1st seminar

Sedatohypnotic-anxyiolytic drugs, Alcohols

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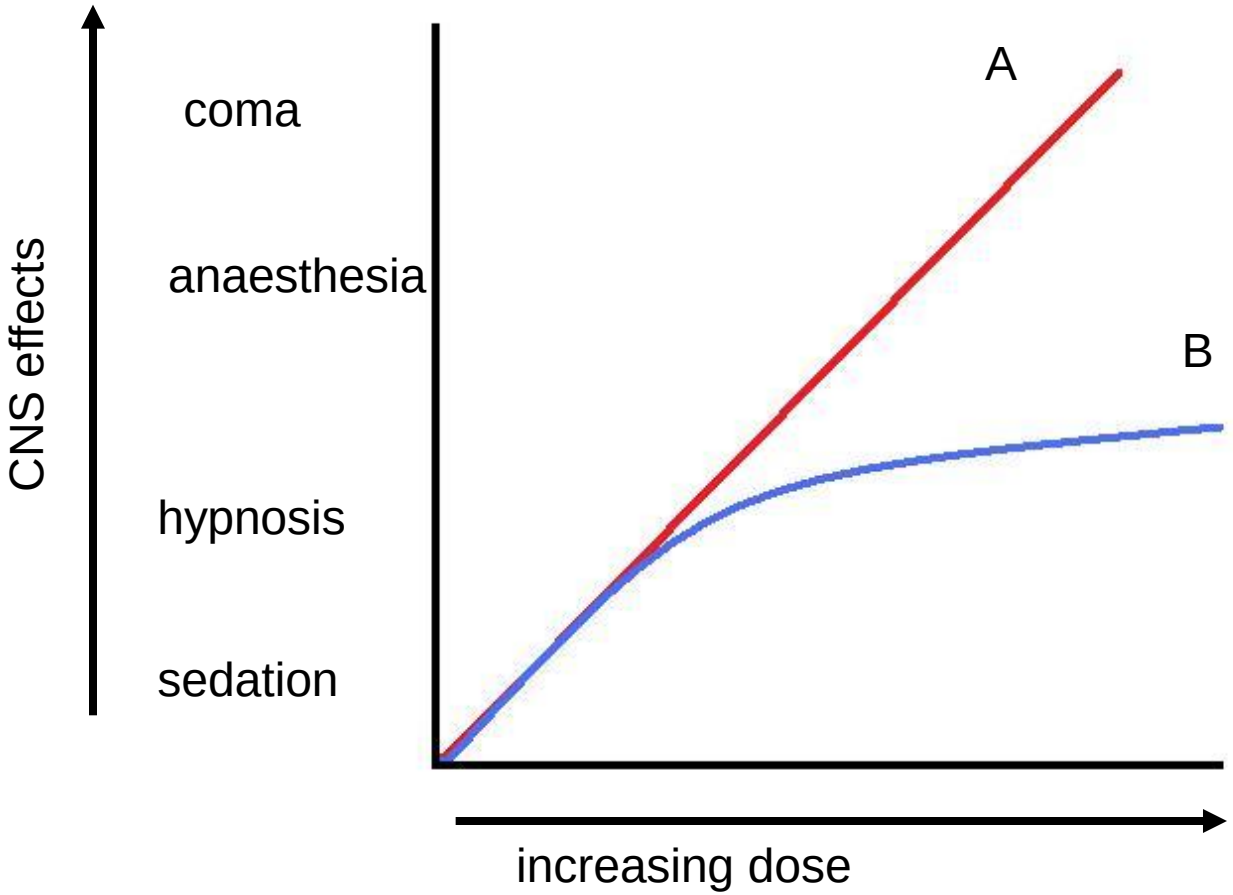
Sedatohypnotics, anxiolytics

- sedative-hypnotic-anxiolytic effects
- anxiety disorders:
  - GAD (generalised anxiety disorder)
  - panic disorder
  - phobias
  - PTSD (post-traumatic stress disorder)
  - OCD (obsessive-compulsive disorder)
- hypnotic disorders
  - insomnia

