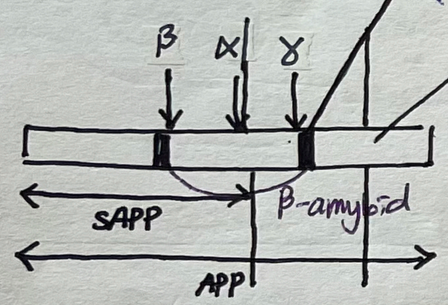
ALZHEIMERS

Pathological Change

- Atrophy at cerebral cortex & hippocampus
- β amyloid plaques
- Neurofibrillary tau tangles
- loss of cholinergic neurones in cortex
- Widened sulki – loss of grey matter

Also GABAergic and monoaminergic neurons.

Aβ plaque formation



① → Early → more Aβ42 production

site of amyloidogenic mutation

within membrane
- transcription factor
- growth factor

Aβ40 – most abundant

Aβ42 – more amyloidogenic

APP (amyloid precursor protein) → large transmembrane glycoprotein

sAPP (soluble amyloid precursor protein)

sAPP production

- cleavage by α secretase produce sAPP (extracellular role)
- then cleavage by γ secretase, liberates C terminal of the protein (intracellular role)

Aβ plaque formation

- β secretase cleave at amyloidogenic mutation site extracellularly
- γ secretase further cleave intracellularly to produce Aβ plaque.
  - → produces Aβ40 plaque
  - → if γ secretase cleave at amyloidogenic mutation – ↑ Aβ42

Amyloid Beta Deposition

Aβ monomer → Aβ oligomer → Aβ fibrils → Aβ plaque

↓

☆ Affect NMDA dependent Ca^{2+} influx
- cause synaptic dysfunction
- disrupt LTP (memory)
- neuronal cell death.

☆ Plaque associated proteins
e.g.) microglia, astrocytes
- inflammatory response to clear plaque
- leads to chronic inflammation
- increased mitochondrial damage + oxidative stress
- neuronal cell death.

☆ Tau neurofibrillary Tangles

→ tau involved in stabilisation + maintenance of MT

→ microtubules – run length of axon, important in axonal transport

→ phosphorylated Tau : detach from MT → depolarisation → loss of axonal transport

→ hyperphosphorylated Tau → aggregated to form paired helical filament (tau tangles) → neuronal cell death.

③ Tau mutation lead to increased phosphorylation
Early
↳ mutation of Tau PPP

Early
② mutation at presenilin 1 (PSEN1)
- component γ secretase → catalytic part
- increases Aβ42 production

LATE
④ ApoE 1~4 (gene) : apolipoprotein
- binds cholesterol
- found in LDL in blood and VLDLs
- → Role in plaque clearance
- → APOE4 less effective w/ clearance
- → APOE4 expression gives increased risk.
  - 2x APOE4 allele1 – greatest risk.

*APOE2 reduces risk

*We get 2 versions of this gene
1 from mum 1 from dad.

☆ Ach pathways :
- nucleus basal → cortex
- septal nuclei → hippocampus.

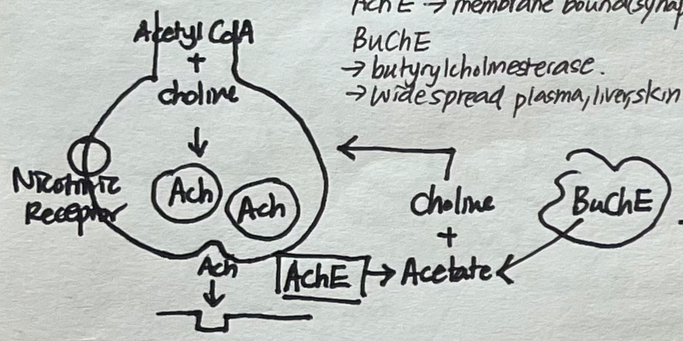
ylcholinesterase Inhibitors – donepezil, rivastigmine, galantamine

→ selective loss of cholinergic neurons – pathophysiology of AD

By using anti-cholinesterase boosting the amount of acetycholine ↑ activity at cholinergic synapse, make up for neuronal loss

- Enhance ACh, by inhibiting the enzyme AChE from breaking down ACh to choline and acetate – stays in synaptic cleft for longer and facilitate down stream action.
- Improves cognitive function in mild, moderate AD → good in early AD before cholinergic neurone damage

AchE → membrane bound (synaptic cleft)
BuChE
→ butyrylcholinesterase.
→ widespread plasma, liver, skin



- Galantamine also inhibit BuChE
  + is a positive allosteric modulator of nicotinic receptors on pre/post

* Nicotinic R at presynpse, modulate positive feedback when Ach binds and cause more Ach to release.
→ more Ach release!

