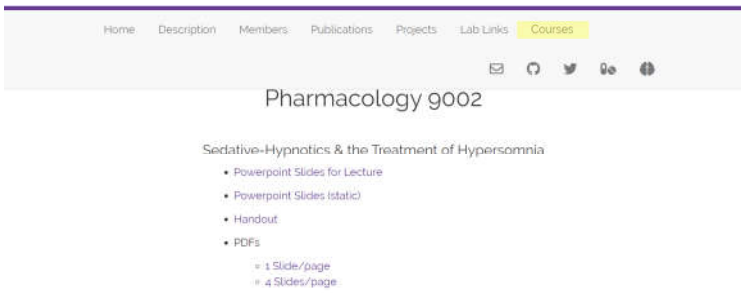
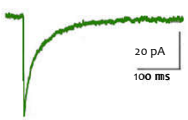
Sedatives, Hypnotics & Amphetamines

Mark Beenhakker
Pharmacology
markbeen@virginia.edu

beenhakkerlab.org/Courses



Sedative-Hypnotics & the Treatment of Hypersomnia



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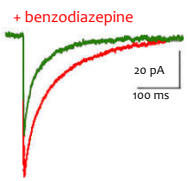

- anxiolysis
- sedation-hypnosis
- anticonvulsant

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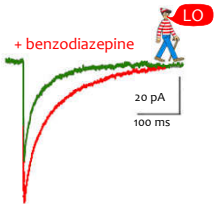

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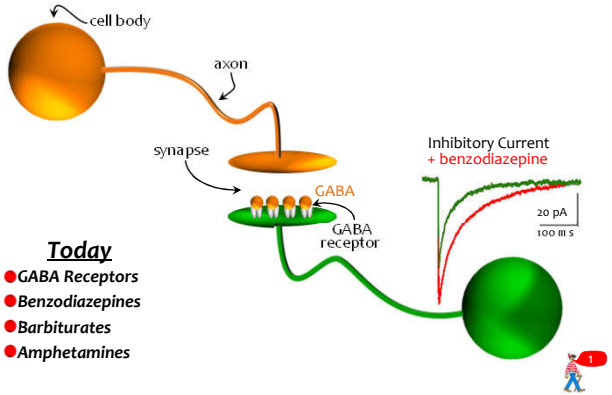
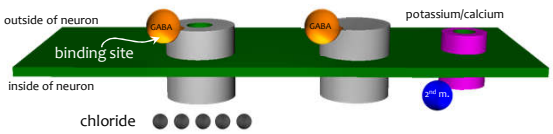
Inhibition in the Brain



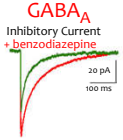
Today

- ***GABA Receptors***
- ***Benzodiazepines***
- ***Barbiturates***
- ***Amphetamines***

Two Types of GABA Receptors



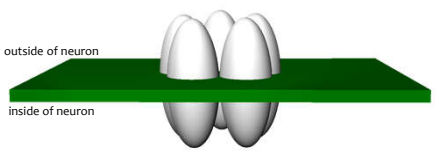
$GABA_A$



$GABA_B$

- epilepsy
- addiction
- anxiety & depression

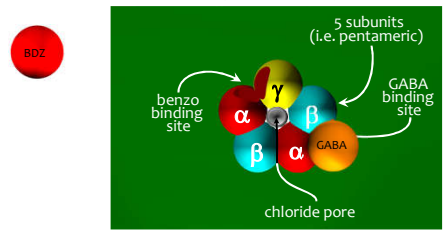
$GABA_A$ Receptor

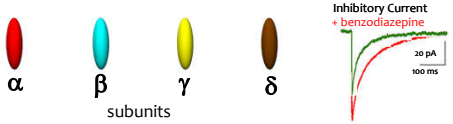


$GABA_A$ Receptor

4

(from above)





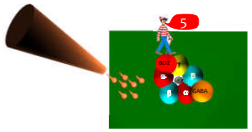
subunits

Allosteric Modulation

- definition: *modulation achieved by binding of a drug to a site distinct from the site required for activation.*

- Rudolph & Knoflach, 2011

5



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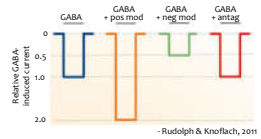

