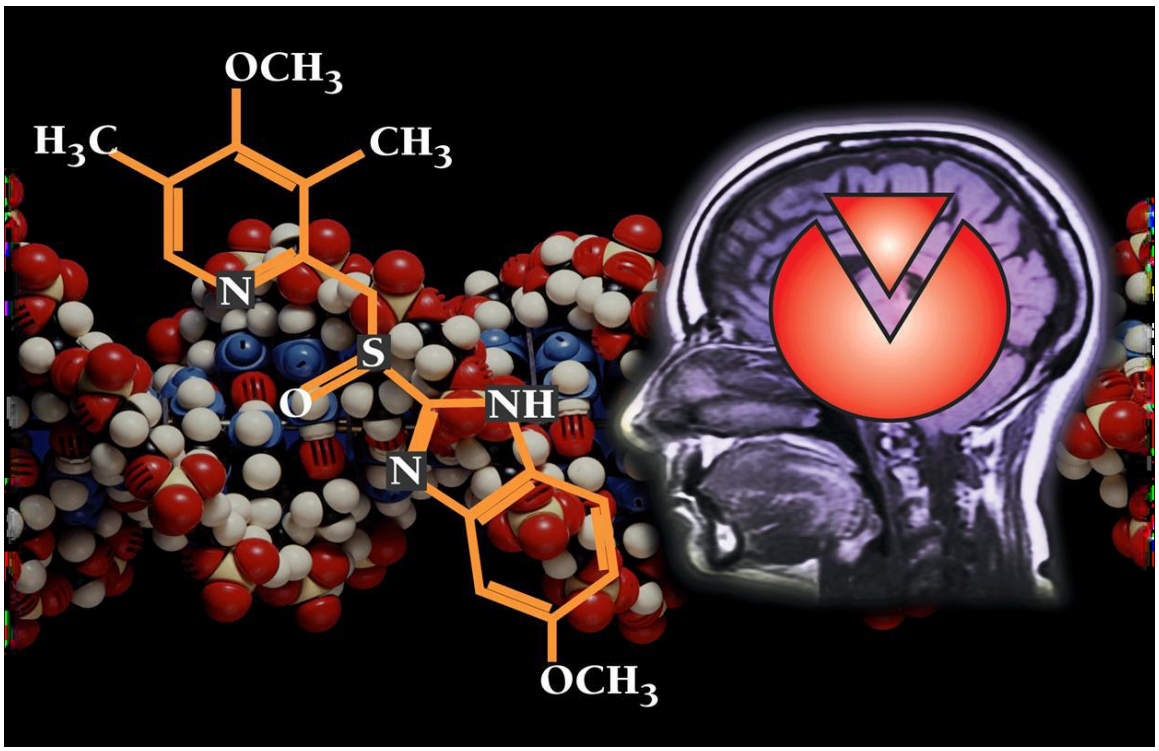
King Saud University
College Of Medicine
Pharmacology Team 430
CNS Block

Antidepressants (Old generation)



Done By:

Mohammed Aldohan

Hissah Alballa

Anfal Alshaya

Arwa Abudawood

Introduction:

- The concept of action of all drugs relay on increase of extracellular biogenic amines (e.g. serotonin and NE) in the brain indirectly by blocking their catabolism (metabolic breakdown) OR directly by preventing their uptake + altering receptor firing.

Most clinically useful antidepressants potentiate the action of 5-HT and NE in the brain. This led to the biogenic amine theory, which proposes that depression in due the deficiency of monoamines, such as NE and 5-HT, at certain sites in the brain.

- **All drugs take weeks to manifest their clinical effect [to control depressive manifestations], even though their pharmacological actions starts immediately**. indicating that secondary adaptive changes must occur before the benefit is gained
- The delay presents>>time needed for inhibitory somatodendritic autoregulatory $5HT_{1A}$ receptors or axonal autoregulatory $5HT_{1D}$ to be sensitized [down regulated] to permit more synthesis & release of transmitter at synaptic cleft with enhanced signaling at postsynaptically serotonergic & adrenergic > (β) neurons → therapeutic effect.

