2nd seminar

Antiepileptic (anticonvulsive, antiseizure) drugs, Antipsychotics

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Epilepsy, seizures

- history:
  - most common neurology disorder
  - epilepsy – 0,1% of population
  - „morbus sacer”

- background:
  - localized or generalized discharge of the cerebral neurons (epileptogen focus)
  - (seizures=somatic manifestations of the CNS discharge)

- definition
  - epileptiform /epileptic seizure (accidental, temporary)
    - fever (neonates, children) – „hyperpyretic seizure/convulsion”
    - hypoglycaemia
    - drug/alcohol withdrawal
    - hyperventillation
    - hypoxia

  - epilepsy (as disease) – at regular intervals, repetitive, periodic
    - idiopathic (genuine)
    - symptomatic
      - trauma (CNS)
      - neoplasma
      - meningitis
      - malformations in CNS

Patomechanism

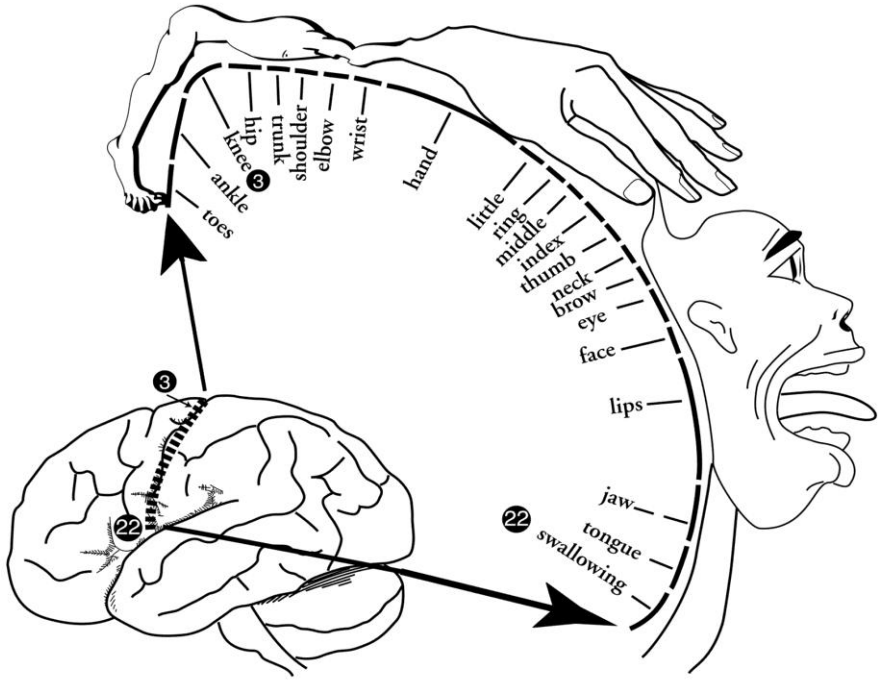
1. excitation – PDS – spontaneous depolarization
2. propagation – spreading into diferrent CNS structures
3. hypersynchronization
4. seizures (somatic manifestation)

Hypothesis:

glutamate ↑

GABA ↓

BDRF ↑



Seizure types

Partial seizures (motoric, sensoric, vegetative) (60%)

simple partial seizure
complex partial seizures
partial seizures (secondarily generalized) to GTCS