- Rudolph & Knoflach, 2011

- types:
  - positive (*agonism*)
    - benzodiazapines
  - negative (*inverse agonism*)
    - βCCE
  - antagonist (*blocker*)
    - Flumazenil

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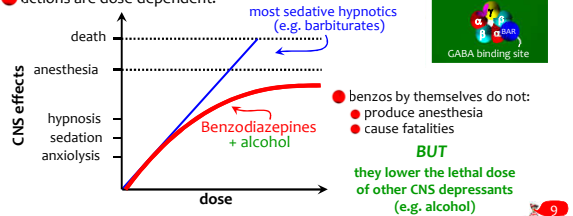
Benzodiazepines

- there are many
  - Diazepam (*Valium*) among the first (launched 1963).
  - 4 benzodiazepines are among the 200 most commonly prescribed drugs in the U.S.
    - Alprazolam (*Xanax*)
    - Clonazepam (*Klonopin*)
    - Diazepam (*Valium*)
    - Lorazepam (*Ativan*)
- actions are dose-dependent:

8



- benzos by themselves do not:
  - produce anesthesia
  - cause fatalities

BUT

they lower the lethal dose of other CNS depressants (e.g. alcohol)

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from Patrice Guyenet, UVA Pharm Dept.

Benzodiazepines

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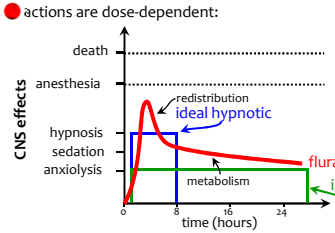


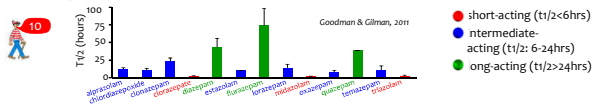
Problems

- pharmacokinetics
- side effects

from Patrice Guyenet, UVA Pharm Dept.

Benzodiazepine Metabolism

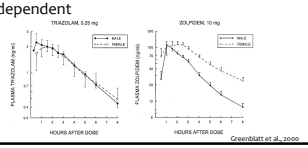
- metabolized by the liver (CYPs)
- pharmacokinetics highly variable



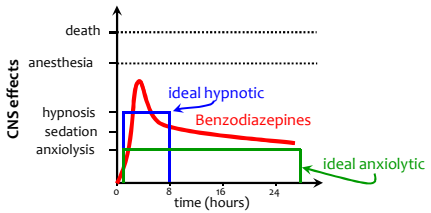
- short-acting (t1/2<6hrs)
- intermediate-acting (t1/2: 6-24hrs)
- long-acting (t1/2>24hrs)

- age-dependent

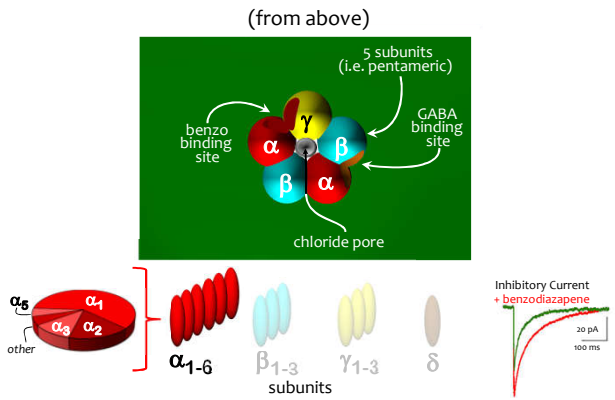
- over-sedation can occur with 'standard doses'
- can be sex-dependent