Sedative-Hypnotic drugs

- Classification:
  - benzodiazepines
    - chlordiazepoxide (Librium®)
    - diazepam (Valium ®, Seduxen ®)
    - clonazepam (Rivotril ®)
    - triazolam
    - alprazolam (Xanax ®, Frontin ®)
    - midazolam (Dormicum ®, Midazolam Torrex ®)
    - flunitrazepam (Rohipnol ®)
  - barbiturates
    - phenobarbital (Phenobarbital ®)
    - pentobarbital (Nembutal ®)
    - thiopental (Trapanal ®)
    - secobarbital
  - 5HT receptor agonists
    - buspirone (Buspar ®)
  - „Z compounds”
    - zolpidem (Stilnox ®)
    - zopiclon (Imovan ®)
    - zaleplon
  - melatonin receptor agonist
    - ramelteon

„Ideal” sedatohypnotics



Physiologic background

GABA (γ-aminobutyric acid)

- main NT in the CNS (inhibitory effect)
- GAD (glutamic acid decarboxylase)
- GABA transaminase
- GABAerg neurons, astrocytes

- Receptors
  - $GABA_A$:
    - ionotropic
    - ligand gated Cl^- channel→Cl^-influx→hyperpolarisation
    - pentamer structure ($\alpha_2\beta_2\gamma_1$)
  - $GABA_B$:
    - G-protein coupled, inhibits adenylyl cyclase
    - inhibiting VG Ca^{2+} ch., opening K+ channels
    - location pre/post synaptically

Benzodiazepines

history: 1960's – chlordiazepoxide

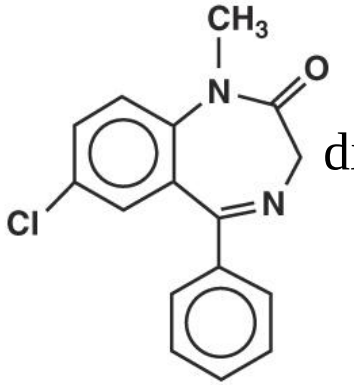
structure:

benzene ring +

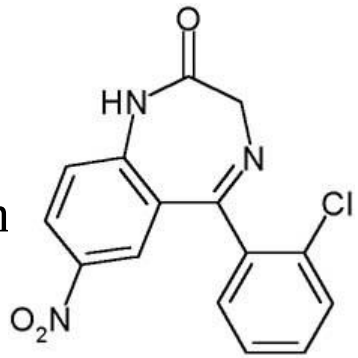
diazepine ring (7 membered heterocyclic) +

5-aryl substituent ring

(+ oxazole/triazole ring - alprazolam, triazolam)

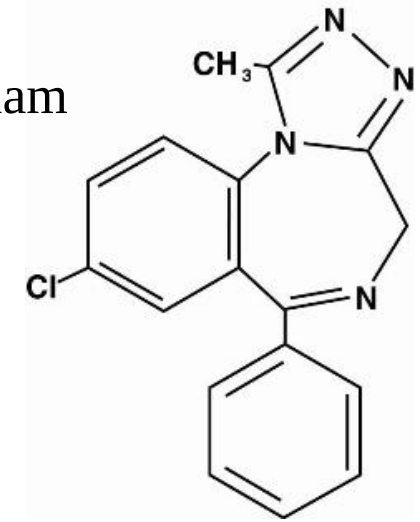


diazepam



clonazepam

alprazolam



Benzodiazepines

Classification

- chemical structure
  - basic:
    - diazepam, chlordiazepoxide, clonazepam, midazolam
  - triazole ring:
    - triazolam
  - oxazole rings
    - alprazolam, cloxazolam

- potency (anxiolytic effect)
  - high potential (eff. dose < 10mg/day)
  - low potential (eff. dose > 10mg/day)

- duration of action
  - ultrashort: midazolam, triazolam
  - short: lorazepam, oxazepam
  - medium: alprazolam
  - long: diazepam, clonazepam, flunitrazepam

Benzodiazepines

mechanism of action:

specific regulatory site on $GABA_A$ receptor

$GABA_A$ R: Cl^- channel, pentamer structure (2α, 2β, ɤ)