The delay present suggests that decrease uptake of neurotransmitter is only an initial effect of the drug, which may not be responsible for the antidepressant effect. It has been proposed that presynaptic inhibitory receptor (e.g. 5-HTA1 and 5-HTD1) densities in the brain decrease over 2- to 4-week period with the use of antidepressant drugs. After this down regulation of inhibitory receptors there will be greater synthesis and release of neurotransmitters into the synaptic cleft and make signaling more powerful in the post synaptic neuron. presynaptic inhibitory receptor sense neurotransmitter then it sends inhibitory signals to the postsynaptic neurons that prevent the further release of neurotransmitter vesicles from the presynaptic neurons

- **Treatment should continue. 6 months at full therapeutic doses before withdrawal.**
- Withdrawal of drugs must be very gradual otherwise >>withdrawal symptoms : Agitation, Worsening of the disease and Withdrawal manifestation

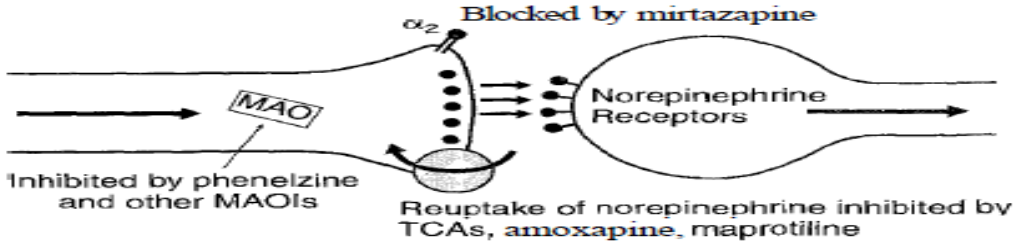


Figure IV-1-10. Antidepressants and Noradrenergic Transmission

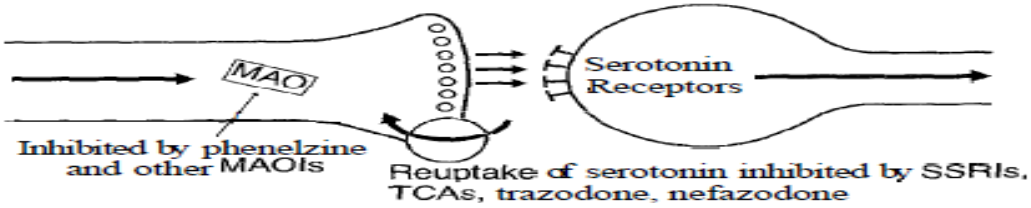


Figure IV-1-11. Antidepressants and Serotonergic Transmission

Mechanism of Action of Antidepressants

1) Inhibition of reuptake of NE and or 5-HT or increases the release of NE or 5-HT.
2) Desensitization (down-regulation) of β-adrenoceptors (decrease c-AMP). **(Very important and related to clinical response).**

Why does it take three weeks to see significant effects of Antidepressants?

Because it takes two weeks to desensitize β-adrenoceptors

How do SSRIs desensitize β-adrenoceptors?

Serotonin will indirectly increase the adrenergic action.

1-Monoamine oxidase inhibitors:

- MAO is a **mitochondrial enzyme** found in nearly all tissues

Two forms of monoamine oxidase exist:

- **MAO-A** responsible for **NE, 5-HT catabolism**. It also metabolizes tyramine of ingested food.
- MAO-B is more selective for **dopamine metabolism.**

MONOAMINE OXIDASE INHIBITORS:

- History: The anti TB **Iproniazide** exhibited mood elevating properties and latter found to inhibit **MOA.**

- **Non Selective Inhibitors (MAO-A & MAO-B):**

Irreversible :**Phenelzine,** long acting [persists 2w after stop]
Reversible: **Tranylcypromine**, [persists 7 days after stop]

- **Selective Reversible Inhibitors:**

Moclobemide, (MAO-A) used in depression

selegiline, (MAO-B) used in Parkinson

Seldom used now because;

