Sedative-Hypnotics & the Treatment of Hypersomnia

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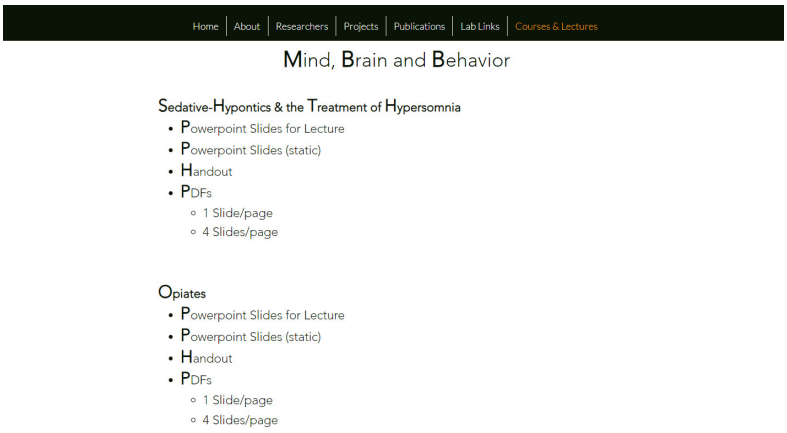

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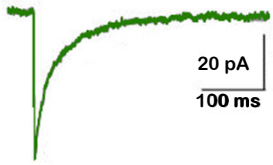

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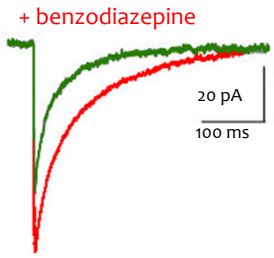

- anxiolysis
- sedation-hypnosis
- anticonvulsant

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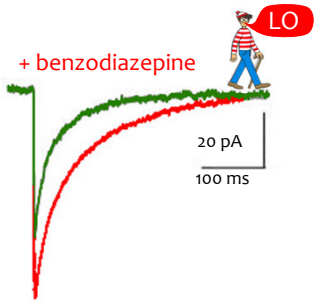

- anxiolysis
- sedation-hypnosis
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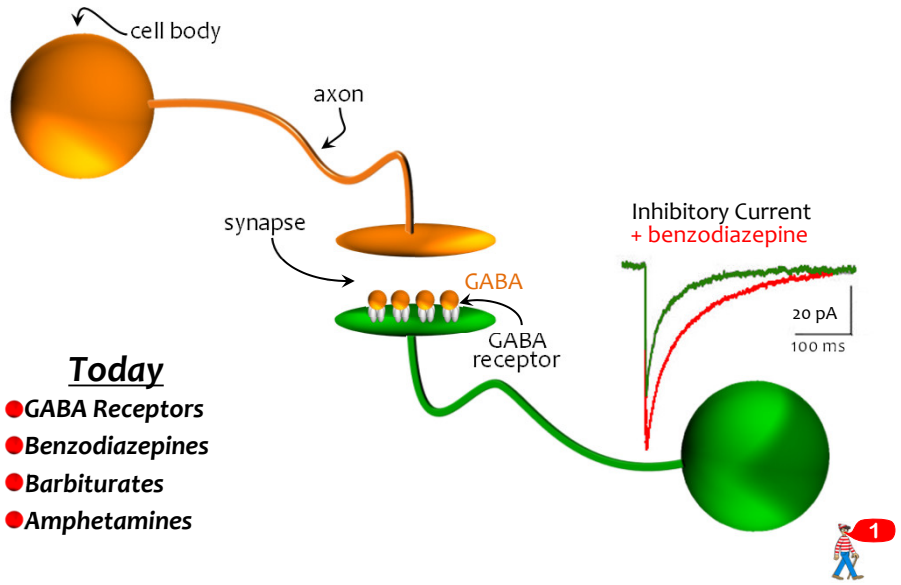
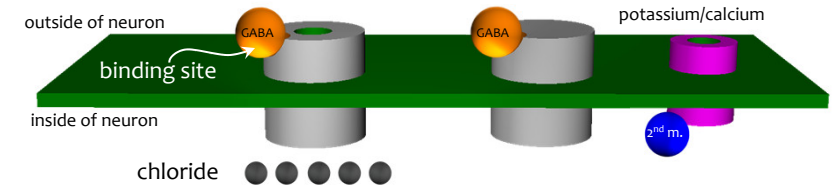
Inhibition in the Brain