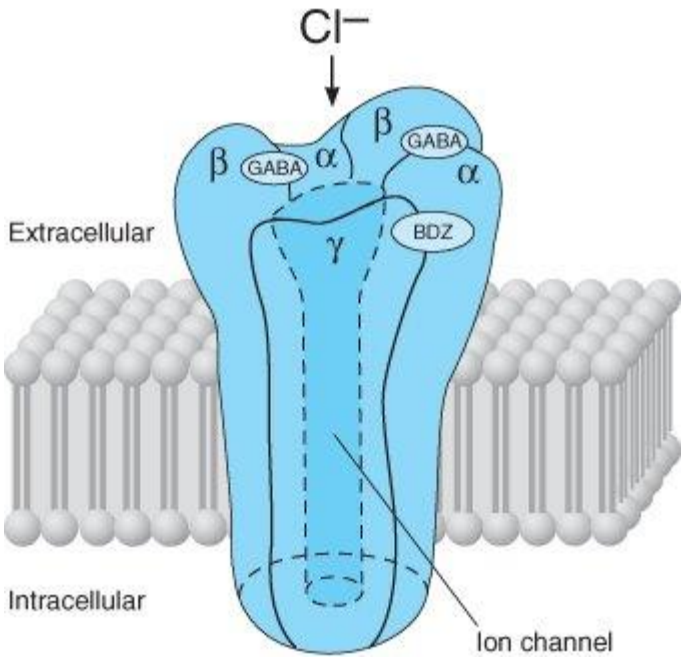
inhibitory function - hyperpolarisation in CNS

binding site for

GABA (ɤ-amino butyric acid),

BZD, barbiturates

ALLOSTERIC MODULATION



BZD R, ω R !

α_1: hypnosis, sedation α_5: amnesia

α_2: anxiolytic, anticonvulsant

↑ frequency of channel opening!!!

Drugs acting on BZD receptor

- BZD receptor agonists: benzodiazepines,
  „Z compounds”
- BZD receptor antagonist: flumazenile (Annexate®) –
  - competitive antagonism
  - short half life ($t_{1/2}$: 0,7-1,3 hours)→intoxication relapse
  - diagnostic and therapeutic
  - antidotum! (NB.! complex therapy of intoxication)
  - 0.2-0.4 mg
- BZD receptor inverse agonist: β-CCB (β-carbolines)
  - bicuculline
  - experimental appl.

Benzodiazepines

Pharmakokinetic features:

absorption: 80-100%, oral application

lipid solubility ↑ - penetrating, accumulating in CNS

PPB: ↑

metabolised by CYP3A4, CYP2C19
(ketoconazole, H_2 blockers, makrolides)

active metabolite: desmethyl-diazepam
(diazepam,clonazepam, chlordiazepoxide) $t_{1/2}$: 40-60 h → prolonged effect!

Benzodiazepines

- sedative, anxiolytic:
  - calming effects, produce drowsiness
- anaesthetic:
  - premedication: ET intubation, etc.
- amnestic:
  - anterograd and retograd amnesia
- hypnotic:
  - ↓ latency of sleep onset
  - ↑ duration of NREM (4 stages)
  - ↓ duration of REM
- anticonvulsant:
  - anti seizure therapy (see below)
- muscle relaxant

Benzodiazepines

Adverse effects:

- tolerance→abuse→dependence
- withdrawal syndrome
  - psychological
  - physical
- cardiovascular/respiratory depression
  - (impaired cardiac/metabolic/respiratory function)

Benzodiazepines

Therapeutical use/Clinical indication:

- relief of anxiety (GAD, Phobias, OCD)
- insomnia
- sedation and amnesia before and during medical and surgical procedures (Anaesthesia, Preoperative phases)
- main component of balanced anaesthesia (i.v.)
- treatment of epilepsy and seizures (GTCS)
- control of ethanol or other sedative-hypnotic withdrawal states

Barbiturates

history: - 1912, barbituric acid

classification: (based on duration of action)

- ultrashort: thiopental (Trapanal)
- short: cyclobarbital
- medium: secobarbital
- long: phenobarbital (Phenobarbital)