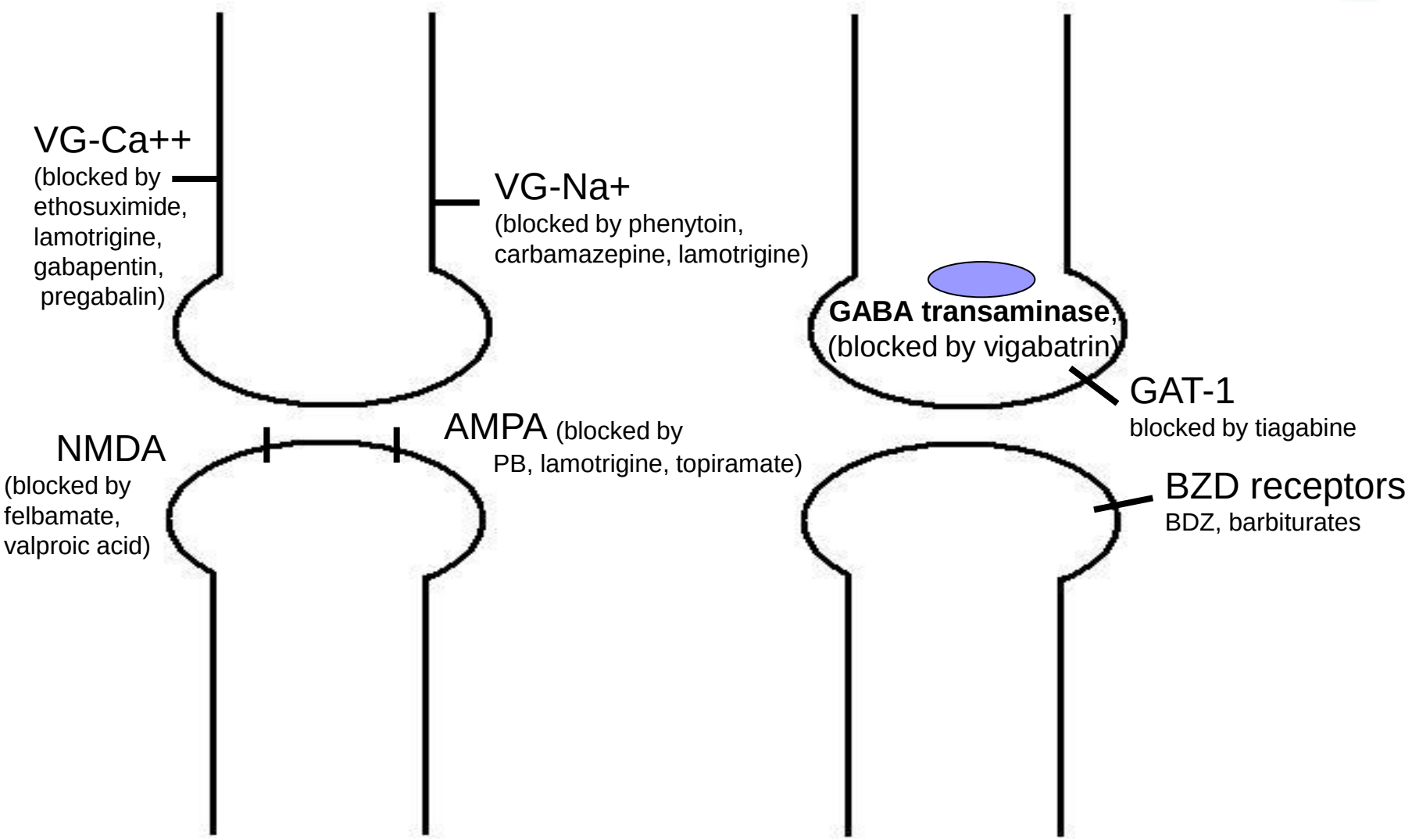
Generalized seizures (40%)

absence seizures
GTCS (generalized tonic clonic seizures)
myoclonic seizures
atonic/akinetic seizures

clinical forms!

- epileptic attack – (ictus epilepticus)
- repeated seizures
- status epilepticus – („permanent epileptic state”)

Patomechanism, targets



Antiseizure drugs

- Phenytoin, fosphenytoin, mephenytoin
  - pharmacodynamic features
    - (diphenylhidantoin)
    - Epanutin®, Diphedan®
    - the oldest antiseizure drug
    - blocking VG Na^+ channels (antiarrhythmic drugs)
  - pharmacokinetic features
    - well absorbed
    - PPB↑, higher cc. of phenylbutazon, warfarin, sulfonamide
    - enzyme induction!!!
  - adverse effects
    - pro-arrhythmic
    - hyperthyreosis-(increased affinity to THBG)
    - diplopia, ataxia
    - gingiva hyperplasia (impaired collagen metabolism)
  - clinical use
    - partial seizures (simplex, complex)
    - GTCS
    - 15-20 mg/kg

Antiseizure drugs

Carbamazepine (Tegretol ®, Neurotop®)

tricyclic structure (see in antidepressants!)