Today

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

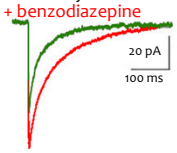
Two Types of GABA Receptors



$GABA_A$

Inhibitory Current

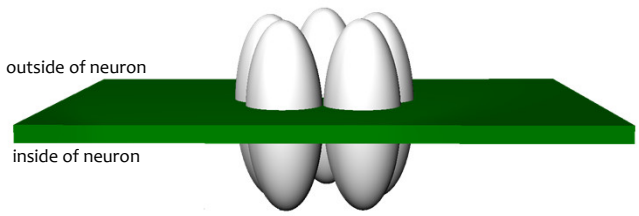
+ benzodiazepine



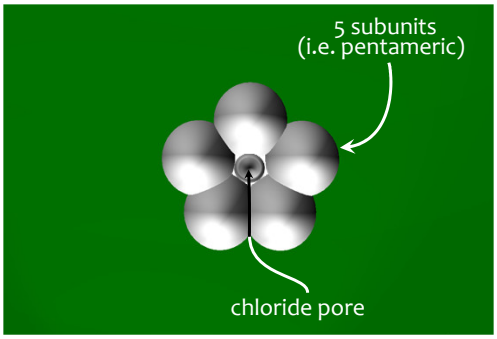
$GABA_B$

- epilepsy
- addiction
- anxiety & depression

$GABA_A$ Receptor



$GABA_A$ Receptor (from above)



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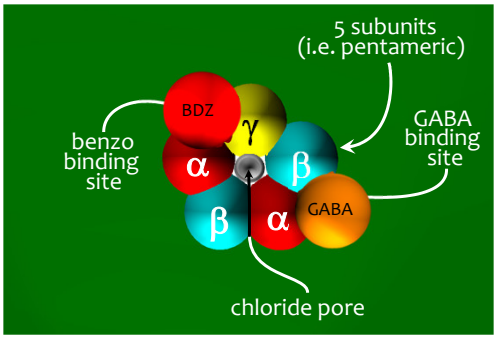
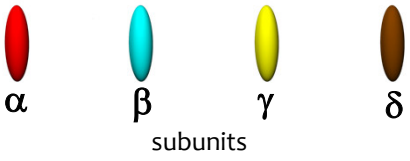
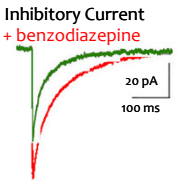




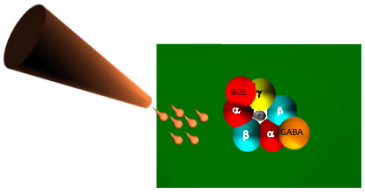


Allosteric Modulation

5

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

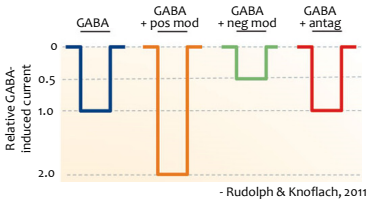
- Rudolph & Knoflach, 2011



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

6

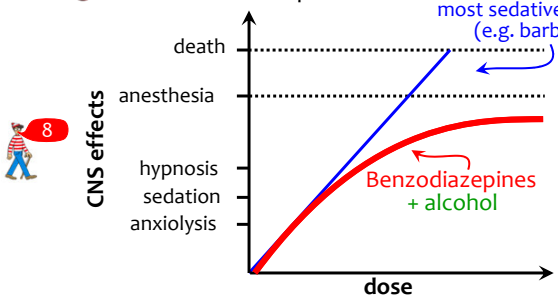
7

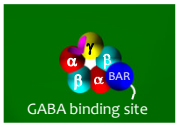


- Rudolph & Knoflach, 2011

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:





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

BUT

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

from Patrice Guyenet, UVA Pharm Dept.

