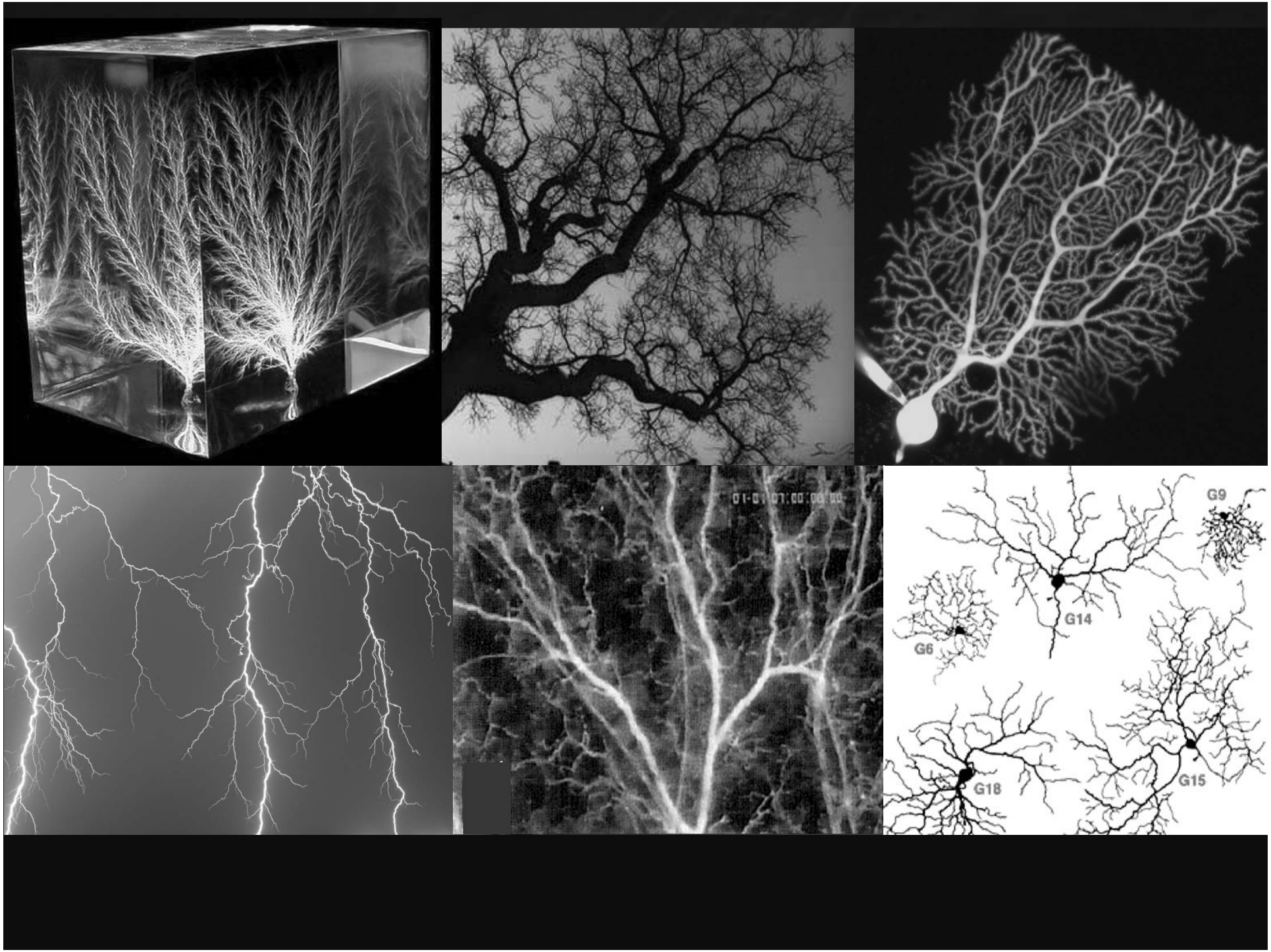
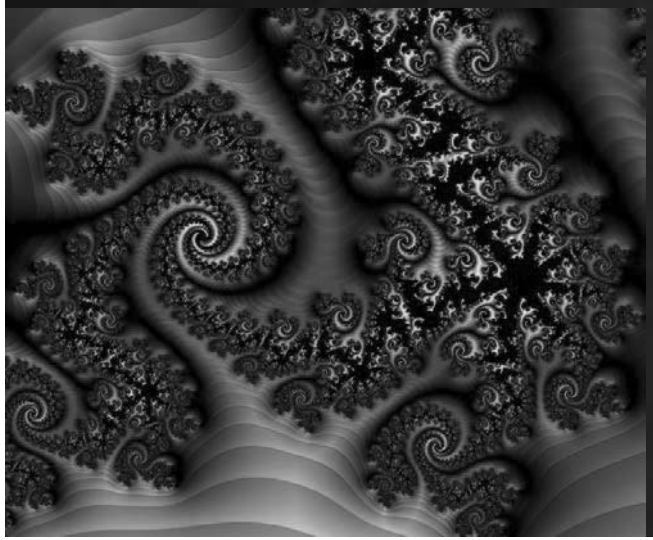