- pharmacodynamic features
  - blocking VG $Na^{+,}$ channels → limits the repetitive firing
- pharmacokinetic features
  - well absorbed
  - PPB ≈ 70%
  - inducing CYP3A4 (like phenobarbital) , ↓ serum cc. of phenytoin, valproic acid, OAC
- adverse effects
  - teratogenic
  - drowsiness,
  - aplastic anaemia, agranulocytosis
- clinical use
  - partial seizures (simplex, complex)
  - GTCS
  - trigeminal neuralgia
  - effective dose: 600-800 mg/day

Antiseizure drugs

Oxcarbazepine (Trileptal®)

- similar to carbamazepine
- less potent enzyme inductor than carbamazepine

Phenobarbital

- pharmacodynamic features
  - GABA R modulating effect - PDS↓
- pharmacokinetic features
  - well absorbed
  - hepatic enzyme induction! CYP3A4, (unwanted pregnancy!)
- adverse effects
  - sedation
  - cardiovascular/respiratory depression
- clinical use
  - partial seizures (simplex, complex)
  - GTCS

Antiseizure drugs

Ethosuximide

- pharmacodynamic features
  - blocking T-type Ca^{++} channels (especially in thalamic neurons)
- pharmacokinetic features
  - rapidly absorbed
  - half life: 40 hours
- adverse effects
  - gastric distress
  - nausea, vomitus
  - paresthesias
- clinical use
  - absence seizures (first-line treatment)
  - 250-500 mg

Antiseizure drugs

Lamotrigine (Lamictal®)

- pharmacodynamic features
  - blocking N-type Ca^{++} channels
  - blocking Na^{+} channel
- pharmacokinetic features
  - rapidly absorbed
  - half life: 24 hours
- adverse effects
  - headache, diplopia
  - somnolence
  - skin rash
- clinical use
  - Lennox-Gastaut syndrome (in childhood, multiple seizure types, mental retardation)
  - 100-300mg/ day

Antiseizure drugs

Gabapentin, Pregabalin

GABA analogs

- pharmacodynamic features
  - not agonise $GABA_A$ R (in spite of structural resemblence to GABA)
  - blocking VG-Ca^{2+} channels (N-type)
  - structural analog of GABA
- pharmacokinetic features
  - not bound to PP
- adverse effects
  - sedation
- clinical use
  - partial seizures
  - pain syndromes
  - 900-1800-3600 mg/day

Antiseizure drugs

Topiramate

- pharmacodynamic features
  - blocking VG Na^+ channels, stimulating K^+ currents
  - enhancing $GABA_A$ mediated Cl^- currents
- pharmacokinetic features
  - rapidly absorbed
- adverse effects
  - fatique, cognitive slowing
  - paraesthesias
- clinical use
  - partial seizures
  - Lennox-Gastaut syndrome
  - migraine, headache
  - 200-600 mg/day

Antiseizure drugs

Vigabatrine (Sabril®)

- pharmacodynamic features
  - structural analog of GABA
  - irreversible inhibitor of GABA-T (GABA transaminase)
- pharmacokinetic features
  - well absorbed
- adverse effects
  - drowsiness, dizziness, weight gain
  - bilateral vision loss
  - intramyelinic oedema (infants)
- clinical use
  - refractory partial seizures

