ANTIANXIETY DRUGS: BENZODIAZEPINES

Sedatives and hypnotics

Drug List
phenobarbital (Luminal Sodium)
diazepam (Valium)
lorazepam (Ativan)
midazolam (Versed)
zolpidem (Ambien)
The Action potential

Basic Neurochemistry, 8th Ed, c2006
Basic structure: voltage gated ion channels

Basic Neurochemistry, 8th Ed, c2006
Generalized structure for voltage-gated ion channels
Voltage Gated Channels

- $\text{Na}^+$ and $\text{Ca}^{2+}$ channels: cations flow in; inside of cell more …
- $\text{K}^+$ channels: cations flow out; inside of cell more …
- $\text{Cl}^-$ channels: anions flow in; inside of cell more …
- Filters are highly selective
Drugs that act at voltage-gated ion channels

- $\text{Na}^+$ channels: local anesthetics, antiepileptic drugs, antimania drugs
- $\text{K}^+$ channels: myocardial ischemia, antiarrhythmics
- $\text{Ca}^{2+}$ channels: antiarrhythmics, hypertension, heart failure, myocardial ischemia
Ligand-gated Ion Channels in CNS

- Ligand-gated
  - Glutamate
  - Gamma-aminobutyric acid (GABA)
  - Acetylcholine
  - Serotonin
High concentrations of glutamate and GABA are present in the CNS

<table>
<thead>
<tr>
<th>Substance</th>
<th>Concentration (nmol/g.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glutamate</td>
<td>14000</td>
</tr>
<tr>
<td>Aspartate</td>
<td>4000</td>
</tr>
<tr>
<td>γ- Aminobutyrate (GABA)</td>
<td>2500</td>
</tr>
<tr>
<td>Glycine</td>
<td>2500</td>
</tr>
<tr>
<td>ATP</td>
<td>2500</td>
</tr>
<tr>
<td>Acetylcholine</td>
<td>25</td>
</tr>
<tr>
<td>Dopamine</td>
<td>6.5</td>
</tr>
<tr>
<td>Noradrenaline</td>
<td>2.5</td>
</tr>
<tr>
<td>Serotonin</td>
<td>2.5</td>
</tr>
</tbody>
</table>
Excitatory Ligand–gated ion channels

- **Glutamate receptors:**
  - NMDA, Ca\(^{2+}\) and Na\(^{+}\). Blocked by phencyclidine and ketamine
  - AMPA, Na\(^{+}\), sometimes Ca\(^{2+}\)
  - Metabotropic; G–protein coupled

- **Nicotinic cholinergic:**
  - permeable to Na\(^{+}\) in periphery, Na\(^{+}\) and Ca\(^{2+}\) in CNS

- **Serotonin, 5–HT\(_{3}\), Na\(^{+}\) permeable.** Blocked by ondansetron
Glutamate neuron

Meyer & Quenzer, Psychopharmacology
Ligand-gated channel subtypes of the glutamate receptor

Meyer & Quenzer, Psychopharmacology
N-methyl-D-aspartate receptor ligands

- Agonist: both glutamate and aspartate are agonists
- Co-agonist: glycine or D-serine
- Permeability: Ca$^{2+}$ and Na$^+$
- Phencyclidine (PCP) and ketamine: noncompetitive antagonists

Meyer & Quenzer, Psychopharmacology
Inhibitory ligand-gated ion channels

- GABA – increases Cl\(^-\) in cell
  - Anticonvulsants, barbiturates, benzodiazepines, convulsants, inhalant anesthetics
  - $\gamma$-aminobutyric acid (GABA)
    \[
    \text{H}_2\text{N}-\text{CH}_2-\text{CH}_2-\text{CH}_2-\text{COOH}
    \]
- Glycine – increases Cl\(^-\) in cell, mainly in spinal cord
  - Blocked by strychnine
  - Glycine
    \[
    \text{CH}_2(\text{NH}_3^+)-\text{COOH}
    \]
Summary

- There are voltage- and ligand-gated ion channels
- Voltage-gated channels show greater selectivity
- Ligand-gated channels get ions moving, then voltage-gated channels come into play
- Multiple subtypes and subunits
Anxiety

- An unpleasant state of anticipation, apprehension, fear or dread

- Physiological symptoms: autonomic arousal, alertness, motor tension

- Psychological symptoms: fear, obsession, nervousness, worry
Anxiety Disorders

- Panic disorder
- Agoraphobia
- Generalized anxiety disorder
- Social phobia/performance anxiety
- Specific phobia
- Posttraumatic stress disorder
- Obsessive compulsive disorder
Anxiolytic Medications

- Antidepressants
- Benzodiazepines
- Buspirone
- β-Adrenergic blockers
GABA
γ-aminobutyric acid
H₂N-CH₂-CH₂-CH₂-COOH
GABA<sub>A</sub> Receptor