SIDE EFFECTS OF THESE DRUGS ✡Parasympathomimetic✡ cholinergic SE

CVD – • bradycardia ↓ cardiac output, vasodilation (via release of NO)
• Hypotension

SMOOTH MUSCLE – • contraction (except vascular SM) ⊕ nausea ⊕ vomiting ⊕ abdominal pain
→ increased gut motility (diarrhoea) → increased bladder contraction (empty of bladder) urinary incontinence
→ bronchoconstriction (shortness of breath)

EYE – • pupil constriction
→ ciliary muscle contraction (accommodation) – blurred vision
→ decreased IOP (treatment for glaucoma)

Glands – • increased salivation, digestive enzymes etc. ~~✗SWEAT✗~~ → sympathetic increased sweating

Ach
All acting at muscaninic receptors.

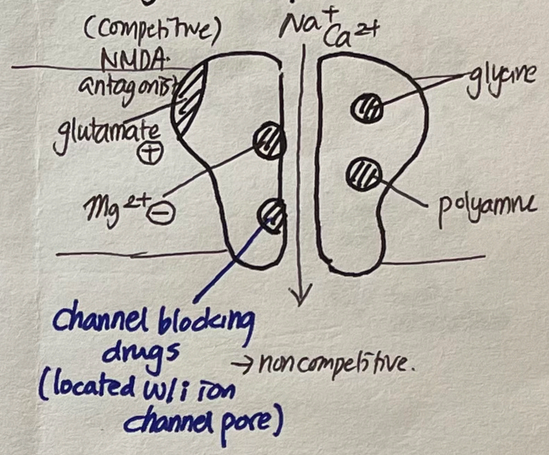
We need more Ach!

Neuromuscular Junction (nicotinic receptor)
→ muscle twitching, by skeletal muscle contraction
muscle spasm / cramps

NMDA antagonist – memantine

need less glutamate!

→ non competitive NMDA antagonist
→ by inhibiting this will limit excitotoxcity → inhibit neuronal cell death (glutamate in excess will cause excitotoxicity) → may cause secondary celldeath.
→ cognitive improvement in moderate – severe AD



Memantine binds to M_2 domain deep inside ion channel pore
'neuroprotective'
→ only work when ion channel is open and can access its pore
'open channel blocker – use dependent'

Carbamazepine, phenytoin.

EPILEPSY

Target 2 Voltage gated sodium channel
→ Blocker

- Use dependent
- inactivated state

Mediate depolarisation of

Uncontrolled repetitive firing of action potential across the brain cause seizures

By blocking the sodium ion channels we can stop action potentials and stop the spread of neuronal activity across the brain

Use dependent: act on cells that are repetitively firing and block inactivated state, making the channel slow to recover from inactivation

- Valproate
- Phenytoin
- Carbamazepine
- Rufinamide
- Lacosamide

Target 3 Voltage gated calcium channel blocker

Allows release of NT for signalling from neurones to neurones tf, by blocking this stop NT firing

- T-type Ca2+ channel blocker
  - Ethosuximide
  - Valproate
  - Clonazepam
- P/Q type Ca2+ channel blocker
  - Gabapentin

Target 4 Glutamate receptor inhibitor

- Phenobarbital
  - also enhance GABA
  - also block Na+ channel

Target 5 AMPA receptor antagonist

- Topiramate
  - also enhance GABA
  - also block Na+ channel
  - also block Ca2+ channel
- Perampanel