Antiseizure drugs

Tiagabine

- pharmacodynamic features
  - inhibitor of GABA re-uptake mechanism
  - blocking GAT-1> GAT-2> GAT-3→e.c. GABA↑
  - modulating VG-Ca++ channels (N-type)→glutamate release↓
- pharmacokinetic features
  - total absorption: 90-100%
- adverse effects
  - nervousness, dizziness, tremor
  - somnolence, ataxia
- clinical use
  - refractory partial seizures
  - partial seizure secondarily generalized

Antiseizure drugs

Felbamate (Taloxa®)

- pharmacodynamic features
  - blocking NMDA R
  - modulating $GABA_A$ R
- pharmacokinetic features
  - well absorbed
  - excreted in urine
- adverse effects
  - hepatitis
  - aplastic anaemia, agranulocytosis
- clinical use
  - partial seizures

Antiseizure drugs

Valproic acid (Convulex®)

- pharmacodynamic features
  - blocking NMDA R
  - facilitating GAD (GABA synthesis)
  - inhibiting GAT-1
  - inhibiting GABA-T (GABA transaminase) - at high concentrations
- pharmacokinetic features
  - well absorbed
  - PPB≈90%
- adverse effects
  - nausea, vomitus
  - hepatitis
  - embriopathy (spina bifida)
- clinical use
  - absence seizures
  - GTCS

Antiseizure drugs

Benzodiazepines

diazepam

clonazepam

clobazam

- pharmacodynamic features
  - allosteric moduation on $GABA_AR$
- clinical use
  - continuous seizure activity
  - repeated epileptiform attack
  - status epilepticus

Therapeutic indications

simple/complex partial seizures
- carbamazepine
- phenytoin
- valproic acid

absence seizures
- ethosuximide
- valproic acid

GTCS
- carbamazepin/oxcarbazepine
- phenytoin
- levetiracetam

status epilepticus
- benzodiazepine
  - diazepam (10-20 mg i.v.), clonazepam (2 mg i.v.)
- O2, glucose i.v., tiamine
- phenytoin (15-20 mg/kg-ECG controll)
- phenobarbital (15-20 mg/kg, 100mg/min i.v.)
- thiopental, muscle relaxation, resp. support

Dopaminergic neurotransmission

Dopaminergic systems

- nigrostriatal pathway
  - substantia nigra→corpus striatum
  - coordination of voluntary movement
  - deficiency!→Parkinson's disease
- mesolimbic-mesocortical pathway
  - mesencephalon→limbic system/cortex
  - cognitive functions, self-reward system, perception, feelings
  - N.B.! – overstimulation!
- tuberoinfundibular pathway
  - hypothalamus-hypophysis
  - endocrine functions
  - dopamin=PIF, prolactin secretion↓
- medullary-periventricular pathway
  - beside the III.-IV. ventricle
  - eating behavior
- area postrema
  - chemosensitive trigger zone
  - antiemesis-antpsychotics

Dopaminergic neurotransmission

Dopamine receptors:

D_1 like, D_2 like

- D_1:Gs→AC→cAMP↑ putamen, cortex, nucleus accumbens
- D_2 :Gi→cAMP↓, seen above
- D_3 :Gi→cAMP↓ frontal cortex, medulla, mesencephalon
- D_4 :Gi→cAMP↓ cortex
- D_5 :Gs→AC→cAMP↑, hippocampus, hypothalamus

Schizophrenia

- psychiatric disease
- etiology:
  - dopamine hypothesis
    - hyperfunction of mesolimbic-mesocortical dopaminergic pathway
    - primarily described (development of typical antipsychotics-D2R antagonism)
    - D_2 R blocking drugs reduce psychotic symptoms
    - D_2 R activating drugs (levodopa, bromocriptine) produce psychosis
    - post-mortem study – increased D_2 R density in midbrain (mesencephalon)
    - increased dopamine levels in putamen, nucleus accumbens
  - serotonin
    - indole hallucinogenes (LSD), mescalin provoke psychotic symptoms
    - $5HT_{2A}$ R agonism – hallucinations
    - inverse agonists of $5HT_{2A}$ R (AAP-clozapine, queitapine) reduce sch. sympt.
  - glutamate hypothesis
    - hypofunction of NMDA R located on GABAerg neurons provoke schizphr.