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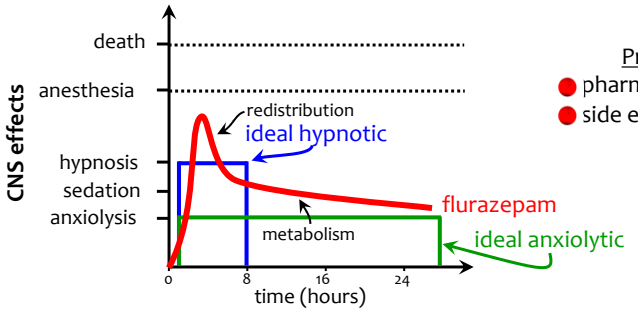
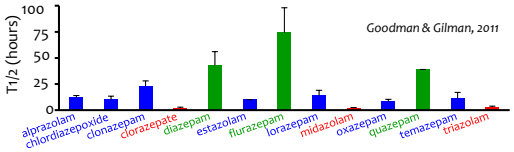


Problems
- pharmacokinetics
- side effects

from Patrice Guyenet, UVA Pharm Dept.

Benzodiazepine Metabolism

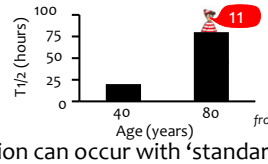
- metabolized by the liver (CYPs)
- pharmacokinetics highly variable



Goodman & Gilman, 2011

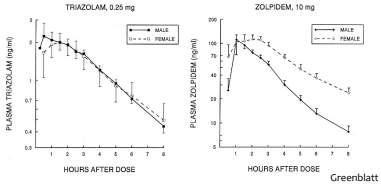
- short-acting (t1/2<6hrs)
- intermediate-acting (t1/2: 6-24hrs)
- long-acting (t1/2>24hrs)

- age-dependent



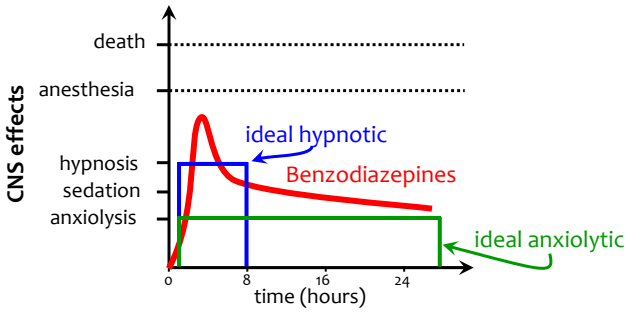
from Patrice Guyenet, UVA Pharm Dept.

