The Neuropharmacology of Benzodiazepines and Drugs with Similar Mechanism of Action

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Disclosures

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Objectives

1. Describe the basic neurophysiology of anxiety and anxiolysis
2. Develop the target and mechanism of BZD anxiolytic activity
   - describe the association and difference between GABA\textsubscript{A} and BZD receptors
   - describe why BZD and ‘Z,E’ drugs share a common anxiolytic mechanism
3. Describe the basic neuropharmacology of BZD and related drugs
4. Describe basic ADME (absorption, distribution, metabolism, elimination) features of these drugs
5. Describe ‘peripheral’ BZD receptors
Underlying principles

• The CNS requires balance of excitatory and inhibitory a.a.
• In brain: Glu and GABA
• Excess excitation – seizure; excess inhibition – coma
Underlying principles

• **Anxiety**: fear or nervousness about what might happen
  - productive for survival
  - transient
  - total elimination is not desirable

• **Clinical anxiety**: an *abnormal* and *overwhelming* sense of apprehension and dread (panic)
  - counterproductive
  - on-going, physiologically draining
  - return to baseline (*anxiolysis*) desirable
  - the optimal approach matches the treatment (non-pharmacologic or pharmacologic) to cause
“Benzodiazepine” pharmacology

- Benzodiazepines (BZDs) are defined based on chemical structure (benzenze ring plus diazepine ring)

- Benzodiazepines (BZDs) produce their major effects through affinity for (binding to) and intrinsic activity (agonist action) at benzodiazepine receptors (BZD-R)
- But substances with non-benzodiazepine chemical structures (e.g., the “Z” drugs) also act at BZD-R
- ➔ The pharmacologic effects are the same
- Thus, it is most informative to speak of BZD-R pharmacology
Non-BZD BZD-R agonists

Benzodiazepines
- Imidazopyridines
  - e.g., Zolpidem
    (AMBIEN, etc.)

Pyrazolopyrimidines
- e.g., Zaleplon
  (SONATA, etc.)

Cyclopyrrolones
- e.g., Eszopiclone
  (LUNESTA, etc.)
- Zopiclone
  (IMOVANE, etc.)

β-Carbolines: Abecarnil, Gedocarnil, SL-651,498, ZK-93423

BZD-R pharmacology

Central BZD receptors
• discovered in 1977\(^1\)
• autoradiographic demonstration in human brain in 1988\(^2\)
• positive allosteric modulation of the GABA-A receptor

Peripheral BZD receptors
• discovered in 1992\(^3\)
• Tryptophan-rich sensory protein (TspO)
  (translocator protein)

\(^3\)McEnery et al. (1992) PNAS 89:3170-3174.
BZD-R pharmacology

BZDs and other BZD Receptor Agonists

BZD receptor-mediated effects

“Off-target” effects
GABA_A ionotropic receptor

https://upload.wikimedia.org/wikipedia/commons/0/06/GABAA_receptor_schematic.png
Central BZD receptor

https://commons.wikimedia.org/wiki/File:GABAA-receptor-protein-example.png
https://upload.wikimedia.org/wikipedia/commons/0/0e/Cell_GABA_Receptor.png
BZD MoA: summary

- Selective binding to BZD receptor site on $\text{GABA}_A$ complex
- No effect on $\text{GABA}_A$ binding site
- Positive allosteric modulation of GABA-induced $\text{Cl}^-$ influx
- BZD effect is attenuated by BZD-R antagonist (flumazenil)
- BZD-R antagonist has no direct effect on GABA
Effect of GABA$_A$ agonist binding

https://upload.wikimedia.org/wikipedia/commons/0/0e/Cell_GABA_Receptor.png
Effect of BZD-R agonist binding

https://upload.wikimedia.org/wikipedia/commons/0/e/Cell_GABA_Receptor.png
Effect of BZD-R antagonist binding
http://ibmmsrvlakit.unibe.ch/sigel/video.mp4
Non-BZD-R agonists

A pharmacophore model of the benzodiazepine binding site on the GABAA receptor.[159] White sticks represent the carbon atoms of the benzodiazepine diazepam, while green represents carbon atoms of the nonbenzodiazepine CGS-9896. Red and blue sticks are oxygen and nitrogen atoms that are present in both structures. The red spheres labeled H1 and H2/A3 are, respectively, hydrogen bond donating and accepting sites in the receptor, while L1, L2, and L3 denote lipophilic binding sites.

Same receptor → same effects (individual differences in PK, off-target Es)
BZD-R: phylogenetically old

Kristin Finno, TU undergrad; TJU Pharmacy
BZD-R in planarians

• BZDs (clorazepate, midazolam) produce dose-related effects (alter behavior)
• The BZD-induced effects are dose-relatedly attenuated by a BZD-R-selective antagonist (flumazenil)
• The non-BZD BZD-R agonist (zolpidem) dose-relatedly produces the same effects as the BZDs
• The non-BZD-induced effects are attenuated by a BZD-R-selective antagonist (flumazenil)
BZD-R in human brain

Receptor autoradiography using $[^3\text{H}]$Flunitrazepam$^1$

- Highest densities localized in cortical and limbic regions (hippocampus, nu. accumbens, amygdala, and mammillary bodies)
- Intermediate densities in basal ganglia and thalamic and hypothalamic nuclei
- Low densities in brainstem
- Very low densities in white matter

Is there an endogenous BZD-R agonist? an endozepine? the brain’s Valium?