Target 6 Synaptic vesicle protein SV2A

- Levetiracetam
  - NT release modulator

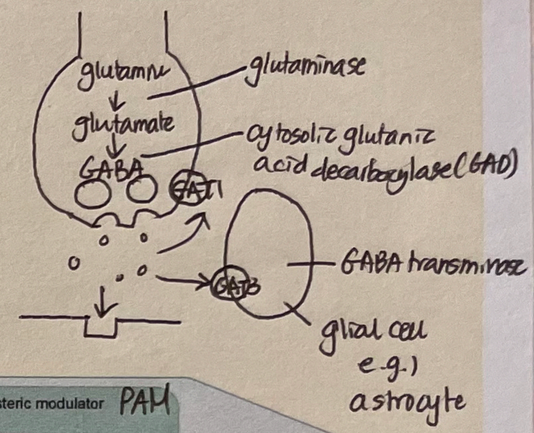
Pathophysiology

- Imbalance in neuronal activity
  - Decrease in GABAa inhibitory activity
  - Increase in glutamate excitatory activity
- Focal seizures
  - Neurones in focal area show sudden depolarisation - 30mV for few seconds, sending burst of action potentials paroxysmal depolarisation shift (PDS)
- Hypothalamus - ANS symptoms
  Reticular system - consciousness
- Absent seizures
  - T type voltage gated calcium channel
  - Oscillatory feedback between cortical and thalamic neurone

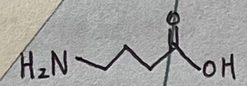
GABA

☆ pentamic ion complex

1. In the presynaptic terminal glutamine is recycled from glial cells and converted to glutamate by glutaminase in the neuronal mitochondria
2. GABA is formed from glutamate by glutamic acid decarboxylase (GAD) w/i the cytosol
3. GABA is loaded into synaptic vesicle by vesicular transporter
4. GABA is released from its vesicle once signal arrives by calcium dependent exocytosis mechanism
5. GABA is now in the synaptic cleft ready to act on post-synaptic receptors or in extrasynaptic regions
6. GABA is taken back up into presynaptic terminal by GAT1
7. GABA is taken back up into adjacent glial cells e.g., astrocytes by GAT3
8. In astrocytes GABA is converted to glutamate by GABA transaminase



Target 1 GABA receptor



1) Enhance GABAa receptor
-> ligand gated ion channel (Cl-)

- Benzodiazepine
  - Positive allosteric modulator PAM
    Increase sensitivity to GABA agonist and allow better efficacy
    Increase the amount of chloride entering, allowing hyperpolarisation, neurones struggle to reach threshold value to reach depolarisation for action potential firing, hence reduced neuronal excitability
    Located between alpha and gamma subunit interface α and γ
    - clobazam
    - Lorazepam
    - diazepam
- Barbiturate
  - Positive allosteric modulator PAM
    Barbiturate bind on channel modulator site
    Enhance chloride influx by leaving to channel to open for longer
    Enhance hyper polarisation - enhancing inhibitory effect of GABA at the post synapse
    - Phenobarbital

Phenobarbital

2) Block GABA degredation

- GABA transaminase: breaks down GABA and synthesise glutamate
  By blocking this there is more GABA in pre-synaptic terminal to inhibit neuronal excitability
  - Vigabatrine
  - Valproate (also increase amount of GABA, mechanism unknown)

Vigabatrine

- In astrocytes GABA is converted to glutamate:
  GABA - succinic semialdehyde - succinate - oxaloacetate - alpha glutamate - glutamate (with the GABA transaminase)

3) Inhibit GABA reuptake

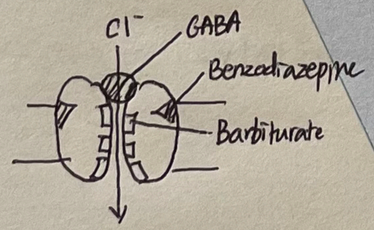
- GABA is taken back up into presynaptic terminal by GAT 1 (GABA transporter 1)
  - Tiagabine
- GABA is taken back into astrocytes to be degraded to glutamate by GAT 3

Tigabine

4) GABA agonist

- GABA site located between alpha and beta subunit interface α and β
  - muscimol
- There are 2 sites within the pentameric ion complex