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

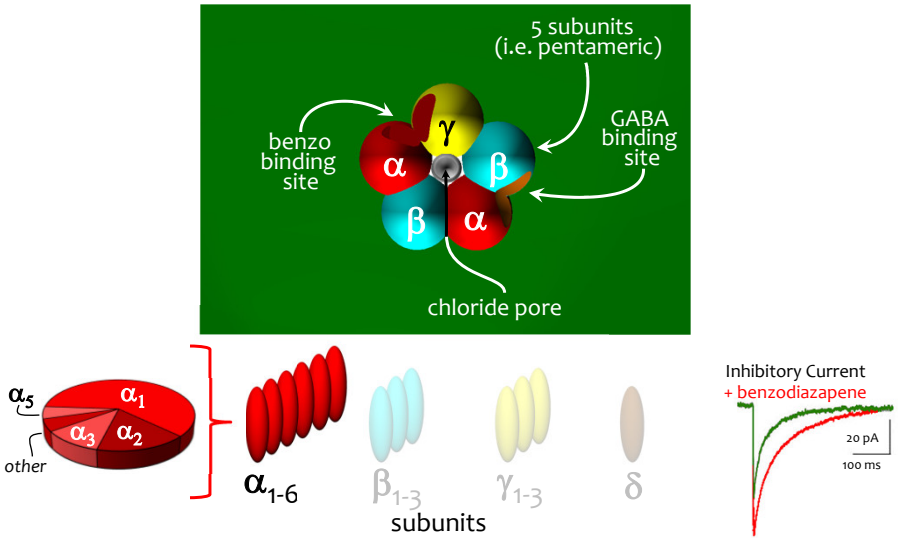


Greenblatt et al., 2000

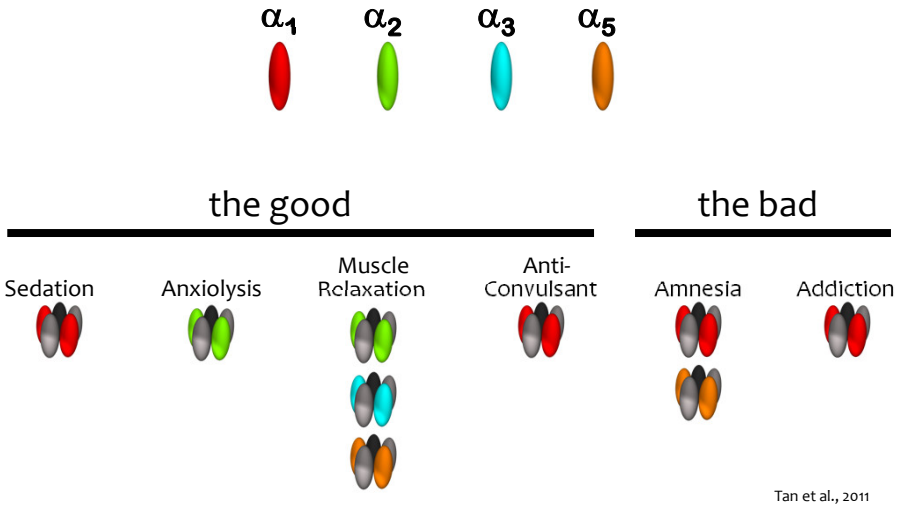
Benzodiazepines: Effect Selectivity



$GABA_A$ Receptor (from above)



α Subunits and Selectivity



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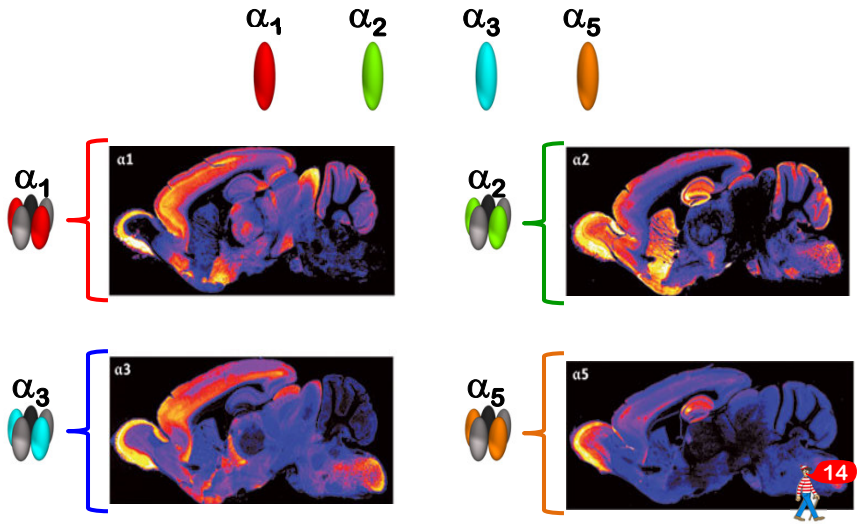
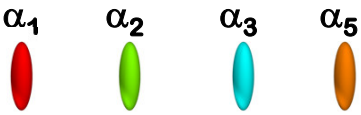
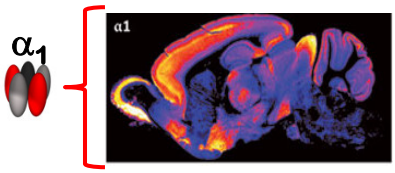