Benzodiazepines

Barbiturates

Neurosteroids

Alcohol

Anesthetics

Amanita muscaria
Barbiturates

Phenobarbital (Luminal)

Pentobarbital (Nembutal)

Thiopental (Pentothal)
# Characteristics of Barbiturates

<table>
<thead>
<tr>
<th></th>
<th>Phenobarbital</th>
<th>Pentobarbital</th>
<th>Thiopental</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lipid solubility</td>
<td>+</td>
<td>++</td>
<td>+++</td>
</tr>
<tr>
<td>Entry → CNS</td>
<td>Long</td>
<td>Intermediate</td>
<td>Ultra-short</td>
</tr>
<tr>
<td>Metabolism</td>
<td>Excreted in urine, 25% unchanged</td>
<td>Totally metabolized, not in urine</td>
<td>Totally metabolized, not in urine</td>
</tr>
</tbody>
</table>
Characteristics of Barbiturates

- Induce P450’s in liver. Can increase metabolism of other drugs
- Tolerance develops to:
  - P450 effect
  - Behavioral effect, can handle more drug
  - Anticonvulsant effect
- Physical dependence, rapid withdrawal leads to overexcitement: seizures, fever, death
Dose response of CNS Depression with Barbs and BZDs
Advantages of Benzodiazepines over barbiturates

- Benzodiazepines don’t induce cytochrome P450’s
- Much less respiratory depression with benzodiazepines
- Much less physical dependence
- No euphoria
Benzodiazepines

- Bind at their own receptor site on the $\text{GABA}_A$ receptor
- Increase binding of GABA
- Elicit more $\text{Cl}^-$ channel openings (barbiturates keep $\text{Cl}^-$ channels open longer)
BDZ–induced shift in GABA Dose Response Curve

ED₅₀ = 8 μM

- Chlordiazepoxide
- Control

GABA concentration (M)

\[ \frac{\text{GABA}}{\text{GABA}} \times 10^{-4} \text{M} \]

140
120
100
80
60
40
20
0

10⁻⁶
10⁻⁵
10⁻⁴
10⁻³
Barbiturates potentiate the actions of GABA on the GABA$_A$ receptor–channel complex
Benzodiazepine structure

Temazepam
Pharmacological actions of benzodiazepines

- Relief of anxiety
- Drowsiness and sedation
- Skeletal muscle relaxation
- Anticonvulsive activity
- Anterograde amnesia

All due to actions in CNS
Absorption, metabolism and excretion

- Relative rates of absorption, metabolism and excretion differ markedly
- Drugs are prescribed for their pharmacokinetics
- Greater lipid solubility leads to greater absorption and more rapid onset of action
- Half-life largely determined by metabolism
Representative of **Diazepam**, a highly lipophilic drug
Metabolism of benzodiazepines

Diazepam
\[ \downarrow \text{P450} \]
Desmethyldiazepam (nordiazepam)
\[ \downarrow \]
Conjugation
\[ \downarrow \]
Urinary excretion

Long lasting active metabolite

Lorazepam
## Pharmacokinetic characteristics

<table>
<thead>
<tr>
<th>Agonist</th>
<th>Trade name</th>
<th>Time to [peak plasma] (hr)</th>
<th>Elim. Half-life (hr)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diazepam</td>
<td>Valium</td>
<td>0.5-2</td>
<td>30-60</td>
<td>Very lipid soluble</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Ativan</td>
<td>1-6</td>
<td>10-18</td>
<td>More H$_2$O soluble</td>
</tr>
<tr>
<td>Temazepam</td>
<td>Restoril</td>
<td>2-3</td>
<td>8-15</td>
<td>Slower oral absorption</td>
</tr>
<tr>
<td>Triazolam</td>
<td>Halcion</td>
<td>1-2</td>
<td>1.5-4</td>
<td>Amnesia at higher doses</td>
</tr>
<tr>
<td>Midazolam</td>
<td>Versed</td>
<td>I.V., I.M.</td>
<td>2-5</td>
<td>Rapidly inactiv., pre-anesthetic, amnesia</td>
</tr>
</tbody>
</table>
Flumazenil

- Benzodiazepine receptor antagonist
- Reverses the effects of benzodiazepines
- Hastening recovery from benzodiazepine sedation or anesthesia
- Only available for IV administration
Half-life advantages to benzodiazepines

- Therapeutic uses of a benzodiazepine depend on half life

- BDZs used as anticonvulsants have a long half life; rapid entry into brain needed for status epilepticus (diazepam or lorazepam)

- Want a short elimination half-life for hypnotics, ex. temazepam

- Anti-anxiety agents should have long half life, ex. lorazepam
# Side effects of Benzodiazepines and Barbiturates