Schizophrenia

Symptoms:

- positive symptoms:
  - illusions / delusions (irreal)
  - auditory/visual hallucinations
  - thinking disorders
  - agitation, agressive behaviour

- negative symptoms:
  - blunted effect and emotion
  - poverty of speech (alogia)
  - inability to experience pleasure (anhedonia)
  - lack of motivation
  - lack of social relationships
  - apathia, agonia

Antipsychotics (neuroleptics)

Classification (based on chemical structure)

- phenothiazine derivatives
  - propyl-amines
    - chlorpromazine
    - promethazine
  - piperidine derivatives
    - thioridazine
  - piperazine derivatives
    - perphenazine
- thioxanthene derivatives
  - thiothixene
- butyrophenon derivatives
  - haloperidol
  - droperidol
- benzamide derivatives
  - tiaprid
  - suliprid
- dibenzodiazepines
  - clozapine
  - olanzapine
  - quetiapine
- benzioxazol derivatives
  - risperidon

Classification
(based on receptor selectivity and side effect profile):

typical antipsychotics

atypical antipsychotics

Antipsychotics

Typical antipsychotics:

- D_2 R antagonism
- anti-cholinerg effect (obstipation)
- anti adrenerg effect (orthostatic hypotension)
- reduction of the positive symptoms of schizophrenia (negatives?)
- broad side effect profile
  - EPS (dopamine depletion of nigrostriatal pathway)
    - acute
      - achatisia (uncontrolled restlessness)
      - acute dystonic reactions (spastic retrocollis/torticollis)
    - chronic
      - pseudo Parkinson syndrome (bradykinesia, rigidity, tremor)
      - perioral tremor („rabbit syndrome”)
      - tardive dyskinesia (choreo-athetoid movements)
      - MNS (malignant neuroleptic syndrome) - th.: bromocriptin, danthrolen
  - endocrine effects (dopamine depletion of tuberoinfundibular pathway)
    - hyperprolactinaemia, galactorrhea-amenorrhea
    - gynecomastia, impotence

Antipsychotics

- broad side effect profile
  - antiemetic effects (D2R blocking in area postrema)
    - promethazine
  - cardiac toxicity
    - thioridazine
      - QTc prolongation, arrhythmias (TdP)

Antipsychotics

Atypical antipsychotics:

- expanded receptor profile
- reduction both of the positive and negative symptoms of schizophrenia
- reduced side effect profile
  - clozapine
    - blocking D_4 R> D2R = $5HT_{2A}$R > D_1R
    - central adrenerg effect
    - mesolimbic selectivity
    - side effects
      - obesity, insulin resistance
      - agranulocytosis!
      - myocarditis
  - olanzapine (Zyprexa®)
    - $5HT_{2A}$R > H1R > D_4 R> D2R
    - mesolimbic selectivity
    - side effects
      - obesity, insulin resistance

Antipsychotics

Atypical antipsychotics:

- risperidone (Risperdal®)
  - blocking D2R > $5HT_{2A}R$ > H1R
  - mesolimbic selectivity
  - side effects
    - EPS
    - hyperprolactinaemia
    - sedation, headache
    - MNS (depot)
- sertindole (Serdolect®), ziprasidone
  - D2R > $5HT_{2A}R$ > α1
  - side effects
    - QT prolongation

Develompent of obesity and insulin resistance during AAP treatment

weight gain

- blocing H_1R in hypothalamus (VMHN, PVN)
- TNF-α hypersecretion
- α_2 adrenergic agonism
- decreased leptin levels, leptin resistance

insulin resistance

- $5HT_{1A}R$ antagonism → ↓response of pancreatic β cells
- M_3R antagonism → ↓response of pancreatic β cells
- inhibitory effect on GLUT transporters in skeletal muscle