Barbiturates

<u>mechanism of action:</u>

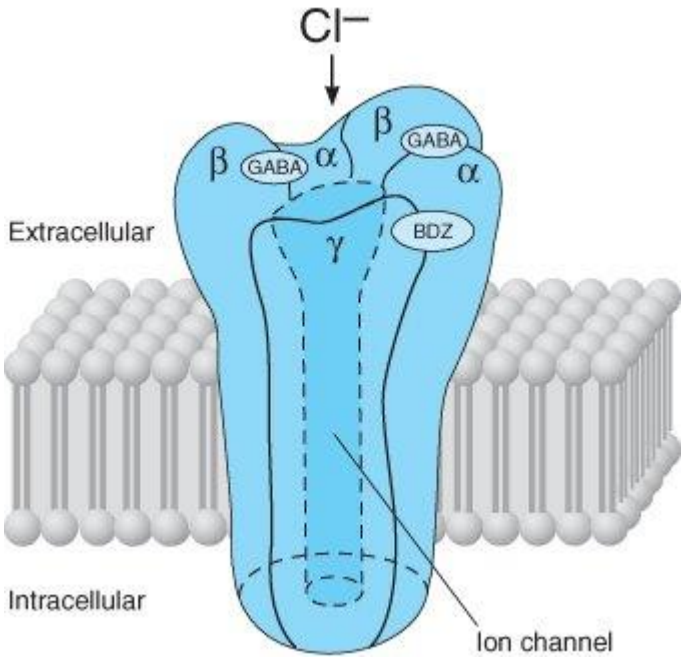
specific regulatory site on $GABA_A$ receptor

binding site for

barbiturates

↑ duration of channel opening!!!

allosteric modulator



Barbiturates

Effects:

- similar to BDZ
  but! extremly depressant on CNS
- cardiovascular/respiratory depression
- hepatic enzyme induction (phenobarbital)
  - OAC, coumarin, phenytoin, digitalis (serum cc.↓)

Barbiturates

Therapeutical use:

- obselete drugs!!!
- anti-seizure therapy: infants, children→phenobarbital
- sedation and amnesia before and during medical and surgical procedures → thiopental
- main component of balanced anaesthesia (i.v.) → thiopental
- therapy of neonatal jaundice → phenobarbital

Barbiturates

Adverse effects:

- tolerance→dependence/addiction→abuse
  → respiratory depression, coma (ethanol!)
- withdrawal syndrome
  - psychological
  - physical
- more marked than, BZDs

„Z compounds”

- zolpidem, zopiclon, zaleplon
  - selective ω_1 receptor agonist (bind selectively to α_1 subunit)
  - ω_1 receptor: cortex, hippocampus
  - novel hypnotic effects – no CNS depression
  - no anxiolytic, sedative, muscle-relaxant effects
  - can be antagonized by flumazenil

Melatonin receptor agonists

- Ramelteon:
  - agonism on MT_1, MT_2 receptors (suprachiasm. nucl.)
  - no direct effects on GABAerg neurons
  - hypnotic drug
    - treatment of insomnia
  - oral administration
    - rapid absorption, excessive first-pass metabolism
  - no anxiolytic, sedative, muscle-relaxant effects
  - adverse effects:
    - dizzines, fatigue
    - endocrine changes: testosterone↓ prolactin↑
  - no withdrawal symptoms, no abuse

5 HT receptor agonists

- Buspirone
  - partial agonist ($5HT_{1A}$ receptor)
  - sedative, hypnotic, euphoric effects
  - no anticonvulsant, muscle relaxant properties
  - no withdrawal symptoms, no abuse
  - no prompt effect (appr. 1 week)
  - active metabolit: α_2R agonism, BP↓
  - other drugs: gepirone, ipsapirone

Other drugs producing sedatohypnotic-anxiolytic effects

- chloralhydrate
- promethazin, cyclizin (antihistamines)
- TCA (imipramine)
- Alcohols

Alcohols

- history: Ancient Aegypt
  Roman Empire
  Medieval ages
  Industrial revolution

„most commonly abused drug”
„French paradox”

- main types:
  - ethyl-alcohol (ethanol)
  - methyl-alcohol (methanol)
  - ethylen-glycol

