MAO inhibitors

Phenelzine
Tranylcypromine
Moclobemide
Mechanism of action of MAO inhibitors

A Trasmissione monoaminergica normale

La MAO inattiva le monoamine (noradrenalina, serotonina e dopamina) che fuoriescono dalle vescicole sinaptiche.

Noradrenalina
Serotonina
Dopamina

Vescicola sinaptica

Metaboliti inattivi

MAO

NEURONE POST-SINAPTICO

Risposta postsinaptica

B Effetto degli inibitori della MAO

Gli inibitori della MAO impediscono l’inattivazione delle monoamine all’interno del neurone, facendo in modo che nella fessura sinaptica diffonda un eccesso di neurotrasmettitore.

Noradrenalina
Serotonina
Dopamina

Vescicola sinaptica

Metaboliti inattivi

NEURONE POST-SINAPTICO

Risposta postsinaptica
<table>
<thead>
<tr>
<th></th>
<th>Type A</th>
<th>Type B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preferred substrates</td>
<td>Noradrenaline</td>
<td>Dopamine</td>
</tr>
<tr>
<td></td>
<td>5-Hydroxytryptamine</td>
<td>Phenylethylamine</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Benzyllamine</td>
</tr>
<tr>
<td>Non-specific substrates</td>
<td>Tyramine</td>
<td>Tyramine</td>
</tr>
<tr>
<td>Specific inhibitors</td>
<td>Clorgyline</td>
<td>Selegiline</td>
</tr>
<tr>
<td></td>
<td>Moclobemide</td>
<td></td>
</tr>
<tr>
<td>Non-specific inhibitors</td>
<td>Pargyline</td>
<td>Pargyline</td>
</tr>
<tr>
<td></td>
<td>Tranylcypromine</td>
<td>Tranylcypromine</td>
</tr>
<tr>
<td></td>
<td>Isocarboxazid</td>
<td>Isocarboxazid</td>
</tr>
</tbody>
</table>
Monoamine oxidase inhibitors (MAOI)

- Main examples are phenelzine, tranylcypromine, isocarboxazid and moclobemide.
- For many years superseded by tricyclic antidepressants (TCA), mainly because of drug and food interactions; currently undergoing a revival.
- Action is long lasting (weeks) because of irreversible inhibition of MAO. Moclobemide has a short duration of action. Reversible binding
- Main side-effects: postural hypotension (sympathetic block); atropine-like effects (as with TCA); weight gain; CNS stimulation, causing restlessness, insomnia; liver damage (rare).
- Acute overdose causes CNS stimulation, sometimes convulsions.
- May cause severe hypertensive response to tyramine-containing foods (‘cheese reaction’); this does not occur with moclobemide.
- MAOI should not be given simultaneously with TCA or 5-HT reuptake inhibitors (SSRI).
- Interact with many drugs (e.g. pethidine, causing hyperpyrexia and hypotension.)
Major interactions with other drugs
<table>
<thead>
<tr>
<th>Antidepressivo</th>
<th>Interazioni pericolose</th>
<th>Interazioni di modesta rilevanza</th>
</tr>
</thead>
<tbody>
<tr>
<td>IMAO</td>
<td>amfetamine, TCA, atomoxetina, β₂-agonisti, trimetazodina, bupropione, buspirone, ciploretamina, cocaina, destrometorfano, dopamina e dopaminomimetici, droperidolo, efedrina, entacapone, fenfluramina, ipero, levodopa, litio, mazindol, meperidina, metildopa, metilfenidato, morfina, nefazodone, nefopam, sibutramina, SSRI, tolcapone, tramadol, triptani</td>
<td>antidiabetici, barbiturici</td>
</tr>
<tr>
<td>TCA</td>
<td>analgesici oppiacei, anestetici generali alogenati, antiaritmici di classe I e III, SSRI, antipertensivi, antimicotici, imidazolici, antipsicotici, antivirali, chinolonici, antibiotici macrolidici, cotrimossazolo, IMAO, linezolid, octreotide, primidone, rifampicina, simpaticomimeticici, triptani, alcool</td>
<td>clonidina, alfametildopa, ansiolitici, ipnotici, β₂-agonisti, anticoagulanti orali, antiepilettici, antimuscarinici, primidone, β-bloccanti, calcio-antagonisti, cannabinoidi, carbamazepina, cimetidina, ipero, miorilassanti, nitroderivati</td>
</tr>
<tr>
<td>SSRI</td>
<td>analgesici oppiacei, desfenfluramina, destrometorfano, droperidolo, IMAO, ipero, sibutramina, tramadol, trazodone, triptofano, triptani</td>
<td>alcool, anestetici, antiaritmici, anticoagulanti orali, antiepilettici, antipsicotici (escluso il droperidolo), anti-H2, barbiturici, β-bloccanti, bupropione, buspirone, cannabinoidi, ciploretamina, clozapina, litio, teofillina, TCA</td>
</tr>
</tbody>
</table>
Side effects of antidepressants