Rudolph & Knoflach, 2011

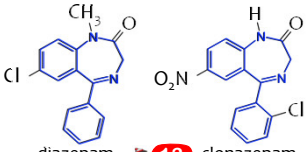
α Subunits and Selectivity

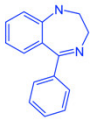


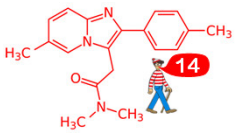


α_1-selective agents

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

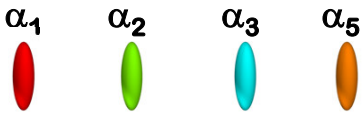






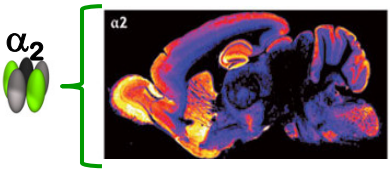
Rudolph & Knoflach, 2011

α Subunits and Selectivity



α_2-selective agents

- non-sedating anxiolytics
- hopefully soon…



Compound	Receptor subtype	Binding/functional selectivity	Indication	Development status
L-838417	Partial agonist at α2, α3, α5	Functional	Anxiety disorders	Preclinical
TPA023 (MK-0777)	Partial agonist at α2, α3	Functional	Anxiety disorders, schizophrenia	Phase II
TPA0238	Partial agonist at α2, α3	Functional	Anxiety disorders, schizophrenia	Phase I
TPA123	Partial agonist at α1, α2, α3, α5	Functional	Anxiety disorders	On hold
MRK-409 (MK-0343)	Partial agonist at α2, α3	Functional	Anxiety disorders	Phase I, halted
TP003	Agonist at α3	Functional	Anxiety disorders	On hold
Ocinaplon (DOV-273547)	Partial agonist at α2, α3, α5. Full agonist at α1	Functional	Anxiety disorders	On hold
NS11394	Agonist at α5. Partial agonist at α3, α5	Functional	Anxiety disorders	Preclinical
MRK-016	Full inverse agonist at α5	Functional	Cognitive impairment	Phase I, halted
α5IA	Partial inverse agonist at α5	Functional	Cognitive impairment	Phase I, halted
RO4938581	Full inverse agonist at α5	17–40-fold binding selectivity for α5	Cognitive impairment	Preclinical
L-655708 (FG8094)	Very weak inverse agonist at α5	30–70-fold binding selectivity for α5	Cognitive impairment	Preclinical
SH-053-2'F-R-CH3	Full agonist at α5. Partial agonist at α1, α2, α3	8–10-fold binding selectivity for α5	Schizophrenia?	Preclinical
Gaboxadol	Supra-maximal agonist at αβδ	>Tenfold binding selectivity for α4	Insomnia	Phase III, halted

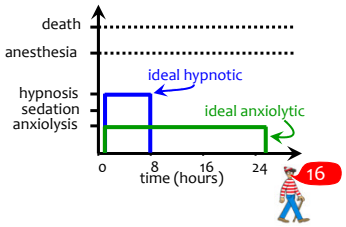
$GABA_A$, γ-aminobutyric acid, type A.