~~Muscimol~~

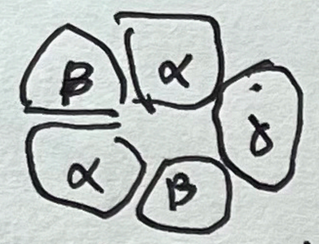


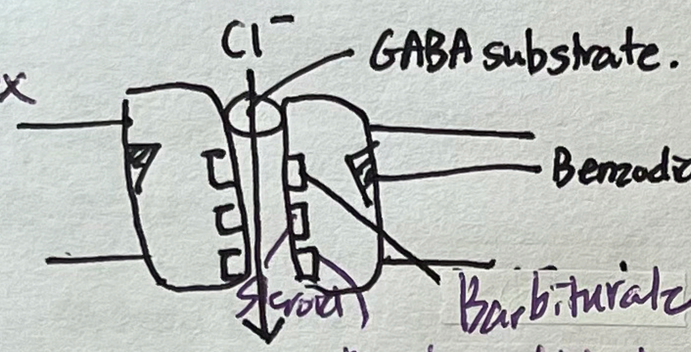
a) Structure of $GABA_A$ Receptor + subunit composition

- pentameric ~~subunit~~ complex

6 α3β3γ

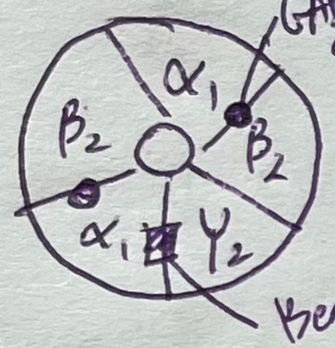
and many others



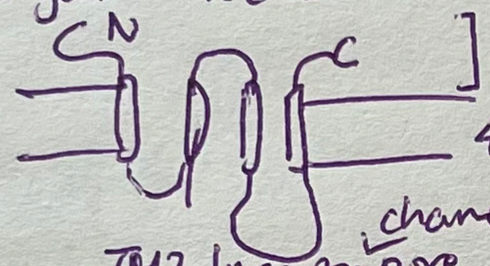


e.g.) diazepam
Lorazepam.

Inhibitory receptor - reduce action potential signaling
- reduce CNS excitability. — cause hyperpolarisation.



→ post synaptically located.
→ ligand gated ion channel. → cis loop



long N termms.
short C termms.
4 Transmembrane.
channel → long intracellular loop.
TM2 lines ion pore.

b) ① Benzodiazepine

When benzodiazepine is attached to the $GABA_A$ Receptor
it keeps the receptor open for longer. allowing influx + better affinity to GABA.
of Cl^- into the postsynaptic cell allowing hyperpolarisation
making action potential signaling harder to reach depolarisation
threshold. By allowing this ~~#~~ less neuronal excitability → seizure subside.

PAM
positive allosteric modulator.
e.g.) diazepam, lorazepam.

② Tigabine is GABA reuptake inhibitor. especially GAT1 at the presynaptic neurone.

~~more GABA~~ more GABA left in synaptic cleft for action at
~~pre synap~~ postsynaptic. Extrasynaptic regions.

Parkinson's Disease

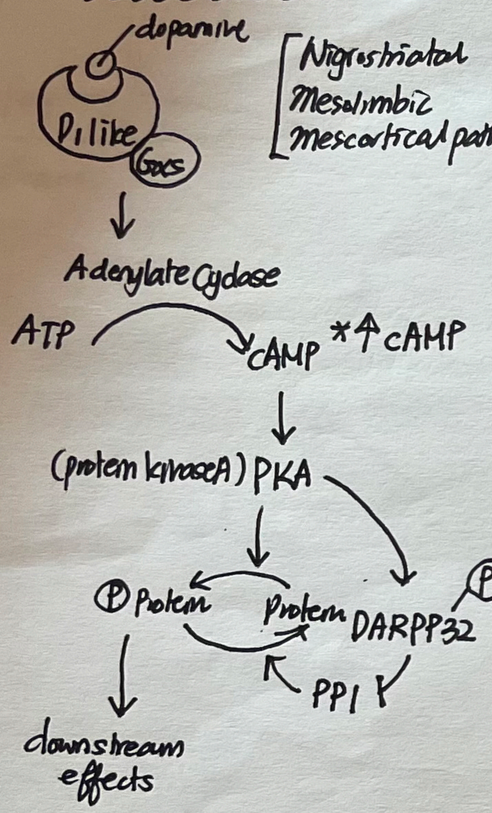
depolarisation (+) in presynapse cause release of NT

Tyrosine → LDOPA → Dopamine → norepinephrine.