- Citalopram
- Escitalopram
- Fluoxetine
- Fluvoxamine
- Paroxetine
- Sertraline

- Venlafaxine
- Duloxetine

- Bupropione
- Mirtazapina
- Nefazodone
- Trazodone

- Amitriptilina
- Amoxapina
- Clomipramina
- Desipramina
- Doxepina
- Imipramina
- Maprotilina
- Nortriptilina
- Protriptilina
- Trimipramina

- Fenelzina
- Tranilcipromina
<table>
<thead>
<tr>
<th></th>
<th>SSRIs (Selective serotonin reuptake inhibitors)</th>
<th>TCAs (Tricyclic antidepressants)</th>
<th>MAOIs (Monoamine oxidase inhibitors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset of action</td>
<td>slow</td>
<td>slow</td>
<td>slow</td>
</tr>
<tr>
<td>Initial exacerbation of anxiety</td>
<td>+/-</td>
<td>+/-</td>
<td>-</td>
</tr>
<tr>
<td>Therapeutic tolerance</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Withdrawal</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Abuse potential</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Interactions with ethanol</td>
<td>+</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Dietary restrictions</td>
<td>-</td>
<td>-</td>
<td>+++</td>
</tr>
<tr>
<td>Sedation</td>
<td>-</td>
<td>++</td>
<td>-</td>
</tr>
<tr>
<td>Overdose risks</td>
<td>-</td>
<td>++</td>
<td>++</td>
</tr>
</tbody>
</table>
SEROTONIN SYNDROME

- At least three of the following symptoms must be present following dose increase of a compound acting by elevating serotonergic function or following its association with other drugs:
  - Agitation
  - Behavioural abnormalities (confusion, hypomania)
  - Hypertension, tachycardia
  - Myoclonus
  - Hyperreflexia
  - Excessive sweating
  - Shivering
  - Tremors
  - Diarrhea
  - Lack of coordination
  - Fever

MAO-I and SSRI
Interaction between MAO-I, tricyclic and other drugs

- Tricyclic Anticholinergic actions
  - MAO inhibitors (tranylcypromine, moclobemide, phenelzine, isocarboxazide)
  - tyramine (food)
    - Sympathomimetic agents
      - bupropion, SSRI

- antiparkinson
- antipsychotic
Citocrome P450 (CYP)

- **CYP1A2**: β antagonist, caffeine, specific antipsychotic, tricyclic antidepressant
- **CYP2C9**: carbamazepine
- **CYP2C19**: barbiturate, imipramine, propranolol, phenitoine
- **CYP2D6**: β antagonist, specific antipsychotic, tricyclic antidepressant
- **CYP3A3/4**: benzodiazepine, carbamazepine, antidepressant, antibiotic
Increase or reduction of antidepressant effects:

✓ Plasma proteins
- The binding between TCA and plasma proteins is decreased due to competition with: fenitoina, fenibutazone, aspirina, aminopirina, scopolamina, fenotiazine

✓ Microsomal Enzymes CYP
- Barbiturates, antiepileptics (carbamazepina), smoking, induce CYP enzymes
- SSRI competes with the metabolism of TCA and inhibits CYP (higher plasma concentration of TCA)
- Slow and ultra-rapid metabolizer (prodrugs)
Interaction between antidepressants and alcohol

Acute Alcohol
- Antidepressants enhance sedative action of alcohol
- Increased duration of action of antidepressants

Chronic Alcohol
- Increased elimination of antidepressants
Hypericum perforatum, St John’s wort

Hyperforin

Mechanisms of action
Inhibition of MAO, inhibition reuptake 5HT, NA, DA, GABA, Glu

Collateral mechanisms
Substrate glycoprotein P and induces activity (intestine, kidney, liver, testicles, brain, blood)
Induction of CYP3A4 e CPY1A2

Interactions

ciclosporina
digossina
teofillina
indinavir
warfarina
amitriptilina
contraccettivi
paroxetina
Glycoprotein P (PGP)

- **Limitation of drug absorption:** transfer of the drug from the enterocytes to the intestinal lumen and elimination of the drug with the faeces

- **Active drug elimination:** a) drug transfer from proximal tubule cells to the tubular lumen and drug elimination in urine; b) drug transfer from hepatocytes to bile