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

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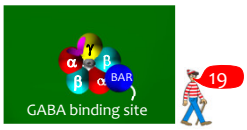
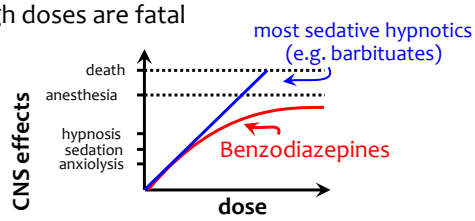
Barbiturates

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

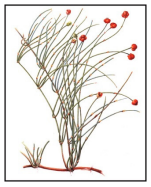


- High doses are fatal



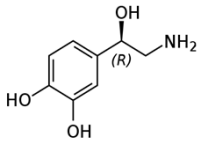
- Once extensively used as sedative-hypnotics. Now largely replaced by the much safer benzos.
  - noteworthy exceptions:
    - Pentobarbital (insomnia, pre-op sedation, seizures)
    - Phenobarbital (seizures)
    - Thiopental (induction/maintenance of anesthesia)….short-lasting

Amphetamine

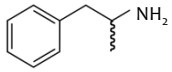


Ma huang

- Resembles catecholamines but more lipid soluble (can cross BBB)
  - catecholamines: norepinephrine, dopamine, serotonin
  - indirectly-acting sympathomimetic amine

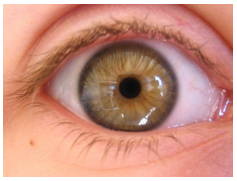


norepinephrine



amphetamine

Amphetamine

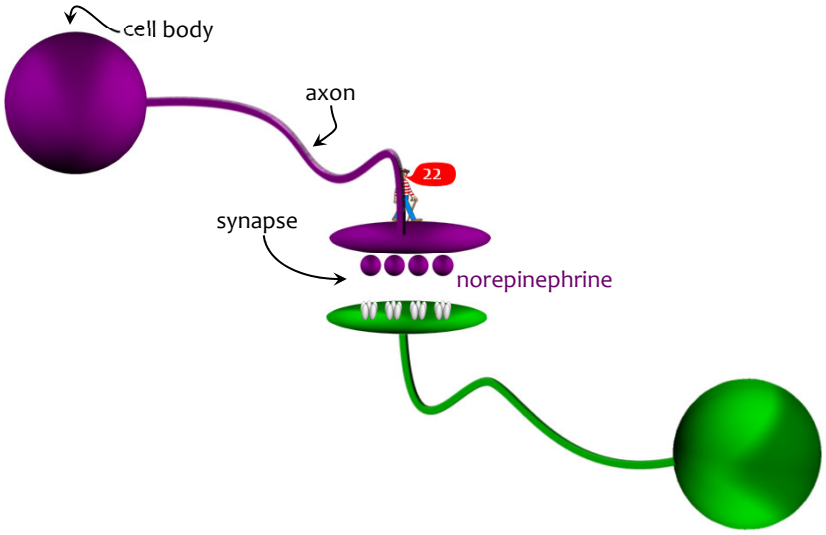


- Resembles catecholamines but more lipid soluble (can cross BBB)
  - catecholamines: norepinephrine, dopamine, serotonin
  - indirectly-acting sympathomimetic amine
    - amphetamine and related drugs stimulate release of:

