do not respond to any drugs
- side effects may vary
- some patients find particular side effects hard to cope with
- Atypical drug frequently used as first line treatment : risperidone

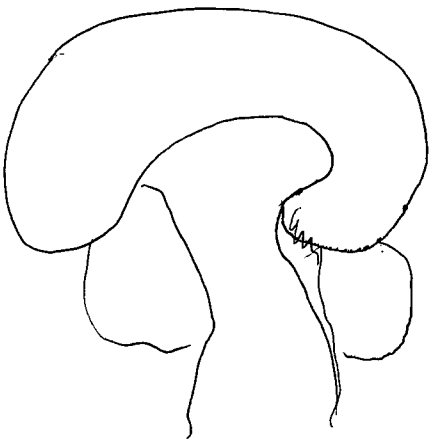
Antipsychotic potency	daily dose
chlorpromazine	100mg
clozapine	300mg
haloperidol	3-5mg
pimozide	2mg
risperidone	4mg
sulpiride	200mg
~~trifluoro~~	
trifluoperazine	1mg

* Potency varies widely, efficacy is very similar (1 or 2 are exception)
↓
clozapine
↳ works better in patients that resist other drugs

Antipsychotics
- 1st generation (typical) – very good at treating +ve symptoms, not -ve symptoms
  ↳ sometimes can get drug-induced -ve symptoms
  – bad side effects
- 2nd (atypical) – very low risk of EPS
  – slightly better at -ve symptoms

Typical
- butyrophenones ①
- phenothiazines ①
- thioxanthines ③
- substituted benzamides
- diphenylbutyl-piperidines

amisulpride – atypical
- clozapine
- olanzapine
- quetiapine
- risperidone
- ~~aripi~~ aripiprazole



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Chlorpromazine

- The 1st effective antipsychotics (Group 1 Phenothiazine)
- Introduced 1952-1954
- "Largactil" Thorazine
- CPZ Eq : Standardisation
- side effects : very sedating, moderate extrapyramidal, neuroleptic malignant syndrome
  muscarinic
  galactorrhea
- derivatives : similar efficacy, differ in side effect profile

Haloperidol

- most commonly used typical
- 'Haldol'
- higher potency than chlorpromazine
- also used as an ~~anaesthetic~~ antiemetic
- variety of formulations
- side effects : lower sedation, lower muscarinic, ↑ risk of EPS, restlessness, neuroleptic malignant syndrome

Risperidone

- atypical antipsychotic
- 'risperdal'
- improves both +ve -ve symptoms
- oral formulation now out to ~~patent~~ patent so very cheap
- also available as I.M. and depot formulations
- side effects : moderate sedation ↑ weight gain, galactorrhea, EPS at higher doses

depot : oily injection into muscle

Quetiapine

- atypical
- 'seroquel'
- side effects
  - ↳ very sedating, causes drowsiness / tiredness
  - ↳ moderate muscarinic effects
  - ↳ moderate weight gain
  - ↳ moderate hypotension
  - ↳ no EPS, galactorrhea

- available in sustainable formulation

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Clozapine-induced agranulocytosis

loss of WBC (suppressed immune system ~1% patients)

↳ infection [treat w antibiotics]

↳ death [4-16% cases]

Clozapine monitoring

- often initiated as in-patient
- white blood cell count
- monitoring - ~~fortnightly~~ (weekly)
  - daily (1 week)
  - weekly (18 weeks)
  - fortnightly (18 weeks)
  - monthly thereafter
- 3 days missed (restart over!)
  of drug

Antipsychotic compliance

- the best medication is of little use unless it is taken
- reasons for non-compliance
  - ↳ lack of belief in illness
  - ↳ side effects
  - ↳ disorganised lifestyle

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Formulations

1) oral (voluntary)
2) intramuscular injection - psychiatry emergency situation
   - involuntary
3) intramuscular depot injection - involuntary
   - disorganised patients

- 2/4 weekly injection
- eliminates covert non-compliances
- sometimes effect delayed
  - ↳ risperidone (Risperdal Consta)
  - ↳ pipotiazine (depot only)
  - ↳ haloperidol
  - ↳ aripiprazole

Non-drug therapies

- 30-40% patients don't benefit from drugs (genetic factors)
- cognitive behavioural therapy (CBT) can be effective (can be combined w other drugs)
- electroconvulsive therapy (ECT)

Antidepressant Discontinuation Syndrome

- Flu-like symptoms, motor and cognitive disturbances when drug is stopped
- usually lasts 1-4 weeks
- particular problem w paroxetine and venlafaxine
- need to taper dose gradually

ECT (producing seizure in brain without major motor effects) → due to pretreatment w muscle relaxants

The oppositional tolerance model

consequence of drug ⟶ ⟵ Response of CNS

- successful in 85% patients w well-defined major depression

→ Indications for ECT

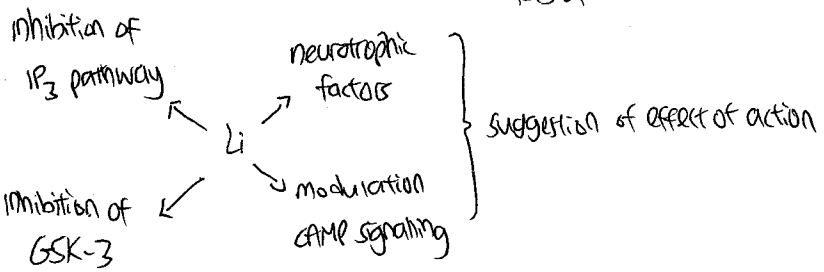
- maybe suicidal
- failed to respond to drugs
- in a debilitating stupor
- suffer other psychotic illness (chance of adverse drug reactions)

Treatment of Bipolar Disorder

- Mood-stabilising drugs
- lithium
- anticonvulsants: [illegible], valproate, carbamazepine
- sometimes give antipsychotics as adjuvant medication eg: risperidone
- occasionally give AD drugs alongside mood stabilisers (may precipitate mania)

Lithium: a mystery

* narrow therapeutic window (need to monitor plasma levels)
lots of adverse effect



Animal models of depression (subject an animal to repeated pain which cannot be escaped)

- chronic stress (pain) → learned helplessness
  ↳ animal does NOT try to escape from pain

Forced Swim Test: normal mouse swim to safety
depression mouse give up

Suspend mouse/tail to induce pain → depression

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