- flumazinil does not bind to \( \text{GABA}_A \)-R, but can induce panic attacks in patients with panic disorder (but not healthy controls)
- BZDs are found in brain tissue – but also in plants
- oleamides, inosine, hypoxanthine, nicotimide: only low affinity for BZD-R; DBI (diazepam-binding inhibitor) actually acyl-CoA-binding protein
- the question remains unanswered

Multiple GABA-A receptors

- 6 different α subunits
- 4 different β subunits
- 3 different γ subunits
- most common mammalian: \((\alpha_1)_2(\beta_2)_2(\gamma_2)_1\)
Neuronal system effects

Inhibition

Governor

Disinhibition
<table>
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<th>Term</th>
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| sedation    | — Beneficial calming
              | — Also used to denote an AE                                                 |
| anxiolytic  | — Reduces anxiety without impairment of alertness                           |
| hypnotic    | — Produces drowsiness and (normal) sleep                                    |
Anxiolytic effect

‘Normal’ anxiety
• normal response of ‘fight or flight’
• normally resolves w/o medication
• but, sensitization to repeated stress can disrupt normal physiology

‘Clinical’ anxiety
• panic attacks, phobias, OCD, possibly PTSD
• clinically significant in ~10% of the population
• endogenous cause, or consequence
- major inhibitory NT in CNS (primarily brain)
- balance with excitatory amino acids
- NT at about 30% of all CNS synapses
- all CNS neurons and glial cells are sensitive to GABA
• Psychotherapeutic, cognitive, behavioral, and
• Pharmacologic (only if appropriate)
  ○ acute attacks
  ○ chronic use = 4 - 8 weeks
  ○ BZDs better TE/AE ratio than barbiturates

○ newer drugs have better TE/AE ratio than BZDs

More specific to anxiety & Fewer AE’s
Place in therapeutic history

**AEs of BZDs less than those of barbiturates:**
- CNS depression
- respiratory depression
- psychomotor function
- daytime sleepiness
- effects on REM sleep
- EtOH interaction
- hepatic enzyme induction
- DDIs
BZD ADME: A, D and E

- most are readily absorbed from GI tract
- drug-specific extent of 1\textsuperscript{st}-pass effect
- available in multiple dosage forms
- many are lipid soluble
  - pass BBB
  - most readily pass placenta
  - redistribution to/from fatty tissue
  - extended duration of effect
- most BZDs are eliminated \textit{via} urinary excretion
BZD ADME: metabolism

- hepatic via Phase 1 (CYP450 and other) and Phase 2 (glucuronide conjugation), commonly in sequence and parallel
- many Phase 1 BZD metabolites active (clorazepate a prodrug to oxazepam)
- oxazepam is also a metabolite of chlordiazepoxide, diazepam, and prazepam
- alprazolam, flurazepam, lorazepam, triazolam: direct glucuronidation
- eszopiclone and zolpidem via CYP3A4
- zaleplon via aldehyde oxidase
DDIs: PD – other GABA$_A$-R modulators

- ethanol, barbiturates, and neurosteroids
- additive or supra-additive CNS depression

![GABA-Receptor Diagram](https://upload.wikimedia.org/wikipedia/commons/0/0e/Cell_GABA_Receptor.png)

EtOH ($\alpha$)
barbiturates ($\beta$)
propofol ($\beta$)
neurosteroids ($\beta$)

https://upload.wikimedia.org/wikipedia/commons/0/0e/Cell_GABA_Receptor.png
DDIs: PK – metabolic

https://upload.wikimedia.org/wikipedia/commons/9/98/PropDrugsMetabCYP.png
Adverse effects

Glu → GABA

Citric Acid Cycle

BZD
Tolerance

- Normal physiologic process
- Develops to most drugs
- Can develop at different rates for different effects
  - TI can decrease with treatment duration
Physical dependence / withdrawal

- Physical dependence is a normal physiologic process
- Develops to most drugs
- Usually compensatory opposite to drug-induced effect
- Revealed during withdrawal (unopposed)
- Most serious for BZDs is excess excitation
Other BZD binding sites

- BZDs also bind to other receptors, located mainly in peripheral tissues and glial cells in the brain
- Originally termed ‘peripheral BZD-R’, also known as translocator protein (TSPO)
- Functions not fully known, but might involve steroid biochemistry/transport, cell proliferation/apoptosis, and immunomodulation
- TSPO null \((Tspo^{-/-})\) mice are viable\(^1\)

\(^1\)Tu et al. (2014) J Biol Chem 289:27444-27454
Peripheral BZD / TSPO distribution

- 6 healthy control subjects (3 men, 3 women)
- $^{11}$C-DPA-713, a specific PET ligand for the assessment of TSPO
- whole-body PET/CT (Positron Emission Tomography – Computed Tomography)
- absorbed dose highest in the lungs, spleen, kidney, and pancreas

Radiation Dosimetry and Biodistribution of the TSPO Ligand $^{11}$C-DPA-713 in Humans

http://jnm.snmjournals.org/content/53/2/330
Recap

1. Perspective on anxiety and anxiolysis
2. Develop a fundamental and working knowledge of the target and mechanism of BZD anxiolytic activity
   - review the association and difference between GABA\textsubscript{A} and BZD receptors
   - develop an understanding of why BZD and ‘Z,E’ drugs share a common anxiolytic mechanism
3. Review basic neuropharmacol of BZD and related drugs
4. Discuss some ADME features of these drugs
5. Broadly discuss ‘peripheral’ BZD receptors