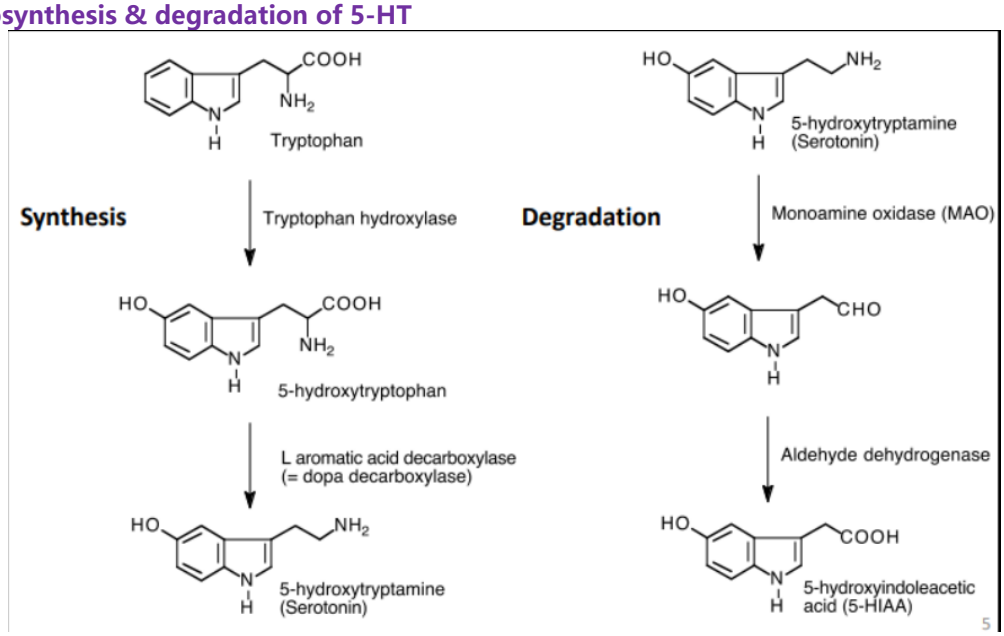
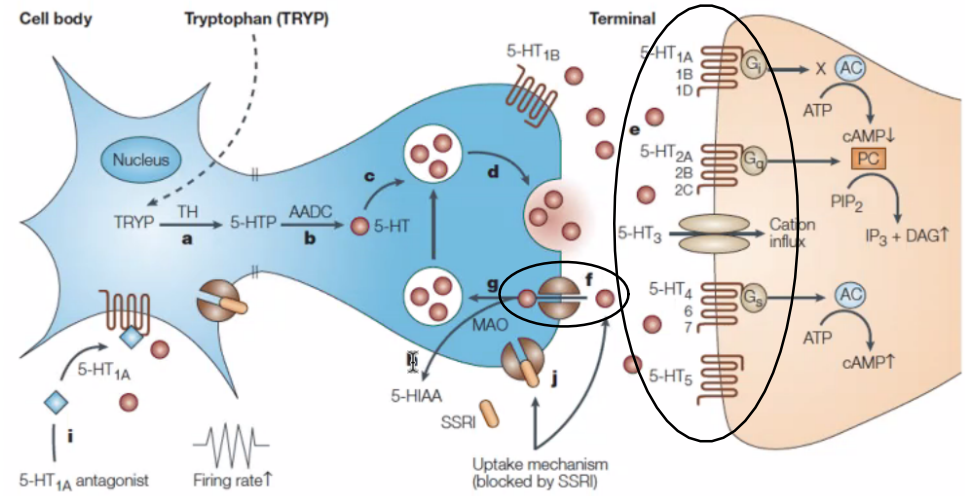
Serotonin - Migraine and Depression

2022年6月29日 13:15

To know about serotonin - how it is synthesised and degraded in cells and its receptors

Biosynthesis & degradation of 5-HT

- 

- 5-HIAA excreted in urine, and is a good marker for high serotonin in CNS (serotonin syndrome/toxicity)
- Oxidation: C=O bonding ↑ C-H bonding ↓
- 

