Drugs Targeting the CNS

- Hypnotics/Anxiolytics
- Antidepressants
- Neuroleptics
- Parkinson
- Epilepsy
Drugs Targeting the CNS

Neurotransmitters in the CNS

- **Norepinephrine:**
  - Excitatory or inhibitory
  - Targeted by: MAO inhibitors (↑); tricyclic antidepressant (↑); amphetamines (↑)

- **Acetylcholine:**
  - Excitatory (M1; N) or inhibitory (M2)
  - Targeted by: M inhibitors (↓); Acetylcholine-esterase inhibitors (↑)

- **Glutamate:**
  - Excitatory
  - Targeted by: antiepileptics, ketamine, phencyclidine (↓)

- **GABA (γ-aminobutyric acid):**
  - Inhibitory (increases gCl- and gK+, but not gNa+ => hyperpolarization (higher threshold for activation
  - Targeted by: hypnotics, sedative, anti-epileptics (↑)

- **Dopamine:**
  - Inhibitory
  - Targeted by: older neuroleptics (↓); anti-parkinson drugs, amphetamines (↑)

- **Serotonin:**
  - Excitatory or inhibitory
  - Targeted by: MAO inhibitors, SSRIs, Tricyclic antidepressants, hallucinogens (↑)
Drugs Targeting the CNS

Glutamate

- Excitatory amino acid:
  - Uniformly distributed throughout the brain
  - Mainly derived from glutamine or glucose
  - Stored in synaptic vesicles
  - Four distinct receptors exist -
    (NMDA receptor subtype most significant for drug action: needs to be “co-occupied” by glycine to become activated)
  - Termination mainly by re-uptake into nerve terminal and astrocytes
  - Astrocytes convert it to glutamine (lack activity) and return it to nerve cells
GABA (γ-amino-butyric acid)

- Inhibitory amino acid:
  - Only found in the brain
  - Mainly derived from glutamate via glutamic acid decarboxylase (GAD)
  - Stored in synaptic vesicles
  - Two distinct receptors exist - GABA_A and GABA_B
    (GABA_A receptor subtype most significant for drug action: mostly post-synaptic: Cl⁻ influx hyperpolarizes the cell => inhibitory)
  - Termination mainly by deamination (GABA transaminase)
Drugs Targeting the CNS

Dopamine

- **Inhibitory amino acid:**
  - Precursor to (nor)epinephrine
  - Termination mainly by reuptake (dopamine transporter - inhibited by Cocaine) and metabolism via MAO_B and COMT
  - Two distinct receptor groups exist (coupled to heterotrimeric G proteins):
    - D_1-group (D_1,D_5: stimulate Adenylate cyclase: CNS, renal arteries)
    - D_2-group (D_2,D_3, D_4: inhibit Adenylate cyclase: CNS)
  - Three main dopaminergic pathways:
    - Nigrostriatal (substantia nigra): motor control (Parkinson’s disease)
    - Mesolimbic/mesocortical: emotion and reward system
    - Tuberohypophysal: from hypothalamus to pituitary
      - (Medulla oblongata: Vomiting center: D2 receptors)
    - Schizophrenia: increased dopamine levels and D_2 receptors
Drugs Targeting the CNS

5-Hydroxytryptamine (5-HT = Serotonin)

- Excitatory or inhibitory amino acid:
  - Generated from tryptophane
  - Termination mainly by reuptake and MAO_B
  - Seven distinct receptor types exist (7-TM):
    - 5-HT_1 group (CNS, blood vessels) (cAMP↓)
    - 5-HT_2 group (CNS, blood vessels) (IP_3/DAG↑)
    - 5-HT_3 group (peripheral nervous system)
    - 5-HT_4 group (enteric nervous system)
  - Main functions:
    - Intestine: increases motility
    - Blood vessel: constriction (large vessels) dilation (arterioles)
    - Nerve ending: triggers nociceptive receptors
      5-HT injection causes pain
      (5-HT found in nettle stings)
    - Neurons: excites some neurons, inhibits others
      inhibition mostly presynaptic (inhibit transmitter release)
      LSD = agonist of 5-HT_2A receptor
Drugs Targeting the CNS