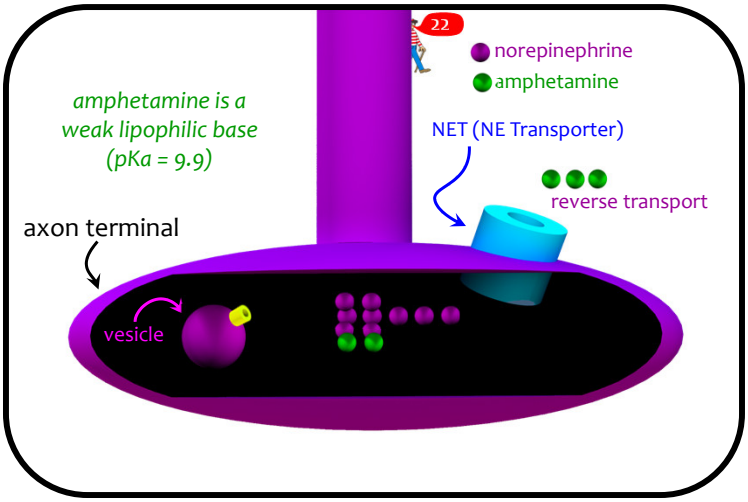
CNS
- dopamine ➔ stimulates reward mechanisms, causes psychosis/addiction
- norepinephrine ➔ increased vigilance, anorexia
- serotonin ➔ increased vigilance, anorexia

sympathetic nerve terminals
- norepinephrine ➔ hypertension, strokes, arrhythmias

Amphetamine: Mechanism



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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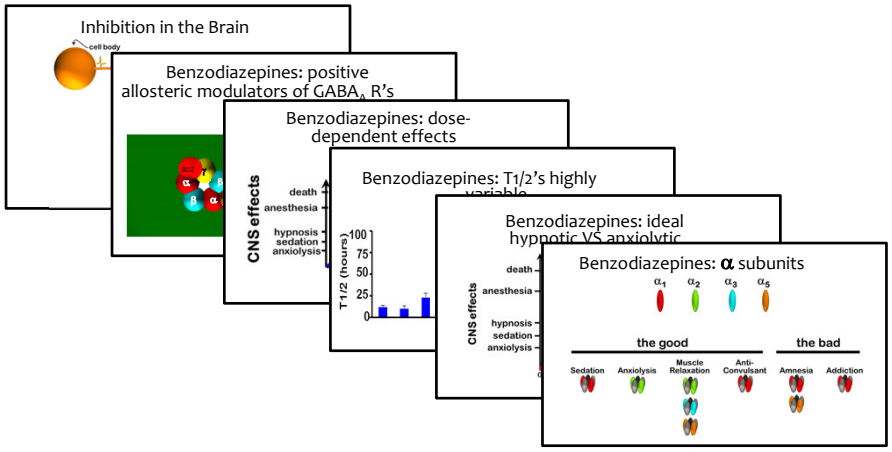
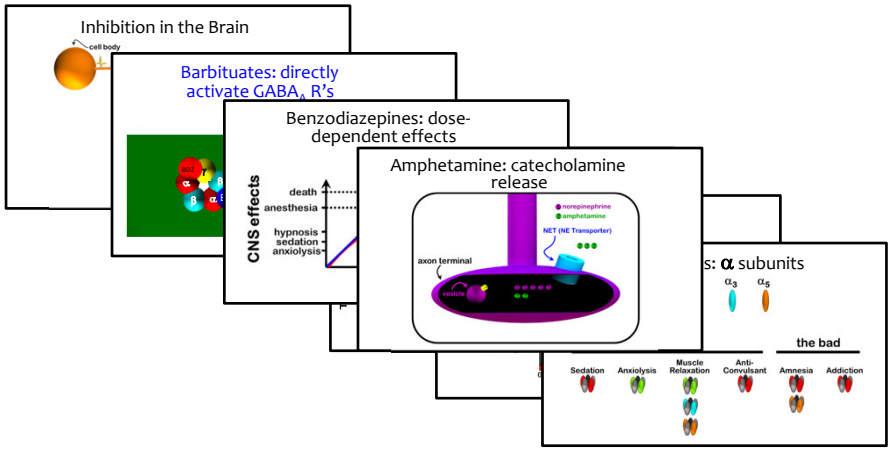
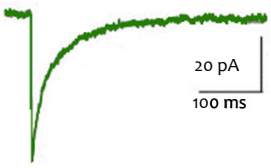


Sedative-Hypnotics & the Treatment of Hypersomnia



Sedative-Hypnotics & the Treatment of Hypersomnia



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