- Describe Signalling pathways for D1 and D2 Receptors.

They are both GPCRs with different down signalling

D1 act via Gαs

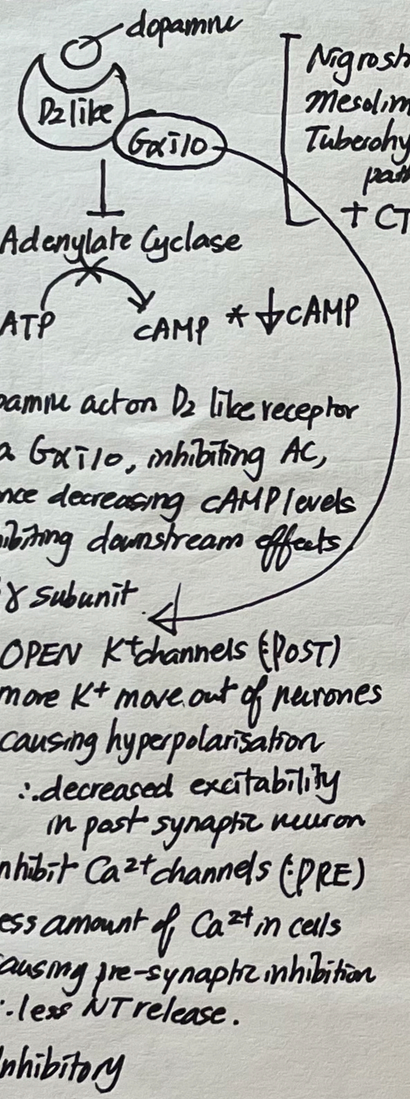


[Nigrostriatal
Mesolimbic
Mescortical pathways]

- Dopamine act on D1 like receptor via Gαs, increasing cAMP levels
- this activates protein kinase A (PKA)
- PKA phosphorylates DARPP-32
- DARPP-32 phosphorylated inhibits protein phosphate 1 (PP1)
- This stops action of PP1, which is dephosphorylating protein
- ∴ more phospholated proteins → increased downstream effects.

*Excitatory (mainly postsynaptic)

D2 act via Gαi/o



[Nigrostriatal
Mesolimbic
Tuberohypophyseal pathways
+ CTZ (medulla)]

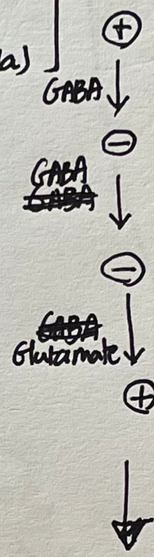
- Dopamine act on D2 like receptor via Gαi/o, inhibiting AC, hence decreasing cAMP levels
- inhibiting downstream effects

*Inhibitory

*Pathophysiology of Parkinson's → loss of dopaminergic neurons in Nigrostriatal pathway

*Nigrostriatal Pathway : most dopamine found here
cell bodies in substantia nigra → striatum

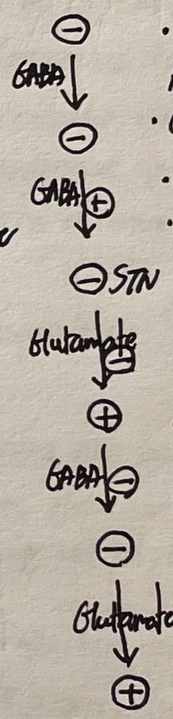
Direct D1 Pathway



- dopamine act on D1 receptors
- stimulate downstream inhibitory ~~neurons~~ GABAergic neurons
- from substansia nigra to striatum
- the inhibitory GABA neurotransmitter released from GABA neurons
- further inhits GABA neurons.
- In the end stimulating the neurons to the Motor cortex from the thalamus
- ∴ Stimulate movement