Sites of drug action in the CNS:

Sites of CNS drug action. Drugs may alter (1) the action potential in the presynaptic fiber; (2) the synthesis of transmitter; (3) the storage of transmitter; (4) the metabolism of transmitter within the nerve ending; (5) the release of transmitter; (6) the reuptake or (7) extracellular disposition of transmitter; (8) the postsynaptic receptor; or (9) the postsynaptic effects that follow receptor activation.
Drugs Targeting the CNS

Anxiety:

- **Panic disorder** (panic attacks) - rapid-onset attacks of extreme fear and feelings of heart palpitations, choking and shortness of breath.
- **Phobic anxiety** is triggered by a particular object, for example; spiders, snakes, heights, or open spaces.

- **Obsessive-compulsive disorder** - uncontrollable recurring anxiety-producing thoughts and uncontrollable impulses (compulsive hand-washing, checking that doors are locked: “Monk”)

- **Generalized anxiety disorder** - extreme feeling of anxiety in the absence of any clear cause

- **Post-traumatic stress disorder** (PTSD) - recurrent recollections of a traumatic event of unusual clarity which produce intense psychological distress.
Hypnotics / Anxiolytics

Barbiturates
- Derivatives of barbituric acid
- Hypnotic/anxiolytic effect discovered in the early 20th century (Veronal®, 1903)
- Until the 60s the largest group of hypnotics (more hypnotic than anxiolytic)
- Act by both enhancing GABA responses and mimicking GABA (open Cl-channels in the absence of GABA) => increased inhibition of the CNS (also block glutamate receptors)
- High risk of dependence (severe withdrawal symptoms)
- Strong depressent activity on the CNS => anesthesia
- At higher doses respiratory (inhibit hypoxic and CO₂ response of chemoreceptors) and cardiovascular depression => very little use today as hypnotics (only for epilepsy and anesthesia)
- Potent inducers of the P450 system in the liver => high risk of drug interactions (oral contraceptives)
Hypnotics / Anxiolytics

**Barbiturates**
Different barbiturates vary mostly in their duration of action

- **Phenobarbital**
  - Long-acting: used for anticonvulsive therapy

- **Thiopental**
  - Very short acting (very lipophilic => redistributed from the brain into the fat tissue => CNS concentration falls below effective levels: used for i.v. anesthesia

- **Amobarbital**
- **Pentobarbital**
- **Secobarbital**
Hypnotics / Anxiolytics

Benzodiazepines

- Derivatives of Benzodiazepin
- Valium (diazepam) in 1962
- Characteristic seven-membered ring fused to aromatic ring
- Selectively activates GABA receptor operated chloride channels (bind to the benzodiazepin receptor which is part of the GABA-receptor/chloride channel complex)
- Increase the affinity of GABA for its receptor
- Used to treat anxieties of all kinds (phobias, preoperative anxiety, myocardial infarction (prevent cardiac stress due to anxiety…)
- Significantly fewer side effects than barbiturates => much safer => more widespread use
- Cause anterograde amnesia (useful for minor surgeries)
Hypnotics / Anxiolytics

Benzodiazepines
Different benzodiazepines vary mostly in their duration of action

- **Chlordiazepoxide (Librium®)**
  - introduced in 1960, first benzodiazepine
- **Diazepam (Valium®), Clonazepam,**
  - Strongly anticonvulsive => therapy of status epilepticus
- **Lorazepam**
- **Flunitrazepam (Rohypnol®)**
  - Known as “date-rape drug”, “roofie”
  - Color- and tasteless,
  - Disinhibiting effect (particularly with EtOH), amnesia !
  - Death unlikely, but high risk of dependence

- **Alprazolam**
  - Has also antidepressive properties
- **Triazolam**
  - Causes paradoxical irritability (=> withdrawn in the UK)
Antidepressants