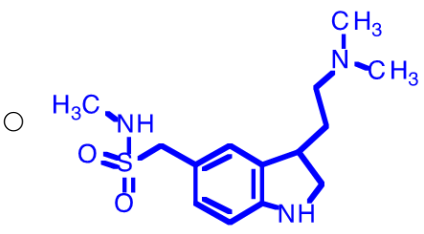
  - 半圆形的是 serotonin reuptake receptor
  - 5-HT --> serotonin receptor

To know about antimigraine, anxiolytics and antidepressants and examples of each

Migraine

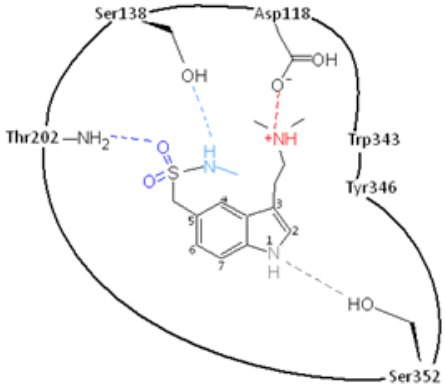
- Unilateral headache
- **Photophobia, phonophobia 怕声音**
- **Calcitonin gene related peptide (CGRP)** and **vasoactive intestinal peptide (VIP)** have shown to be changed during migraine headache

Antimigraine

- **Triptans 5-HT$_{1B/D/F}$ agonists**
  - 

- **Sumatriptan**
- Bind to **5-HT$_{1D}$ on nerve terminals and 5-HT$_{1B}$ on blood vessels**
  - **1D:** Prevent release of **Calcitonin gene related peptide (CGRP)**
  - **1B:** vasoconstriction

○ Structure Activity Relationships of Triptans

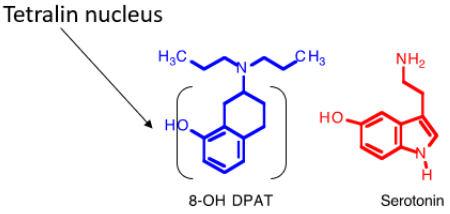
○ 

- An aromatic
- Protonated nitrogen (ionic bonds)
- Hydroxyl or amino groups; electro-negative group
- H-bonding potential
- Lipophilicity
- Large group on C2 position of indole ring converts agonist to antagonist

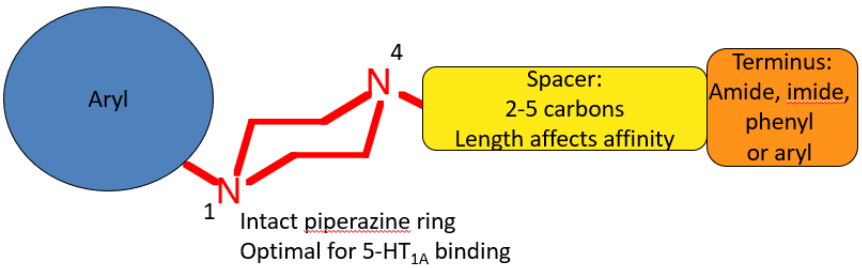
- Olcegepant
  - CGRP antagonist high efficacy in inhibiting neurogenic vasodilatation with no effect on basal blood pressure or heart rate

Depression

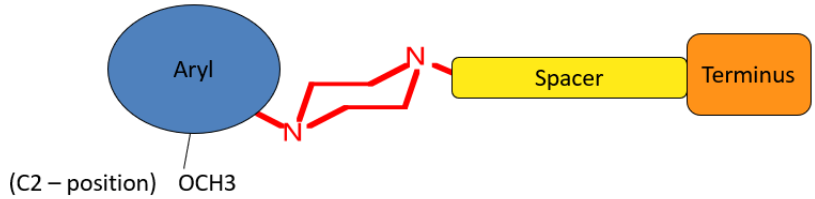
Anxiolytics and antidepressants – 5-HT$_{1A}$ agents