- dopamine act at D1 Receptor
- stimulating the downstream inhibitory GABAergic neuron
- This neuron releases inhibitory GABA NT
  ∴ inhibiting the further GABAergic neuron from substantia nigra to the thalamus
- By inhibiting the inhibitory neuron, it stimulates the glutamatergic neurone from the thalamus to the motor cortex
- Resulting in purposeful movement

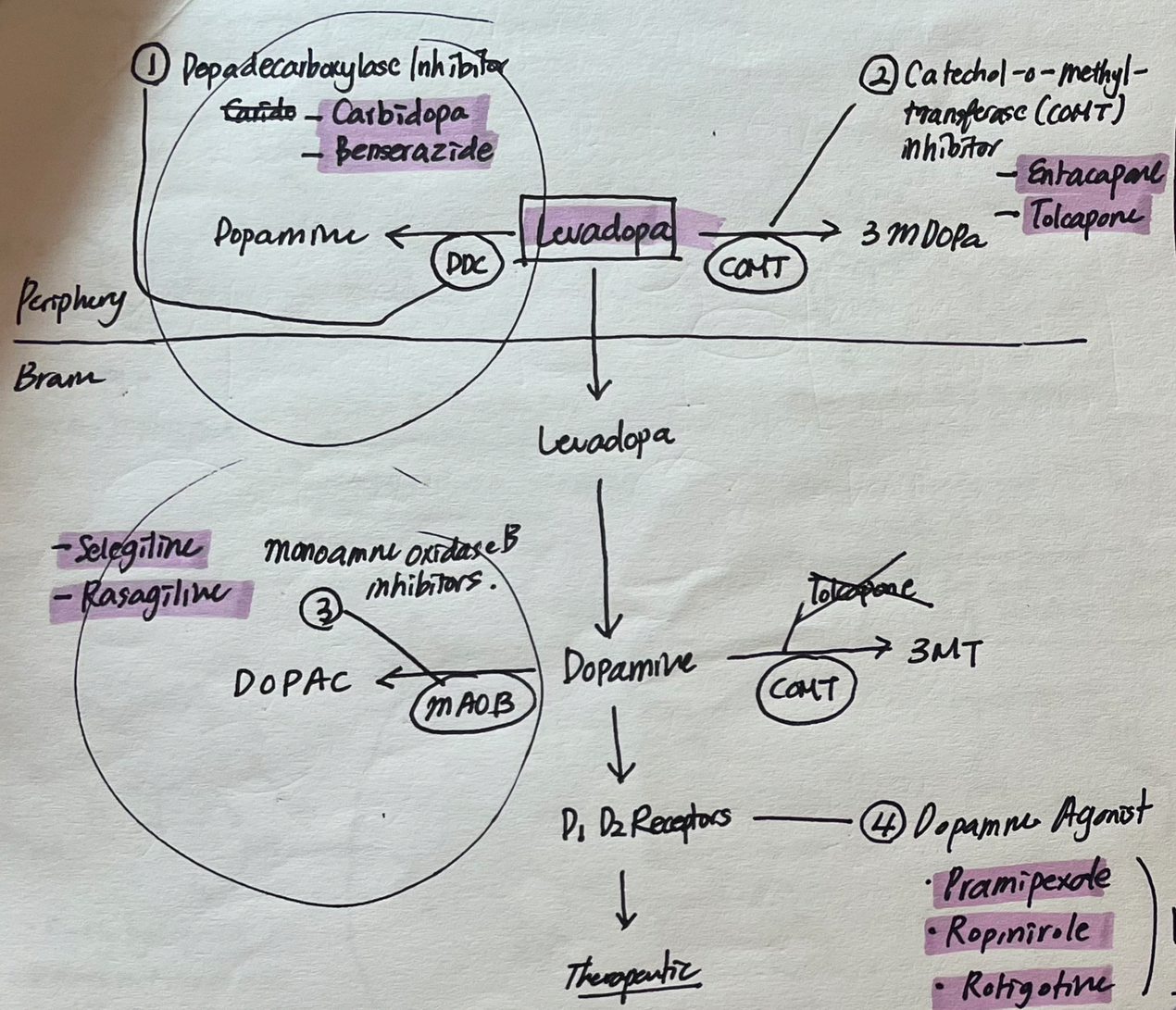
Indirect D2 Pathway



- Dopamine released from nigrostriatal pathway act on D2 receptors
- ~~GABAergic neuron~~
- Inhibitory GABAergic neuron is inhibited.
- Thus stimulating the next GABAergic neuron to STN (subthalamic nucleus)
- Glutamatergic neuron from STN to substantia nigra is inhibited.
- Inhibited stimulatory neurones causes the GABAergic neuron from substantia nigra to thalamus to be inhibited.
- By inhibiting the inhibitory neuron stimulates the glutamatergic neurone from thalamus to the motor neuron
- ∴ Resulting in purposeful movements.