Clinical Depression
Characterized by feelings of misery, guilt, low self-esteem without cause
Lack of motivation, missing drive to act
Mania: opposite symptoms

Unipolar depression: Depressive phase only
Bipolar disorder: Depression alternates with mania

“Amine hypothesis of depression”:
States that a functional decrease in brain norepinephrine and/or serotonin is responsible for the disorder (maybe over-simplified, BUT =>)
Most anti-depressive drugs facilitate the activity of these brain amines

• Several drug classes
  – MAO inhibitors
  – Tricyclic antidepressants (TCAs)
  – Selective Serotonin Reuptake Inhibitors (SSRIs)
  – Misc. Heterocyclic antidepressants
  – Lithium (bipolar disorder only)
Antidepressants

**MAO Inhibitors:**
- Increase levels of norepinephrine, serotonin and dopamine by preventing their metabolism
- Use is declining due to side effects (can cause fatal hypertensive crisis) => Last choice of treatment today (only if other drugs fail)
- Possibility of severe food-drug interaction (“cheese reaction”: Tyramine is usually metabolized and inactivated in the gut by MAOs. MAO-inhibition allows for uptake of tyramine, which displaces norepinephrine in the storage vesicles => NE released => hypertension and cardiac arrhythmias.

- **Tranylcypromine**

- **Phenelzine**
Antidepressants

Tricyclic antidepressants:
- Increase levels of norepinephrine and serotonin by preventing their neuronal reuptake => extended duration of post-synaptic effects
- Strong interaction with alcohol
- Side effect: Sedation (H1-block)

- Imipramine
- Desipramine
- Clomipramine
- Amitriptyline
- Nortriptyline
Antidepressants

Selective Serotonin Reuptake Inhibitors (SSRIs):

- Increase levels of serotonin specifically by preventing their neuronal reuptake => extended duration of post-synaptic effects
- Same efficacy as TCAs, but fewer side effects
- Main side effect: inhibition of sexual climax
- Rare, but severe side effect: aggression, violence

- Fluoxetine (Prozac®)
  Most widely prescribed antidepressant
  Sales exceed 1 bill. $ / year

- Paroxetine (Paxil®)
- Sertraline (Zoloft®)
- Citalopram (Celexa®)
Neuroleptics

Schizophrenia

Endogenous psychosis characterized by:

Positive symptoms: thought disorder (illogical, incoherent, garbled sentences), mood inappropriation, paranoia (persecution mania) and hallucinations (voices) and

Negative symptoms: withdrawal from society, flattened emotional responses, defect in selective attention (can’t distinguish between important and insignificant)

Affects up to 1% of population, high suicide rate (10%)

Amphetamines promote dopamine release => mimic schizophrenia

“Dopamine hypothesis of schizophrenia”: States that a functional increase in brain dopamine is responsible for the disorder. In addition, 5-HT might play a role, possibly by modulating dopamine responses.

Anti-psychotic drugs act as dopamine D2 (and 5-HT) receptor blockers

• Several drug classes
  – Typical (older, pre-1980s) neuroleptics: phenothiazines, butyrophenones relieve mostly positive symptoms
  – Atypical (newer) neuroleptics: fewer extrapyramidal side effects relieve both positive and negative symptoms
Neuroleptics

Classical neuroleptics:

Phenothiazines
- Chlorpromazine
- Triflupromazine
- Fluphenazine…

Butyrophenones
- Haloperidol
- Triluperidol
- Spiroperidol
Neuroleptics

Classical neuroleptics:

Adverse effects:

- Mostly extensions of dopamine-receptor antagonism (extrapyramidal effects due to dopamine blockage in the striatum):
  
  • **Acute dystonia**: Motor impairment, involuntary movements of face, tongue, neck.. (reversible; develops immediately after start of treatment)
  
  • **Akathesia (Pseudo-Parkinsonism)**: motor restlessness, rigidity, tremor (reversible; develops days to month after start of treatment)
  