- 

5-HT$_{1A}$ Agonists: Long-chain arylpiperazines (LCAPS)

- 

5-HT$_{1A}$ "silent" antagonists or very weak partial agonists: LCAPS

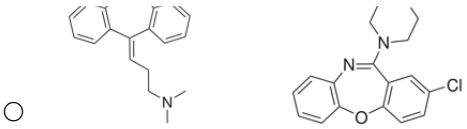
- 

Serotonin Reuptake Inhibitors as Antidepressants

- Tricyclic -- Amitriptyline
- Tetracyclic -- Mirazipine
- SNRI -- Desvanlafexine
- SSRI -- Sertraline, Fluoxetine, Escitopram

Structures of tricyclic antidepressants (TCA)

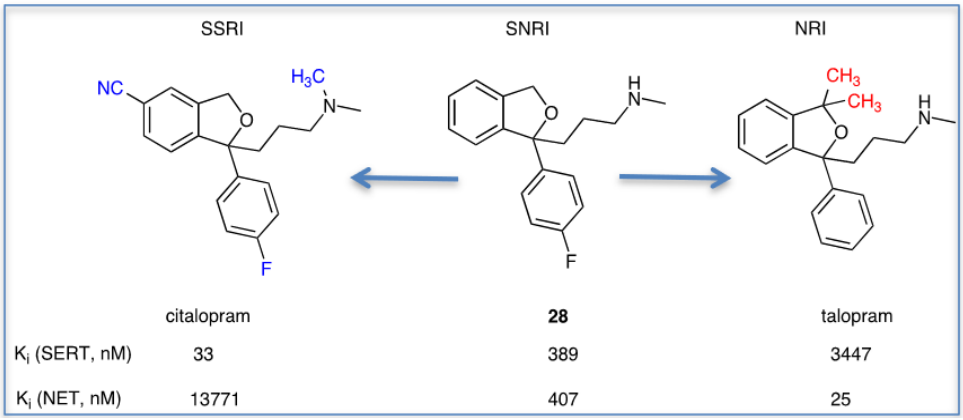
- Aromatic ring pockets
- Protonated distal nitrogen
- Bind to SERT, NET and monoaminergic receptors
- **Non-selective** inhibitor



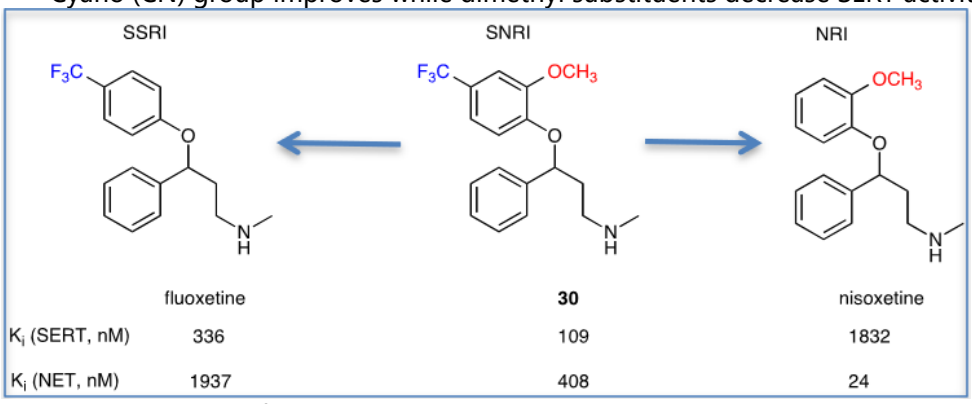
Amytriptyline Amoxapine

- 2-3 Carbon spacer before dimethylamino group “A-shape” or “butterfly shape”
- Distal protonated amine
- Metabolised in liver to N-desmethyl analogues and metabolites are active

Structure activity of citalopram



- Cyano (CN) group improves while dimethyl substituents decrease SERT activity



- CF3 -- Necessary for SERT
- Introducing OMe in ortho position introduces NET activity
- Removal of CF3 from para position eliminates SERT and retains NET
- Therefore phenoxy group determines selectivity