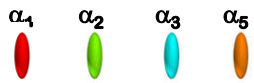
Benzodiazepines: Effect Selectivity

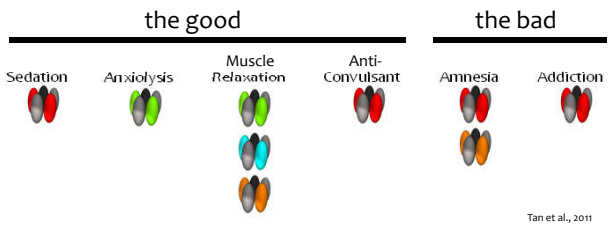


$GABA_A$ Receptor



α Subunits and Selectivity





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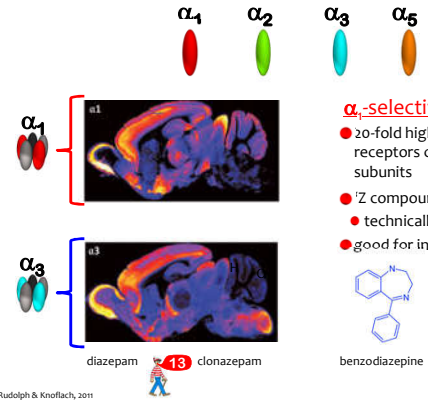
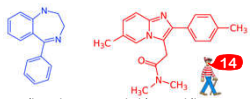


α1-selective agents

- 20-fold higher affinity for receptors containing **a**1 subunits
- 'Z compounds'
  - technically non-benzos
- good for insomnia

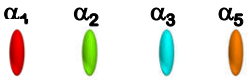


benzodiazepine

imidazopyridine (*zolpidem*)

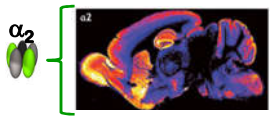
Rudolph & Knoflach, 2011

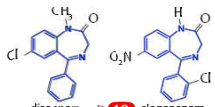
α Subunits and Selectivity



α2-selective agents

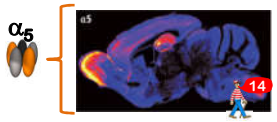
- non-sedating anxiolytics
- hopefully soon…





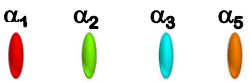
diazepam

clonazepam



Rudolph & Knoflach, 2011

α Subunits and Selectivity



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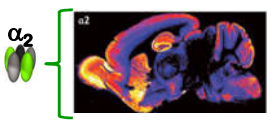
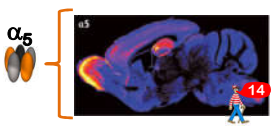


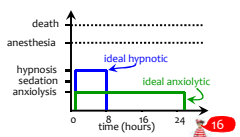


Rudolph & Knoflach, 2011

Benzodiazepines: Therapeutic Uses

maximize therapy, minimize side-effects

- sedation-hypnosis
  - true benzodiazepines
    - Triazolam (closest to 'ideal hypnotic')
    - Flurazepam (less 'early morning insomnia')
  - Z compounds
    - Zolpidem (*Ambien*)
    - Zaleplon (*Sonata*)
    - Eszopiclone (*Lunesta*)
- anxiolysis
  - most benzos with medium- to long-$T_{1/2}$ work
  - low doses often used
  - α_2-selective benzos are actively being developed
  - severe anxiety:
    - associated with prominent autonomic signs (e.g. panic disorders)
    - high-potency benzos used
      - Alprazolam (*Xanax*)
      - Clonazepam (*Klonopin*)
      - Lorazepam (*Ativin*)
- anticonvulsant
  - only a few used (e.g. lorazepam, clonazepam, clorozepate)



Benzodiazepines: Last Couple of Things

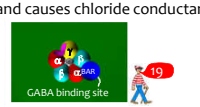
- Tolerance
  - primarily observed with anticonvulsant actions
  - limited tolerance observed with sedative-hypnotic & anxiolytic effects

- Dependence/Addiction
  - physical dependence is usually mild
  - follows general rule of drug dependence:
    - higher dosage = more severe withdrawal
    - longer t1/2 = less severe withdrawal
  - estimated that 0.1-0.2% of adult population abuse or are dependent upon benzos (300,000-600,000 people in the U.S.)
  - GABA receptors live in the VTA (ventral tegmental area)
    - modulating GABA receptor activity in the VTA hypothesized to increase dopamine release
- Benzodiazepine blocker
  - Flumazenil (*Romazicon*)
  - benzodiazepine stupor
  - potential risk of seizures

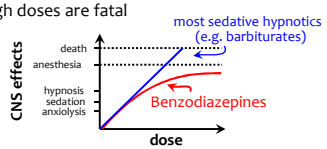
Sedative-Hypnotics & the Treatment of Hypersomnia