  • **Tardive Dyskinesia**: involuntary movements of most body parts (head, lips, limbs..) (irreversible; develops after extended treatment in 20-40% of patients) - main problem of classical neuroleptic therapy

- Sedation (results from H1-receptor blockage)
- Also block muscarinic cholinergic and α-adrenergic receptors (=> dry mouth, constipation, urinary retention)
- Lactation (dopamine suppresses prolactin release)
- Strong interaction with alcohol
Neuroleptics

Atypical neuroleptics:
- Inhibit 5-HT and D2 receptors
- Act predominantly in the limbic system, but not in the striatum => fewer extrapyramidal side effects (might also be due to adrenergic receptor blockage)

- Clozapine
  - Can cause agranulocytosis
  (=> strict monitoring required)

- Olanzapine
  - Same efficacy as Clozapine, but no agranulocytosis

- Risperidone
- Olanzapine
Parkinson’s Disease

Pathology:

- Loss of dopaminergic neurons in the **Pars compacta of the Substantia nigra**
- The excitatory influence of ACh becomes unopposed => movement disorders (tremor, muscle stiffness, slow movements, and difficulty walking)
- Symptoms: stooped and rigid posture, shuffling gait, tremor, a masklike facial appearance, and "pill rolling"
Parkinson’s Disease

Pathology:
• Loss of dopaminergic suppression of the cholinergic neurons in the striatum => increased GABA output to the thalamus => suppression of stimulating input into the motor cortex => movement disorder

Treatment strategies: Dopamine replacement Dopamine agonists Cholinergic antagonists (Atropine - see Lecture 6)
Parkinson’s Disease

Dopamine replacement:
Dopamine does not cross blood-brain barrier => use of

- **Levodopa (L-Dopa)**
  - Metabolic precursor of dopamine
  - High concentrations required, as *most of L-Dopa is decarboxylated* in the periphery => high concentration of peripheral dopamine => side effects!
  - L-Dopa combined with

- **Carbidopa**
  - L-Dopa decarboxylase - inhibitor
  - Does not cross blood-brain barrier => only peripheral effect => increases the amount of L-Dopa that reaches the brain
Parkinson’s Disease

**Dopamine agonists:**

- Actions and side effects similar to L-Dopa
  - **Bromocriptine**
    - Derived from ergot alkaloids
    - Potent D2 agonist
    - Initially used to treat galactorrhoea (inhibit Prl release)
  - **Pergolide**
  - **Pramipexole**

**Indirect dopamine agonists:**

- **Selegiline**
  - Inhibitor of MAO_B (mostly in the CNS => few peripheral side effects, e.g. cheese reaction etc.)
  - Extends half-life of dopamine
Epilepsy

Pathology:
- Group of disorders characterized by excessive excitability of neurons within the central nervous system (CNS)
- Characteristic symptom is seizure
- ~0.5% of population is affected

Classification:
- Simple (patient remains conscious, often involves brain lesions) or complex (patient loses consciousness)
- Partial (only localized brain region is affected) or generalized

Generalized seizures are divided into:
- Tonic clonic seizures (grand mal): strong contraction of entire musculature => rigid spasm, often accompanied by salivation, defaecation and respiratory arrest. Tonic phase is followed by series of violent jerks, which slowly die out in a few minutes
- Absence seizures (petite mal): often in children. Less dramatic, but more frequent (several seizures/day): patient stops abruptly what (s)he was doing and “spaces out”
Epilepsy

Treatment strategies:

Enhancement of GABA action
Mostly for partial and generalized convulsive seizures (not effective in absence seizures)

- Carbamazepine
  - Benzodiazepine => increases Cl⁻-influx in response to GABA => counteracts depolarization

