

Biological Treatments in Psychiatry

Level 4 (2017/2018)

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Background

- **Types of therapies (Treatments)**
 - Physical treatments (Biological)
 - Pharmacotherapy
 - ECT (Electroconvulsive therapy)
 - Surgery
 - Non Biological treatments (Psychotherapy)

Background

- **History of treatments in Psychiatry**
 - Mid 20th century- Insulin coma to treat morphine addiction and schizophrenia
 - 1930's- shock therapy (cardiazole/ camphor 1930)
 - ECT 1950's
 - 1st antipsychotic, chlorpromazine-1952
 - Tricyclic antidepressants and MAO Inhibitors 1950's:
 - Benzodiazepines: 1960's
 - Psychoanalysis –first half of the 20th century

Introduction

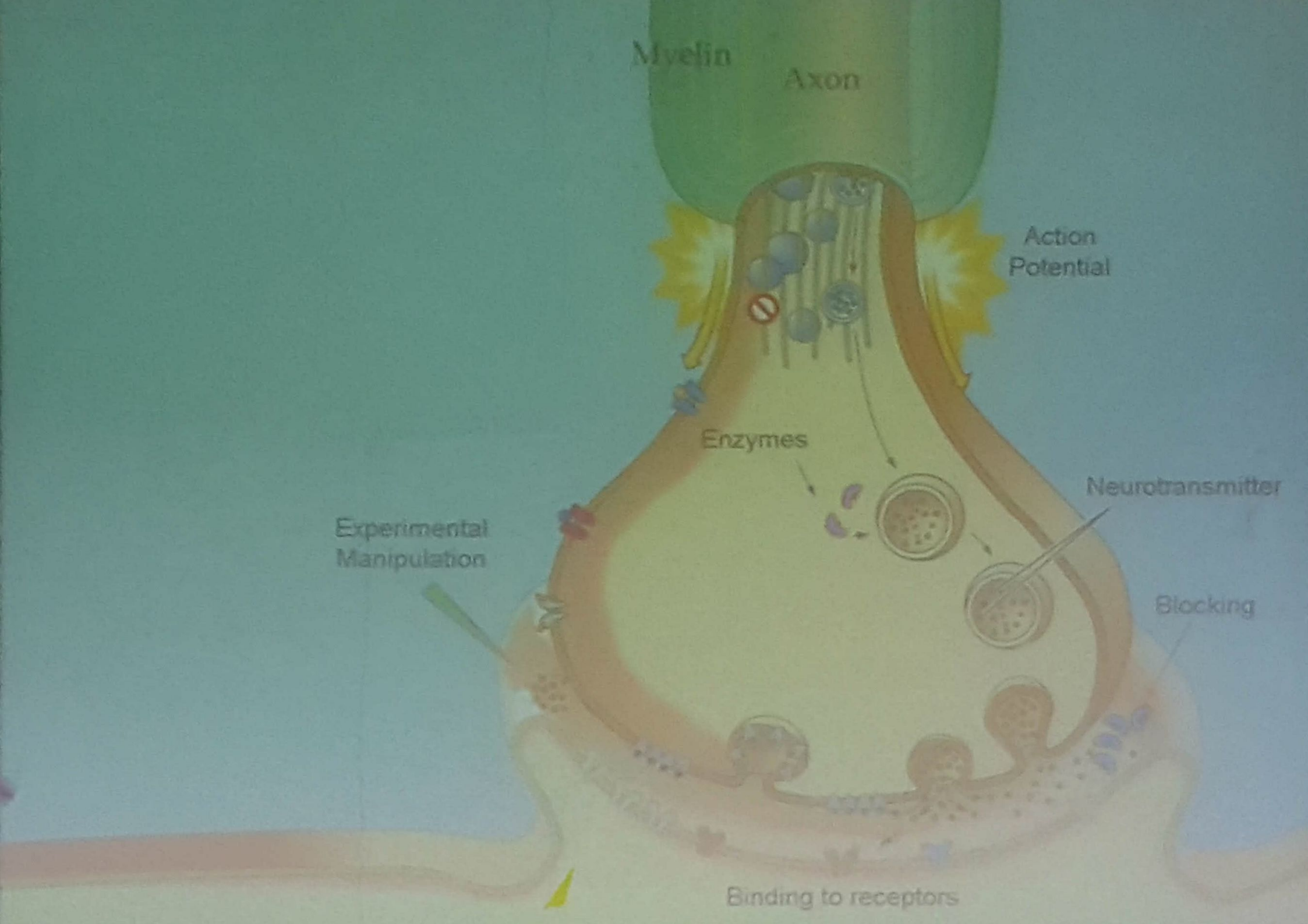
- Psychopharmacology: study of drugs that influence the human mental state and behaviour
- Pharmacokinetics:
 - Absorption
 - Distribution
 - Metabolism
 - Excretion