<table>
<thead>
<tr>
<th>Effects</th>
<th>Barbs</th>
<th>BDZ</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hangover</td>
<td>+</td>
<td>+</td>
<td>Longer half–life drugs</td>
</tr>
<tr>
<td>Withdrawal &amp; dependence</td>
<td>+</td>
<td>+</td>
<td>Short–acting drugs</td>
</tr>
<tr>
<td>Ataxia &amp; nystagmus</td>
<td>+</td>
<td>+</td>
<td>Unsteady gait, cerebellum</td>
</tr>
<tr>
<td>Paradoxical excitement</td>
<td>+</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Drug–drug interaction</td>
<td>+</td>
<td>–</td>
<td>P450 effects</td>
</tr>
<tr>
<td>Respiratory depression</td>
<td>+</td>
<td>–</td>
<td>BDZs + other CNS depressants</td>
</tr>
<tr>
<td>Anterograde amnesia</td>
<td>–</td>
<td>+</td>
<td>Forward amnesia</td>
</tr>
</tbody>
</table>
Other effects of benzodiazepines

- Lightheadedness
- Increased reaction time
- Motor uncoordination
- Confusion

- Less of a problem when given at night
- Big problem if combined with alcohol
Drug interactions with benzodiazepines

- Benzodiazepines are safe, but are CNS depressants
- Have potentiative effects with other CNS depressants: antipsychotics, opioids, alcohol, antihistamines, MAO inhibitors, tricyclic antidepressants, anticonvulsants
- Inhibitors or activators of CYP3A4 will affect some benzodiazepines
Contraindications to benzodiazepine use

- Alcoholics and older patients with liver problems
  - Older patients can use a benzodiazepine not metabolized by a P450
Therapeutic uses for benzodiazepines

- Anxiety (lorazepam)
- Sleep disorders (lorazepam, triazolam, flurazepam, temazepam)
- Seizures (clonazepam, lorazepam)
- Skeletal muscle spasms (diazepam)
- Alcohol withdrawal (diazepam)
Tolerance, abuse, dependence of BDZs

- Tolerance develops to sedative effects, more rarely to anxiolytic effects
- Some risk for dependence and abuse but much less than for other drugs like barbiturates
- Abuse may be more prevalent in people that also abuse other substances
- May be no abstinence syndrome following gradual withdrawal of drug
- May be physical dependence after long-term use
GABA<sub>A</sub> Receptor subtypes matter

Benzodiazepines

Cl⁻

Barbiturates

Neurosteroids

Alcohol

Anesthetics
### Role and location of $\text{GABA}_A$ receptor subtypes

<table>
<thead>
<tr>
<th>Subtype</th>
<th>Brain Location</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\alpha_1$</td>
<td>Widespread, cerebral cortex</td>
<td>★ <strong>Sedation</strong>, amnesia, seizure protection</td>
</tr>
<tr>
<td>$\alpha_2$</td>
<td>Limbic region, striatum, cortex</td>
<td>★ <strong>Anxiolytic</strong></td>
</tr>
<tr>
<td>$\alpha_5$</td>
<td>Hippocampus</td>
<td>Associative learning &amp; memory</td>
</tr>
<tr>
<td>$\beta_2, \beta_3$</td>
<td>Widespread</td>
<td>Consciousness (required for iv anesthetic action)</td>
</tr>
</tbody>
</table>
Zolpidem, a GABA\textsubscript{A} \(\alpha 1\)–subunit selective drug

- Non-benzodiazepine, acts at benzodiazepine receptor
- Shortens sleep latency, prolongs sleep time
- Plasma half-life = 2 hrs
- Wakeful behavior and amnesia
- New zolpidem extended release
Other GABA_A α1 subtype-selective drugs

- Zaleplon (Sonata): hypnotic, t ½ = 1 hr
- Eszopiclone (Lunesta): hypnotic, t½ = 6 hr
- Not limited to short term use
Safety and Adverse effects

- Risk of abuse and tolerance low when used as directed

- Few withdrawal reactions, although some have been reported

- No tolerance to therapeutic effect
Drugs found in Michael Jackson upon autopsy

- Diazepam (Valium)
- Alprazolam (Xanax)
- Zolpidem (Ambien)
- Propofol
- Hydromorphone (Dilauded)
- Hydrocodone (Vicodin)
- Fentanyl
Drugs found in Heath Ledger upon autopsy

- Alprazolam (Xanax)
- Diazepam (Valium)
- Temazepam (Restoril)
- Oxycodone (OxyContin)
- Hydrocodone (Vicodin)
- Doxylamine or diphenhydramine (Unisom)
Buspirone (Buspar)

- Used to treat generalized anxiety with limited severity
- Partial agonist at 5-HT$_{1A}$ receptors
- Lacks CNS depressant properties ★
- Slow onset of action
Chloral hydrate

- Rapidly converted to ethanol in liver
- Useful for sedation in children or elderly undergoing uncomfortable procedures