We need more dopamine!

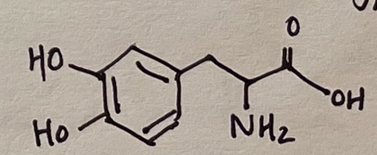
Pharmacological Rationale for using peripheral DOPA decarboxylase Inhibitor together w/ Levadopa.



- Levadopa is first line agent in treatment of PD, a pre-cursor of dopamine
- In PD, we lose dopaminergic neurons (nigrostriatal pathway) and this will replace the dopamine loss.
- Can be given orally, absorbed ~~then~~ peripherally, then cross BBB where dopamine is synthesised by the enzyme dopa decarboxylase.
- However, this enzyme is also present peripherally. DDC and it breaksdown Levadopa to Dopamine.
- Which, increases peripheral dopamine levels leading to side effects. such as nausea, vomiting, headache, dizziness and cardiac arrhythmia.
  → sympathetic ~~side effects~~ prolonged ↑ s/E. ↑HR, vasoconstriction
- To reduce this side effects it is recommended to take a dopadecarboxylase inhibitor with Levadopa
  e.g.) Carbidopa, Benserazide

MED CHEM *
- Dopamine not given, but L Dopa given because dopamine is highly protonated at physiological pH, meaning, cannot cross BBB

BTB
L-Dopa less protonated – actively transported into brain by ~~LNAA transporter~~ LAT1
L type amino acid transporter.
→ carrier mediated transporter.



L Dopa.

- D2 selective
- Pramipexole
- Ropinirole
- Rotigotine
- Bromocriptine
- Apomorphine

× selective, more side effects.

BRAIN

Add on therapy

- Amantadine (NMDA Receptor Antagonist)
- mAChR (muscarinic antagonist)
  - Procyclidine
  - Orphenadrine
  - Trihexyphenidyl

Rarely used due to side effects

Anticholinergic S/E
– dry mouth, mydriasis (blurred vision), tachycardia, agitation, constipation, hot flushed skin
→ sympathetic s/E, due to blockade of parasympathetic. (not sweat gland – sympathetic)

Schizophrenia

☆Due to neurochemical imbalance – DA, Glu
↳ ACh, 5-HT, GABA

Pathophysiology
- ↑ ventricle size ↓ grey matter
- ↓ white matter (↓ oligodendrocyte that make myelin sheath)
- altered activity in dorsolateral pre frontal cortex (decision making)
  + ventromedial pre frontal cortex (emotional)
  + amygdala (emotion) + hippocampus (memory)

DOPAMINE HYPOTHESIS

We need less dopamine!

1) Overactivity of dopaminergic neurons in mesolimbic pathway → + symptoms
   VTA → hippocampus, amygdala (behavioural)

2) Decreased activity of dopaminergic neurons in mesocortical pathway → – symptoms
   VTA → frontal cortex (cognition, thoughts)

☆
↑ activity in mesolimbic pathway ↑ + symptoms
↓ activity in mesocortical pathway ↑ – symptoms

⇒ ↑ Dopamine → ↑ pyschosis
↓ Dopamine → ↓ pyschosis

(
- amphetamine / cocaine ↑ dopamine → cause psychosis
- D2 agonist exacerbate psychosis → PD treatment S/E hallucination
)

ALL ANTIPSYCHOTICS BLOCK D2 RECEPTORS

GLUTAMATE HYPOTHESIS

☆Glutamate is the fundamental NT imbalance that underlines schizophrenia

☆Decreased activity at glutaminergic synapses in pyramidal neurons in pre-frontal cortex leads to reduced signalling via NMDA R
→ Pyramidal neurons downstream is mesolimbic and mesocortical pathways.
→ reduced NMDA R signalling ↑ activity at mesolimbic, ↓ activity at mesocortical

↓ Glutaminergic neurons in pyramid neurons ↓ NMDA R signalling
↳ ↑ mesolimbic pathway activity ↑ + symptoms
↳ ↓ mesocortical pathway activity ↑ – symptoms

We need more glutamate!