Introduction

- Neurotransmitters: endogenous chemicals in the human body responsible for transmission of nerve impulses between neurons and target cells across a synapse
- For a signal to be transmitted across, an optimum amount of neurotransmitters in the synaptic space must be present
- In mentally healthy individuals there is a balance between the amount of neurotransmitters in the synaptic space and the presynaptic neuron.
- A disruption of this balance leads to mental and metabolic disorders

Introduction

- Pharmacodynamics
- Psychotropic drugs interfere with neurotransmitter function in several ways:
 - On neurotransmitter receptors
 - Storage
 - Release
 - Reuptake
 - Metabolism
- Drugs can be agonists (mimic endogenous neurotransmitters) or antagonists (bind receptors and block the action of agonists)



Introduction

- Important neurotransmitters implicated in psychopharmacology include:
 - Acetylcholine: reduction implicated in Alzheimer's
 - Serotonin: regulates mood, anxiety and arousal
 - Dopamine: plays a role in Schizophrenia and Parkinson's disease
 - Norepinephrine:
 - Epinephrine
 - Glutamate: Excitatory neurotransmitter
 - GABA: Inhibitory neurotransmitter

Prescribing principles

- Thorough medical evaluation
- Beware of side effects, current and previous and previous response
- Inform family of benefits and risks, delay in therapeutic response
- Start low and increase slowly (dosage)
- Special considerations for special populations (children, geriatrics, pregnant and nursing women)
- Beware of drug interactions

Classification

- Anxiolytics and hypnotics
- Antipsychotics
- Antidepressants
- Mood stabilizers
- Prescription stimulants

Antipsychotics

- Used to treat psychosis (disorders resulting from abnormal perception of reality accompanied by defective insight) e.g. In schizophrenia and mania.
- Psychotic patients experience delusions, hallucinations, cognitive impairments, personality changes and thought disorders
- Also useful for sedation and tranquilisation
- Non psychotic indications: Tic disorders

Antipsychotics

- Typical antipsychotics
 - (typically) Produce extrapyramidal side effects (EPSE)- Parkinsonism (muscle rigidity, tremor, bradykinesia), acute dystonic reactions, dyskinesia, akathasia, tardive dyskinesia
- Atypical antipsychotics
 - Lower propensity to produce EPSE

Antipsychotics

- Typical (1st generation):
 - Older (1950's)
 - Propensity to cause extra-pyramidal side effects (EPSE) due to action on basal ganglia.
 - EPSE- Parkinsonism (muscle rigidity, tremor, bradykinesia), acute dystonic reactions, dyskinesia, akathasia, tardive dyskinesia

Antipsychotics

- Examples of typical antipsychotics include:
 - Phenothiazines:
 - Chlorpromazine
 - Thioridazine
 - Fluphenazine
 - Thioxanthines:
 - Flupenthixol
 - Butyrophenones:
 - Haloperidol

Antipsychotics

- Atypical (2nd generation):
 - Lower incidence of extrapyramidal side effects and prolonged elevated prolactin levels
- Greater effects on negative symptoms of schizophrenia
- Include: Clozapine, Risperidone, Olanzapine, Quetiapine, Aripiprazole, Sertindole, Amisulpiride, Ziprasidone

Antipsychotics

- Mechanism of action:
 - Dopamine receptor blockade (D2)
 - This accounts for antipsychotic activity and propensity to cause extra-pyramidal side effects
 - Some atypical anti psychotics with low D2 receptor occupancy and high 5HT receptor occupancy

Antipsychotics

- Depot antipsychotic drugs
 - Slow release preparations
 - Where compliance cannot be assured
 - Given I/M
 - Include: fluphenazine decanoate, flupenthixol decanoate, zuclopenthixol decanoate, Haloperidol decanoate

Antipsychotics

Side effects include:

