Lecture 23 – Antidepressants

MOOD DISORDERS

MAJOR DEPRESSIVE DISORDER

- Characterised by a sustained (at least 2 weeks) depressed mood, decreased energy/interest/pleasure in activities, low self-esteem, feelings of guilt, inability to concentrate, sleep disturbances (eg early morning awakening – not always), changes in appetite etc.
- Suicidal thoughts and attempts are common
- No manic episodes
- Anxiety can also be present → panic attacks, obsessive compulsive disorder → can occur in children as well (but drugs are not approved for young people – can get them privately though)
    - Some drugs increase the anxiety
- Change in level of transmitters

BIPOLAR AFFECTIVE DISORDER

- Characterised by swings of mood from extreme elation and hyperexcitability (mania or hypomania (slightly less intense form of mania), sustained for at least 1 week) to extreme melancholia and withdrawal.
- During a manic episode:
    - Delusions
    - Inflated self-esteem → capabilities are endless – doesn't need to sleep much
    - Distractive flight of ideas
    - Excessive involvement in pleasurable activities
- Depressive periods are more frequent than the periods of elevated mood.

TREATMENT

- Beneficial effects may not become apparent until 1-3 weeks of treatment with most antidepressant drugs. Optimal beneficial effects may take 6-8 weeks.
- Tricyclic antidepressants and anti-psychotic drugs (extremely sedative compared to tricyclic antidepressants)
- Tricyclic antidepressants, chlorpromazine and other like drugs which are the anti psychotic drugs → almost virtually have the same chemical structure (rearranged)
- Tricyclic drugs can kill you very easily if overdosed
- ***Major Depressive Disorder***
    - Tricyclic antidepressants:
        a) Imipramine
        b) *Amitriptyline* – when people get herpes zoster, this drug is very effective in relieving this pain
        c) Doxepin
    - "Second Generation" Antidepressants:
        a) SSRIs (selective serotonin reuptake inhibitor) – *Fluoxetine* (first drug that came through - prototype), Paroxetine, Sertraline, Citalopram, Escitalopram
        b) Venlafaxine
        c) Mirtazepine
        d) Reboxetine
    - Monoamine Oxidase Inhibitors: -
        - Maoa
            - responsible for deactivating NA, serotonin, dopamine [adrenergic]
            - maoa in the brain is involved in depression
            - Also present in gut → tyramine (in food) acts as an indirectly acting

sympathomimetic amine → high tyramine absorption will lead to a release in NA in sympathetic nerve terminals and blood pressure will increase a lot → but maoa deactivates so we don't have this problem

- Maob

a) Hydrazines – Iproniazid (irreversible)
b) Non-hydrazines – Tranylcypromine (irreversible?)
c) *Reversible* inhibitors of *monoamine oxidase A* (RIMAs) - *Moclobemide* → only used for mild depression

- ***Bipolar Affective Disorder***
  a) Lithium carbonate
     - Acts in controlling great swings that occurs in bipolar disorder
     - Known as a 'mood stabiliser
     - A lot of side effects – very toxic so be careful with dose
     - Mood stabiliser
  b) Antiepileptic drugs – Carbamazepine, Valproate, Lamotrigine
     - Mood stabiliser
  c) Antipsychotic drugs – Chlorpromazine, Olanzapine, Risperidone, Quetiapine, Asenapine
     - The earlier ones are very sedative
     - Now combine these with lithium → but be careful as sometimes combining these drugs can cause quite severe toxic effects
     - Anti-psychotic (not a mood stabiliser)

TRICYCLIC ANTIDEPRESSANTS (TCA)

- Similar in structure to phenothiazine's. Major difference – in 3D, tricyclics are more "buckled" i.e. the rings are at angles to each other.
- Inhibitors of neuronal uptake of noradrenaline and serotonin (5-HT).
  - Serotonin is blocked when used much higher doses
- Antagonists at **α_1-adrenoceptors**, **muscarinic receptors**, histamine H_1- and H_2 - receptors and 5-HT receptors (in high concentrations)
- ***Side effects***:
  - anti-cholinergic – anti-SLUD effect → dry mouth, blurred vision, constipation, urine retention (usually in elderly men
  - cardiovascular
    - cardiotoxicity – can cause arrhythmias because muscarinic receptors are blocked (NA reuptake is blocked – a lot of NA floating around → this happens to us normally as well but our Vagus prevents us from having cardiotoxicity)
    - Can cause a particular effect on the ECG
  - central nervous system
    - Drug combined with alcohol is very dangerous
  - weight gain

SELECTIVE SEROTONIN REUPTAKE INHIBITORS (SSRI)

- High therapeutic index – minimal toxicity in overdose unless combined with other drugs e.g. TCAs or neuroleptics. (serotonin syndrome)
- ***Side effects***: insomnia, sexual dysfunction (the others don't have this), GIT disturbances, restlessness.

- ***Venlafaxine*** – inhibitor of serotonin and noradrenaline reuptake, weak inhibitor of dopamine reuptake.
- ***Mirtazepine*** – antagonist at α_2-adrenoceptors → more release of NA, 5-HT_2 and 5-HT_3 receptors.
- ***Reboxetine*** – inhibitor of noradrenaline re-uptake, weak inhibitor of serotonin reuptake.

MONOAMINE OXIDASE INHIBITORS (MAOI)

- Originally developed from the anti-TB drug isoniazid. These drugs increase levels of noradrenaline, 5-HT & dopamine.
- ***Moclobemide*** – currently the most commonly used MAOI
- ***Side effects***: dizziness, nausea, insomnia.
- Less likely to cause 'cheese reaction'.

LITHIUM CARBONATE

- Very low therapeutic index (2-3).
- Plasma levels must be monitored very regularly, otherwise serious toxicity may result.
    - Lithium ion replaces the Na ion
    - Lithium toxicity
- ***Side effects***: renal, thyroid, neurological.

MECHANISM OF ACTION OF DRUGS USED IN AFFECTIVE DISORDERS

- It was originally thought that tricyclics and MAO inhibitors were effective in depression through increasing availability of noradrenaline, 5-HT and other neurotransmitters in the central nervous system, either by blocking neuronal uptake or breakdown of the transmitters.
- However, studies on 'second generation' antidepressants have shown that this is not the case.
- It is now thought that adaptive changes in receptors are more important in the mechanism of action of antidepressants, such as a ***reduction in β-adrenoceptor sensitivity or numbers, desensitization of 5-HT_2 receptors and α_2-adrenoceptors***.
- In the case of lithium carbonate, the mechanism of action is unknown. Evidence suggests that interactions with second messenger systems may play a role. It may also affect levels of different transmitters by altering synthesis, storage, release and reuptake etc.
- People with depression not only have low levels of transmitters but their receptors have changed → tend to be super sensitive → could be mechanism adopted to deal with low levels of transmitters
    - But why doesn't the existence of sensitive receptors and the low level of transmitters 'fixes' depression? → we don't know why
    - Antidepressants take a while to work as receptors become desensitised
    - This is the proposed mechanism
- ECT (electro conducting therapy) also does the same thing as SSRI's and tricyclic antidepressants
- During stress, there is an increased level of cortisol
- Brain derived neurotropic factor (BDNF) is lower in depressed patients
- Major depression is associated with neuronal loss in the hippocampus and prefrontal cortex → get neurodegeneration in depression
- Exercise helps depression → helps to regenerate neurons
- (See Golan et al, 2012, Principles of Pharmacology: The Pathophysiologic Basis of Drug Therapy, 3rd edition, p. 218)
- Rang and Dale – chapter 46