Ethanol

- Pharmacokinetic aspects
  - water-soluble
  - rapid absorption (stomach, small intestine)
  - rapid distribution, CNS („well perfused”)
  - metabolized in the liver
    - ADH (ethanol→acetaldehyde), ADH1A, ADH1B, AD1C
    - MEOS (CYP2E1) (when ADH is saturated)
    - ALDH (acetaldehyde →acetic acid), (mutation:ALDH2*2)
  - excreted by kidney, lungs

Ethanol (acute consumption)

- mechanism of action
  - CNS:
    - inhibiting glutamate R (NMDA channel)
    - enhancing the action of GABA on $GABA_AR$
    - blocking VG sodium/calcium channels
    - activating VG potassium channels
    - release of β endorfins
  - Heart
    - cardiodepressive effect
  - Respiratory system
    - depression
  - Smooth muscle
    - vasodilation

BAC (mg/dl)	symptoms
50-100	sedation, „subjective high”, slower reactions
100-200	impaired motorium, slurred speech, ataxia
200-300	emesis, stupor
300-400	coma, blackout
>500	respiratory depression, death

Ethanol (chronic consumption)

- Liver and GIT
  - fatty liver, alcohol induced hepatitis, cirrhosis
  - enzyme induction (early phases)
  - chronic pancreatitis
  - malabsorption syndrome
- CNS
  - neurotoxicity (Wernicke-Korsakoff syndrome)
  - tolerance – dependence – alcohol withdrawal syndrome
    - delirium tremens
- Cardiovascular system
  - cardiomyopathy
  - heart failure
  - arrhythmia
  - CHD
- Blood/Immune system
  - anaemia
  - infections
- Fetal alcohole syndrome
  - intrauterine growth retardation
  - microcephaly
  - abnormalities in development of midfacial region

Ethanol

Management of acute alcohol intoxication

- prevent respiratory depression
- prevent aspiration (vomitus)
- glucose i.v.
- thiamine i.v. (Vitamin B_1)
- prevent electrolyte disturbances: antiemetic drugs (metoclopramide, Vitamin B_6)

Ethanol

Management of alcohol withdrawal syndrome

- sedation, anxiolysis, anti-seizure therapy
  - diazepam, clonazepam, chlordiazepoxide
- antipsychotic
  - haloperidol, carbamazepine, mepobramate
- ICP↓
  - glycerol, mannisol, Oradexon®
- neuroprotection
  - thiamine (Vitamin B_1)
  - glucose
- electrolyte, saline suppl.

Ethanol

Treatment of alcoholism

- disulfiram (Antaethyl®)
  - blocking ALDH → acetaldehyde↑, „hangover”
  - sweating, facial flushing, nausea, vomiting, hypotension, confusion
- acamprosate
  - NMDA antagonist, $GABA_AR$ activator
  - effects based on receptor occupancy – partial agonism
- naltrexone

Methanol

- industrial application, detergents
- accidental/suicide intoxication
- absorbed from skin, GIT
- metabolized by ADH, ALDH
  (methanol→formaldehyde→formic acid)

- Symptoms
  - visual disturbances (snow storm)→(retina destruction)
  - nausea, vomitus, seizures (metabolic acidosos)
  - respiratory distress, coma

Intoxication of methanol

- Therapy
  - decontamination
  - ethanol (p.o., i.v.) – saturating ADH
  - fomepizole – inhibitor of ADH
  - alkalization (Na_2HCO_3)
  - haemodialysis
  - support of respiration
  - anti seizure therapy

Ethylene glycol

- windshield washing, anti-freeze formulations
- accidental/suicide intoxication
- rapid absorption from GIT
- metabolized by ADH

- Symptoms
  - headache
  - nausea, vomitus, seizures (metabolic acidosos)
  - acute renal failure
  - respiratory distress, coma

Intoxication of ethylene glycol

- Therapy
  - decontamination
  - ethanol (p.o., i.v.) – saturating ADH
  - fomepizole – inhibitor of ADH
  - alkalization (Na_2HCO_3)
  - haemodialysis
  - support of respiration
  - anti seizure therapy