- Extra pyramidal side effects (anti-dopaminergic)
 - Acute dystonia, akathasia, parkinsonian syndrome, tardive dyskinesia
- Anticholinergic effects:
 - dry mouth, urinary retention, constipation, blurred vision
- Antiadrenergic effects:
 - Sedation, postural hypotension, inhibition of ejaculation
- Cardiac: arrhythmias, prolongation of QT interval
- Metabolic effects
- Sensitivity reactions
- Neuroleptic malignant syndrome
 - Muscle rigidity, breakdown of muscle fibres, fever, altered consciousness, death)
- Amenorrhoea
- Galactorrhoea

Antidepressants

- Indicated to treat the various symptoms of depressive disorders
- According to the biogenic monoamine theory, depression results from a deficiency of **monoamines** (norepinephrine, serotonin) in certain brain areas
- Exert antidepressant activity by increasing the availability of monoamines via:
 - Presynaptic inhibition of reuptake of 5HT, NE, Dopamine
 - Inhibition of monoamine oxidase reducing neurotransmitter breakdown
 - Increasing the availability of neurotransmitter precursors

Antidepressants

- Initial resolution of depressive symptoms generally takes 10-20 days
- Off label: Anxiety, Sleep disorders, OCD, Eating disorders, Neuropathic pain, Migraines, ADHD

Antidepressants

- **Tricyclic antidepressants**
 - Inhibit reuptake of both 5HT & noradrenaline
 - Include: amitryptiline, clomipramine, imipramine
 - S/E: autonomic, psychiatric, cardiovascular, neurological, withdrawal effects
 - Toxic effects

Antidepressants

- **Monoamine oxidase (MAO) inhibitors & reversible monoamine oxidase inhibitors (RIMAs)**
 - Inactivate enzymes that oxidise noradrenaline, 5HT, dopamine, tyramine (MAO A and MAO B)
 - Include: Phenelzine, Isocarboxazid, Tranylcypromine
 - Moclobemide- RIMA
 - Interactions with food and drugs
 - S/E: hypertensive crises, antimuscurinic, hepatotoxicity, insomnia, anxiety, weight gain, hypotension, ankle oedema

Antidepressants

- **Selective Serotonin Reuptake Inhibitors (SSRIs)**
 - Inhibit the reuptake of 5-HT with high potency and selectivity leading to increased 5-HT in the synaptic cleft
 - Include: paroxetine, sertraline, fluoxetine, fluvoxamine, citalopram, escitalopram
 - Easier dosing
 - Better tolerance than TCAs & MAOs
 - Fewer anticholinergic side effects, low toxicity in overdose, not sedating
 - S/E: gastrointestinal, neuropsychiatric, sexual dysfunction, suicidal behaviour
 - Serotonin syndrome

Antidepressants

Other antidepressants:

- Serotonin/noradrenaline reuptake inhibitors (SNRIs)
 - Venlafaxine, duloxetine
- Tetracyclic antidepressants
 - MOA similar to TCA but with less anticholinergic side effects
 - Mianserin
- Serotonin antagonist/ reuptake inhibitors (SARIs)
 - Trazodone

Mood stabilizers

Effective for treating both mania and depression in bipolar patients.

- **Lithium**

- MOA: Intracellular signalling effects through second messengers. (inhibits formation of cAMP and attenuates formation of inositol lipid derived mediators)
- S/E: polyuria, polydipsia, weight gain, cognitive problems, tremor, hypothyroidism, GI problems, teratogenic
- Narrow therapeutic index
- Toxicity: marked tremor, nausea, diarrhoea, ataxia, drowsiness, confusion, seizures, coma,

Mood stabilizers

- **Anticonvulsants**

- Valproate/Valproic acid:

- Acute mania, mixed episodes, prophylactic agent, rapid cycling bipolar
- S/E: nausea, tremor, sedation, hair loss, weight gain, deranged LFTs. is teratogenic
- Wide therapeutic index though can be fatal in overdose

- Carbamazepine

- Acute mania, bipolar depression; prophylactic agent
- Interacts with many drugs: decreases plasma levels of antipsychotics, benzodiazepines, TCAs, hormonal contraceptives; levels can be decreased by: erythromycin, calcium channel blockers

Mood stabilizers

- **Anticonvulsants...**
 - Lamotrigine
 - maintenance treatment
 - Especially for bipolar depression
 - Gabapentin
 - Used in non response

Anxiolytics

- Used to curb anxiety

Benzodiazepines

- Reduce anxiety, agitation and tension
- Uses: anxiolytic, sedative, muscle relaxant, anticonvulsant
- MoA: Enhance GABA neurotransmission
- Are addictive
- Should not be routinely prescribed for longer than a month

Anxiolytics

Benzodiazepines...