- ADR, Food & Drug Interactions
- Low antidepressant efficacy = Low benefit/risk ratio

i.e their benefits are little compared to their hazards

Pharmacokinetics :

All are well absorbed, metabolized & excreted in urine

Mechanism of Action:

* MAOIs decrease activity of MAO, thus preventing monamine break down of NE & 5HT so increase its availability indirectly
* Possess both α Adrenoceptor & mAch blocking effects **(so there will be antiadrenergic and anticholinergic side effect)**

Indications:

MAOIs :now only reserved in atypical depression and depression resistant to other therapy
In treatment of social anxiety (agrophobia) but 1st choice is beta blocker

ADRs:

- Antimuscarinic effects.
- 2- Postural hypotension.**(antiadrenergic side effect)**
- 3- Sexual dysfunction mainly with **phenelzine.**
- 4- Sedation, sleep disturbance.
- 5- Weight gain mainly with **phenelzine.**
- 6- Hepatotoxicity (with **phenelzine)**
- **Weight loss with Tranylcypromine**

Food interactions:

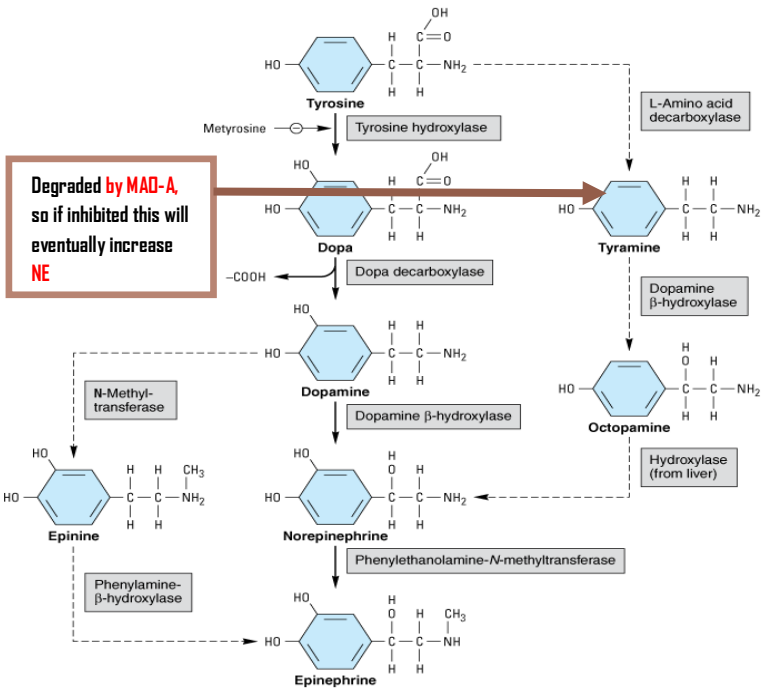
Many foods containing tyramine are normally degraded in the gut by MAO-A
MAOIs inhibit this process, so tyramine is absorbed and then taken up into adrenergic neurons >>converted into a false transmitter >>replaces NE in vesicles & when massively released>>

Results in hypertensive crisis.

Individuals taking MAOI aren't able to degrade tyramine(an amino acid) received from diet. tyramine causes the release of large amount of catecholamines, resulting in hypertension.

So avoid foods rich in

Tyramine ; Aged cheese, liver, sausages, fish , some meat & yeast extracts.
Levodopa ; Broad beans, FAVA beans.



Drug interactions:

1**. If with** (indirect acting sympathmimetic, flue medications, local anesthetics & TCA)>>severe hypertension >> hypertensive crisis
2**- If with SSRI (**because both increase serotonin level) >> fatal serotonin syndrome [hyperthermia, muscle rigidity, cardiovascular collapse], so keep 6 weeks space between their use
3- If with pethidine >>inhibition of metabolism
>> ↑ its levels >> leads to hyperpyrexia, irritability, hypotension and coma.