TREATMENTS

→ all act at D2 R (mesolimbic pathway to ↓ + symptoms)
→ also at 5HTR, adrenergic R, muscarinic R, histamine R

S/E of blocking D2 Rs

☆ D2 R is inhibitory ☆

① Nigrostriatal Pathway
– EPSE S/E (motor)
- Parkinsonism (tremor, rigidity)
- Akiathisia (inner restlessness)
- Dystonia (muscle spasm)
- Tardive dyskinesia (involuntary face limbs)

} Acute

② Tuberoinfundibular Pathway
– hyperprolactinaemia ↑ prolactin production
(bc DA usually inhibits secretion via D2 R)
- breast development, lactation, pain
- irregular menstrual, ↓ fertility
- sexual dysfunction

③ Mesocortical pathway
– blocking an already inhibitory pathway
– ↑ negative symptoms

④ Mesolimbic Pathway
– inhibition of reward pathway
– ↓ psychosis, but ↑ negative symptoms

Other S/E

- NMS : neuroleptic malignant syndrome
- Prolonged QT interval – arrhythmia
- Blood disorder : neutropenia (neutrophil ↓)
  agranulocytosis (WBC ↓) > Clozapine monitor WBC

Metabolic Syndrome (
- Weight gain 2 week 2 kg
- Insulin resistance
- Hyperlipidemia.
)

(
- NMDA antagonist (e.g.) Ketamine) → cause psychosis, negative symptoms, cognitive symptoms
- changes in glutamate R and VGLUT + decrease in post-synaptic density
- structural changes in pyramidal neurons.
)

GENES → neuronal development, synaptic formation, maintenance, function

① GRIN2A NMDAR
② GRIA3 AMPAR
> gene coating

③ DAAO and DAOA (AA turnover e.g.) d serine NMDA modulator)
④ CACNA1G (VGCC α subunit)
⑤ Dysbindin (synaptic structure)
⑥ Neuregulin (neuronal development)
⑦ COMT and MAO
⑧ DRD2 (D2 Receptor)
⑨ RGS4 (GPCR signalling)

SGA Pharmacology

workby: ...

* Antagonist of 5HT2AR
  1. Increased DA release in striatum
     → help w/ EPSE, bc even though D_2 is blocked, increased level of dopamine + D_1 isn't blocked so good yea.
     ↳ excitatory Receptor!
  2. Inhibition of 5HT2A
     → 5HT increase prolactin secretion, by inhibition, decreases secretion ∴ help w/ hyperprolactinaemia S/E
  3. Increase glutamate release in pyramidal cells
     → increased glutamate levels in synapse in cortex help w/ positive + negative + cognitive function

e.g.) Clozapine
Olanzepine

- Risperidone – D_2 selectivity or D_1
  ↳ more associated w/ positive symptoms

- Sulpiride – D_2 receptor antagonist

Quetiapine – Rapid dissociation from D_2R
↳ antagonism not enough to cause EPSE

Aripiprazole – Partial agonist at D_2
↳ needs to be just right, may exacerbate mesolimbic positive symptoms or if too little stimulate EPSE and endocrine SE

↓

Stimulate D_2R, not shutting down other signalling pathways but control mesolimbic overactivity

used to be
first to treat parkinsons bc if low dopamine Ach unopposed

* Muscarinic Receptor Antagonist → help w/ reduce EPSE

S/E
- → cause anticholinergic S/E
  dry mouth, dry skin, tachy-cardia, constipation etc...
- → adrenergic 1 antagonism (constriction of vascular sm)
  - postural hypotension
- → H_1 antagonism
  - sedation

FUTURE
- NMDA AMPA allosteric modulators
  → NMDA agonist at glycine site can ↑ NMDA activity
  → more chance of depolarisation – neuronal excitation (good?)
- mGluR / 5HT2R heterodimer.