- Tiagabin
  - Prevents GABA re-uptake

Inhibition of sodium channels

- Phenytoin
  - Blocks voltage-gated Na⁺-channels in the inactivated (refractory) state => preferential inhibition of high-frequency discharges
    (very limited effect on normal frequency excitation = “use-dependent inhibition”)
  - Eliminated following zero-order kinetics
  - Used for convulsive seizures (not effective in absence seizures)
  - gingival hyperplasia (fairly high percentage)
Epilepsy

Treatment strategies:
Inhibition of calcium channels

- **Ethosuximide**
  - Blocks T-type channels
  - Drug of choice for absence seizures

- **Valproate**
  - Exact mechanism unclear (causes GABA increase in the brain)
  - Useful for convulsive and absence seizures
  - Teratogenic
  - Hepatotoxic (elevated liver enzymes, even fatal hepatic failure)
Strychnine

Glycine receptor antagonist

Glycine:
- Non-essential amino acid
- Major inhibitory neurotransmitter (similar to GABA)
- Binds NMDA receptor (not strychnine sensitive)
- Glycine receptor (Cl⁻ ion channel) - binding is Strychnine sensitive

Strychnine:
- Main alkaloid in *Strychnos nux-vomica* seeds
- Among the most bitter substances known
- Poisoning causes most severe muscle spasm (“arching”):
  - Convulsions progress to death by asphyxiation ($LD_{50}=10mg$)
  (Considered one of the most painful deaths: horrific seizures without losing consciousness)
- Popular use as a rodent pesticide
- Antidotes: Anticonvulsants (Diazepines)
  - Muscle relaxants
Ethanol

Most widely consumed “drug”:
1 drink = ~ 8-12g ethanol (= 0.17-0.26 mole) =>
not unusual to consume >1mole/session
(equivalent to ~ 0.5 kg of most other drugs)

• Biological effects
  Resembles actions of general, volatile anesthetics
  Acts on many different levels:
  • Low concentrations:
    • enhancement of excitatory effects of N-ACh and 5-HT3 receptors => agitation
  • Higher concentrations:
    • Inhibition of neurotransmitter release by blocking Na+ and Ca^{2+} channels
    • Inhibition of NMDA receptor function
    • Enhancement of GABA-mediated inhibition (similar to benzodiazepines)
  Peripheral effects:
  • Cutaneous vasodilation (heat loss!!)
  • Increased salivary and gastric secretion (=> hunger)
  • Increased glucocorticoid release
  • Inhibition of anti-diuretic hormone (ADH) secretion => diuresis
  • Inhibition of Oxytocin release (=> delay of labor induction)
Ethanol - Alcoholism

- **Alcoholism**
  - **Long-term effect:**
    - Liver damage: increased fat accumulation due to increased “stress” => increased release of fatty acids from fat tissue, and impaired fatty acid oxidation due to “metabolic competition”
    - Chronic malnutrition (ethanol satisfies the “caloric requirement”, but no vitamins etc.)

- **Addiction:**
  - Alcohol use linked to endorphine system (AA Wistar rats more sensitive to endorphine release after alcohol consumption => prone to alcoholism)
  - Endorphines are part of the bodies “reward system” => re-inforced behavior

- **Withdrawal:**
  - Long-term alcohol use leads to reduced GABA levels
  - Abrupt stop of alcohol consumption => lack of GABA input => Seizures, hallucinations, tremor, convulsions, “Delirium tremens”

- More than 15 mill. Americans are considered Alcoholics !!!
Ethanol - Alcoholism

Treatment strategies:

• **Disulfiram (Antabuse®)**
  - Blocks **Aldehyde-dehydrogenase** =>
    accumulation of Acetaldehyde after alcohol consumption:
    nausea, vomiting,”hang-over”
  - Also inhibits dopamine-hydroxylase =>
    blocks dopamine->NE conversion =>
    rise in dopamine: schizophrenic symptoms

• **Naltrexone (“Sinclair Method”)**
  - Opioid receptor antagonist
  - Prevents the “reward response”
  - Patient is allowed to consume alcohol in usual setting =>
    BUT: urge to drink diminishes over time
  - Very simple and successful (~80%) regimen