Barbiturates

- Directly bind to GABA binding site (at high doses)
  - activates channel and causes chloride conductance



- High doses are fatal



alcohol

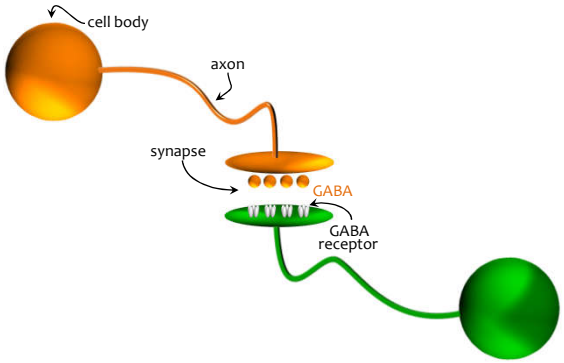
- Once extensively used as sedative-hypnotics. Now largely replaced by the much safer benzos.
  - noteworthy exceptions:
    - Pentobarbital (insomnia, pre-op sedation, seizures)
    - Phenobarbital (seizures)
    - Thiopental (induction/maintenance of anesthesia)….short-lasting

Amphetamine

Ma huang
'looking for trouble'

- Resembles catecholamines but more lipid soluble (can cross BBB)
  - catecholamines: norepinephrine, dopamine, serotonin
  - indirectly-acting sympathomimetic amine
    - amphetamine and related drugs stimulate release of:
      - CNS
        - dopamine ➔ stimulates reward mechanisms, causes psychosis/addiction
        - norepinephrine ➔ increased vigilance, anorexia
        - serotonin ➔ increased vigilance, anorexia
      - sympathetic nerve terminals
        - norepinephrine ➔ hypertension, strokes, arrhythmias

Amphetamine: Mechanism



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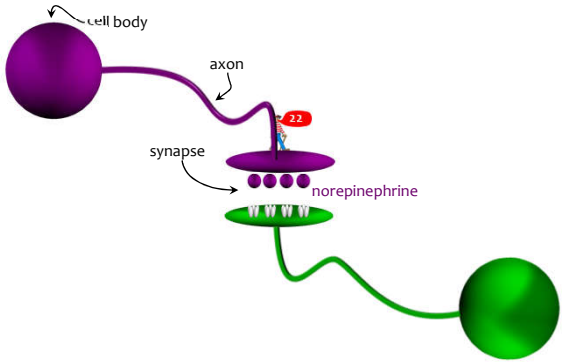

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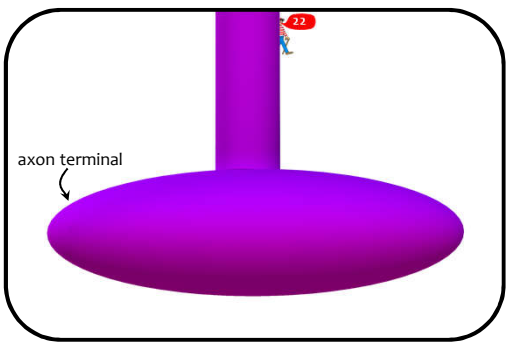

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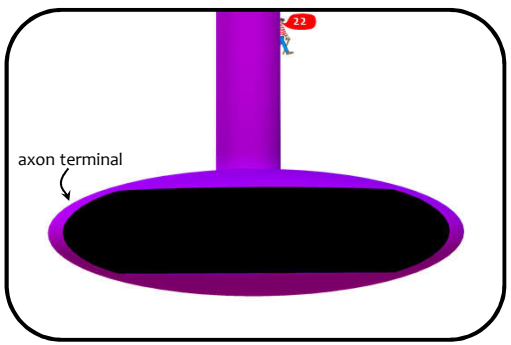