2-Tricyclic antidepressants:

1st Generation Tricyclic Antidepressants >>have three-ring nucleus structure

Tertiary amines:
Block 5HT& NE reuptake
More side effects
Imipramine (Tofranil)
Amitriptyline (Elavil)
More selective to 5-HT
-Doxepin,Clomipramine

Secondary amines:
More selective to NE
Fewer side effects
Desipramine (Norpramin)
Nortriptyline (Pamelor)

Mechanism of Action:

- **Inhibit neurotransmitter reuptake by presynaptic neuron** :block NE and 5-HT reuptake into neurons so increase availability directly
- Block ADR (α1), Histamine (H1) & Ach (M1)receptors.

Pharmacokinetics:

- Given once daily
- Some of them give active metabolites
  Imipramine >> Desipramine
  Amitriptyline >> Nortriptyline
- **Highly bound to plasma proteins(highly concentrated to tissues → No dialysis if toxicity)**

Clinical Indications:

Used for long duration without loss of effectiveness [preferable to MAOIs]

- Elevate mood
- Improve mental alertness.
- Increase physical activity

1- Treatment of depression;

- With lithium in depressed phase of bipolar depression
- In resistant depression if other therapy fail
-With antipsychotics in depressed psychotic patients.

2-Other psychiatric disorders;

- Obsessive-compulsive disorders (OCD)
  (OCD: decrease of DA & NE in the brain's prefrontal cortex.)
- Generalized anxiety disorders
- Panic disorders
- Anorexia nervosa

3-Other disorders;

- Control bed-wetting in children; **Imipramine** >> contraction of
- Internal sphincter of bladder. Better desmopressin **(antidiuretic)**
  Gradually withdrawn / Treatment period do not exceed 3 months.
- Neuropathic pain; better Tertiary amines >>modulate endorphins
  Give in smaller doses than that prescribed for depression.
- Prophylaxis of migraine

ADRs:

- **Anti-cholinergic:** Dry mouth, blurred vision, constipation & urine
- retention, aggravation of glaucoma
- Anti-histaminic: **Sedation, confusion.** Stop sedatives 1-2 w before use
- Anti-adrenergic (>α)>> C.V.S ; **Postural hypotension, arrhythmias**
- conduction defects (prolonged Q-T interval - heart block)
- Weight gain, sexual dysfunction & impotence
- Lower seizure threshold
- Aggravation of psychosis

- Hypomania

EARLY IN USE >>During 1st month >> aggravate suicidal thoughts specially in young aged. Can happen less upon change of dose.

DURING USE: >>narrow therapeutic index >> toxicity can develop

Excitement, delirium , convulsions, respiratory depression , coma, atropine like- effects, cardiac arrhythmias, sudden death. NO DIALYSIS

STOPAGE OF USE: Withdrawal Symptoms; characterized by **cholinergic rebound, flu-like symptoms.**

Interactions:

- Being strongly bound to plasma proteins their toxicity is increased by other drugs that are too highly bound to Plasma Protein as aspirin, phenylbutazone, ….etc Because they displace them from their protein binding sites >> so level of free form rise in blood. Vice versa, TCAs can induce elevation in aspirin or phenylbutazone blood levels.
- Being metabolized by hepatic microsomal enzymes >>toxicity enhanced by enzyme inhibitors. enzyme inhibitors will inhibit its metabolism in the liver >> its level in the blood will increase
- With MAOIs, SSRIs or any sympathomimetic drugs >>cause hypertensive crisis
- Additive to sedatives or other CNS depressants >> depress respiration
- Additive to antipsychotics & anti-parkinsonisms>> increase anti- cholinergic effects.

Contraindications :

- Glaucoma **because of its anticholinergic effect**
- Heart disease **because of its anti-adrenergic effect**
- Liver disease **because the liver is where the drug is being metabolized**
- Seizure disorder **because it lower seizure threshold**
- Thyroid disease
- Prostate hypertrophy **because it causes contraction of internal sphincter muscle**
- Pheochromocytoma
- Chronic bronchitis **because of its antihistaminic effect**