- **Limitation of drug distribution to tissues:** a) drug transfer from the endothelial tissue of the testis and brain to the blood capillaries; b) drug transfer from fetal tissue or capillaries to the syncytium trophoblast on the maternal side of the placenta and from there to the maternal blood; c) drug transfer from lymphocytes (e.g., CD4+) to the blood
Bipolar disorder

- Maniac episodes followed by depression (1% of population)
- Significant genetic component (10-15%)
- Young, adult and older people can be affected
Bipolar I Disorder

Diagnostic Criteria

For a diagnosis of bipolar I disorder, it is necessary to meet the following criteria for a manic episode. The manic episode may have been preceded by and may be followed by hypomanic or major depressive episodes.

**Manic Episode**

A. A distinct period of abnormally and persistently elevated, expansive, or irritable mood and abnormally and persistently increased goal-directed activity or energy, lasting at least 1 week and present most of the day, nearly every day (or any duration if hospitalization is necessary).

B. During the period of mood disturbance and increased energy or activity, three (or more) of the following symptoms (four if the mood is only irritable) are present to a significant degree and represent a noticeable change from usual behavior:

1. Inflated self-esteem or grandiosity.
2. Decreased need for sleep (e.g., feels rested after only 3 hours of sleep).
3. More talkative than usual or pressure to keep talking.
4. Flight of ideas or subjective experience that thoughts are racing.
5. Distractibility (i.e., attention too easily drawn to unimportant or irrelevant external stimuli), as reported or observed.
6. Increase in goal-directed activity (either socially, at work or school, or sexually) or psychomotor agitation (i.e., purposeless non-goal-directed activity).
7. Excessive involvement in activities that have a high potential for painful consequences (e.g., engaging in unrestrained buying sprees, sexual indiscretions, or foolish business investments).

C. The mood disturbance is sufficiently severe to cause marked impairment in social or occupational functioning or to necessitate hospitalization to prevent harm to self or others, or there are psychotic features.

D. The episode is not attributable to the physiological effects of a substance (e.g., a drug of abuse, a medication, other treatment) or to another medical condition.

**Note:** A full manic episode that emerges during antidepressant treatment (e.g., medication, electroconvulsive therapy) but persists at a fully syndromal level beyond the physiological effect of that treatment is sufficient evidence for a manic episode and, therefore, a bipolar I diagnosis.
Lithium mechanisms of actions
(Chronic treatment)

- Therapeutic doses:
  - 0,5-1 mmol/L
  - 1,5 mmol/L (toxic)

- Simil – Na+
  - No pump Na+/K+

- Inhibition hydrolysis of IP

- Inhibition kinases
  - Glycogen synthase

- Inhibition cAMP PKC
Mechanism of action of Li⁺

- pro-apoptotic factors (p-53, Bax)
+ anti-apoptotic factors (Bcl-2)

↓ PKC activity, phospholipase A2
Pharmacokinetic parameters

- Dose: 900-1500 mg of Lithium carbonate
- Half Life: 20-24 hrs
- Peak: 1-2 hrs
- Toxic plasma concentrations: 1.5 - 3 mEq/l
- Stable concentrations: 5-6 days
Lithium side effects

- Nausea
- vomiting
- diarrhea
- tremor
- Weight gain
- Confusion
- Thyroid, kidney effects

Propanolol

Hypothyroidism (TSH, FT4)
Bipolar Li + (gray matter)

(a)

Hippocampus

<table>
<thead>
<tr>
<th>Total hippocampal volume (mm³)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy subjects (n = 298)</td>
</tr>
<tr>
<td>H</td>
</tr>
</tbody>
</table>

Amygdala

<table>
<thead>
<tr>
<th>Total amygdala volume (ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healthy subjects (n = 255)</td>
</tr>
<tr>
<td>H</td>
</tr>
</tbody>
</table>

(b)

Cortical GMD differences as a function of lithium treatment

Significance

<0.01 0.05 >0.1

Bipolar Li -

(c)

Subgenual PFC

(d)

Left subgenual volume (mm³)

<table>
<thead>
<tr>
<th>Group</th>
<th>ON</th>
<th>OFF</th>
<th>Major depression</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar on chronic Li/VPA</td>
<td>n = 6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bipolar off chronic Li/VPA</td>
<td>n = 15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MDD</td>
<td>n = 21</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Carbamazepina, Valproic acid
Valproic acid

- Inositol depletion
- Increased production of Bcl-2
- Inhibition of PKC
- Activation of ERK MAP kinase
- Inhibition histone deacetylase
- Transcriptions