- Long acting compounds preferable for management of anxiety. (half life more than 12 hours)
 - Include: diazepam, chlordiazepoxide, alprazolam, clonazepam
- Side effect: headache, confusion, ataxia, blurred vision, GI disturbance, jaundice, paradoxical excitement.....
- Potentiate effects of alcohol
- Cause dependence which is associated with a withdrawal syndrome- apprehension, insomnia, nausea, tremor heightened sensitivity to perceptual stimuli
- Flumazenil is a benzodiazepine receptor antagonist, useful in reversing toxicity

Anxiolytics

Azapirones

- Buspirone
 - Useful in treatment of Generalised Anxiety Disorder, not for panic disorder
 - Effects take several days to develop
 - MoA: stimulates 5-HT_{1A} receptor
 - Not sedative but associated with light headedness, nervousness headache

Anxiolytics

- **Antidepressant drugs:**
 - TCA, SSRIs, MAOIs
 - Onset of effect much slower than of the benzos
- **Beta-adrenoceptor antagonists**
 - Relieve autonomic symptoms of anxiety
 - Especially if main symptoms are tremors and palpitations
 - Include propranolol
 - Contraindicated in hypotension, bradycardia, heart block, bronchospasms

Hypnotics

- Are used to improve sleep
- Primary chronic insomnia is rare
- Comorbidity is the rule
- Non pharmacological methods tried first- Sleep Hygiene
- The ideal hypnotic would increase the length and quality of sleep without residual effects the next morning.
- Many anxiolytic drugs also act as hypnotics
- Antihistamines and low doses of sedating anti depressants e.g. amitriptyline are also used to facilitate sleep

Hypnotics

- Most enhance the action of GABA
 - Benzodiazepines:
 - shorter acting compounds lack hang over effects the next day (e.g. temazepam)
 - Longer acting compounds produce some cognitive impairment the next day (e.g. flurazepam, nitrazepam)
 - Non benzodiazepine ligands: Zopiclone, Zolpidem, zaleplon
 - Melatonin: not addictive; nudges one to sleep

Psychostimulants

- Include:
 - Amphetamines- dextroamphetamine
 - Methylphenidate
- MoA: increase the release and block the reuptake of dopamine and noradrenaline
- Indications:
 - Narcolepsy
 - ADHD
- Side effects: restlessness, insomnia, poor appetite, dizziness, tremor, palpitations, arrhythmias

Other biological treatments

Electroconvulsive therapy (ECT)

- Introduced in the late 1930's
- Initially Cardiazol, or just passing an electric current into the brain
- Now made safer with use of brief anaesthesia and muscle relaxants

Electroconvulsive therapy (ECT)

Indications:

- Major depression
 - Not responding to antidepressants
 - With psychotic symptoms
 - With failure to eat or drink
 - Depressive stupor
 - High suicide risk

Electroconvulsive therapy (ECT)

- Schizoaffective depression
- Catatonic schizophrenia
- Mania not responding to drug treatment
- Post- partum psychosis

Electroconvulsive therapy (ECT)

- MoA:
 - Neurochemical effects of ECT- changes in the brain monoamine pathway
 - Down regulation of noradrenaline beta adrenoreceptors
 - Increased expression of D2 receptors
- Side effects:
 - Retrograde amnesia
 - Anterograde amnesia
 - Brief disorientation
 - Headache

Neurosurgery for mental disorder

- Began in 1936- work of Moniz- Nobel prize in 1949
- Controversial
- Indications :
 - Severe mood disorders, OCD, Severe anxiety disorders
 - Patient must want the operation
 - All reasonable treatments have completely failed
 - Patient remains ill but has capacity to provide consent

Neurosurgery for mental disorder

- Stereotactic procedures used include:
 - Sub caudate tractotomy
 - Anterior cingulotomy
 - Limbic leucotomy
 - Anterior capsulotomy
- Adverse effects; operative mortality, haemorrhage, hemiplegia, epilepsy, personality changes

Light therapy

- Treatment of seasonal affective disorder
- Used to ameliorate symptoms of winter depression due to effects on circadian and seasonal rhythms
- Administered using a light box, 2 hours/30 minutes a day for 1-3 weeks
- Dawn stimulating alarm clocks

Repetitive Transcranial magnetic stimulation (rTMS)

- Experimental treatment for treatment resistant depression
- An electromagnetic coil is placed on the scalp, pulses of current then produce a powerful magnetic field