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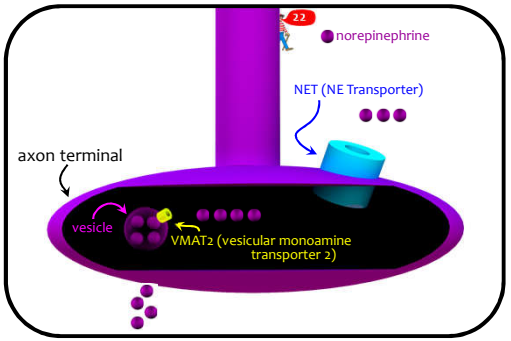
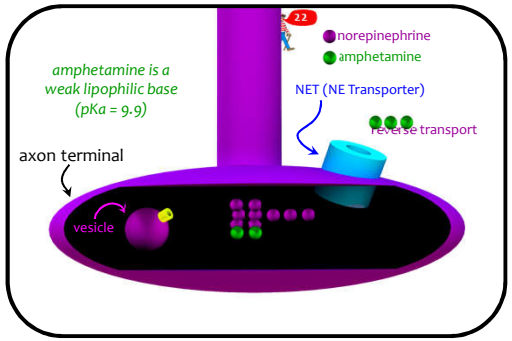


- Catecholamine uptake via plasmalemmal transporter
- Packaged in vesicles for subsequent release

Amphetamine: Mechanism



- Catecholamine uptake via plasmalemmal transporter
- Packaged in vesicles for subsequent release

plus amphetamine →

- Reverse transport leads to catecholamine release
- Alkalinization shuts down vesicular catecholamine sequestration

Amphetamine

- Powerful CNS stimulant
  - *d*-isomer 3-4 times more potent than *l*-isomer
    - *d*-amphetamine: Dextroamphetamine (*Dexedrine*, *Dextrostat*)
    - Lisdexamfetamine (*Vyvanse*): inactive, prodrug of *d*-amphetamine
  - Clinical uses:
    - Hypersomnia (Excessive Daytime Sleepiness [EDS])
      - narcolepsy (0.03-0.06% of the US population)
      - obstructive sleep apnea
      - shift-worker disorder (EDS affects >30% of night-shift workers)
    - Attention Deficit Hyperactivity Disorder

- Adverse/toxic effects
  - Usually result from overdosage
  - Acute toxic effects usually an extension of therapeutic effects.
    - restlessness, dizziness, tenseness, insomnia
  - Cardiovascular/GI side effects
- Alternatives
  - Modafinil (*Provigil*): promotes wakefulness, reduces EDS in narcoleptics

- mechanism(s) not well-understood (but activates wake-promoting neurons)
- little/no cardiovascular/cognitive side effects (main side effect = headaches)
- may be used to reduce cocaine dependence

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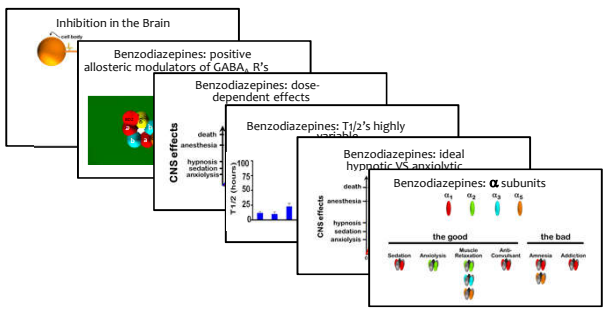

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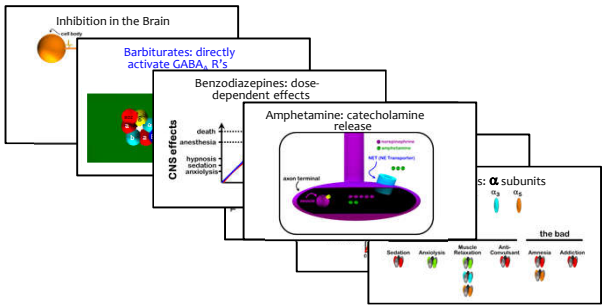

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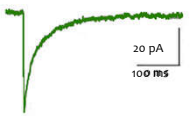

suggested reading

- Basic & Clinical Pharmacology, 12th ed. (chapter 22)
  Bertram G. Katzung, Susan B. Masters, Anthony J. Trevor
- Pharmacological Basis of Therapeutics, 12th ed. (Chapter 17)
  Goodman & Gilman

questions:
markbeen@virginia.edu

"Nobody ever asks 'How's Waldo?'"