G9
G14
G6
G18
G15

Pharmacology of mood altering substances

I. Central nervous system, basic properties

II. CNS stimulants / psychomotor agents

III. Anti-depressants / mood stabilizing agents



Source material: Harvey and Champe "Pharmacology" 2000; Kalant and Roschlau " Medical Pharmacology" 1998; Kandel et al. "Principles of Neural Science" 2000

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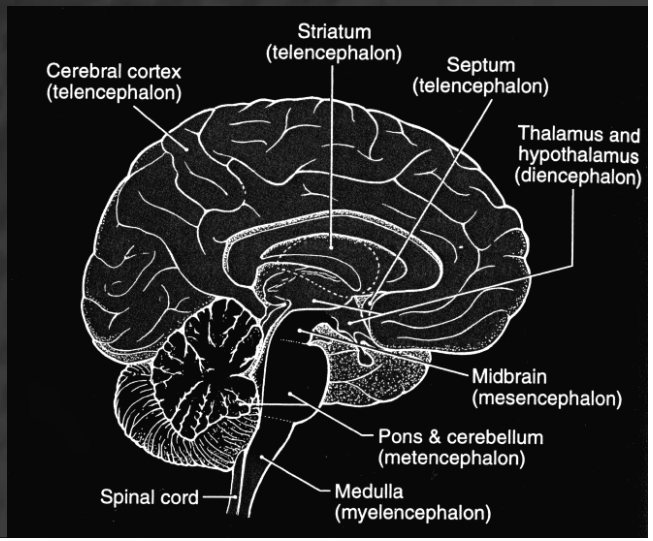
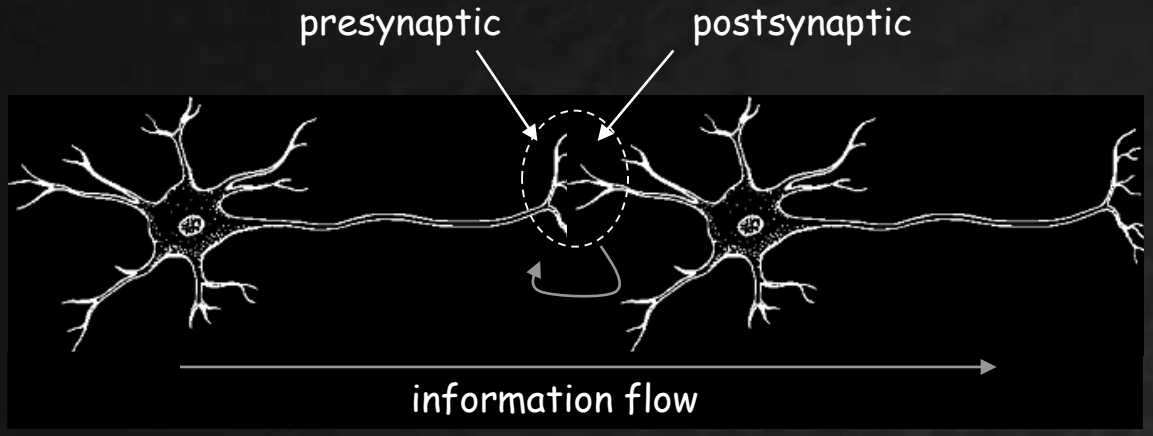
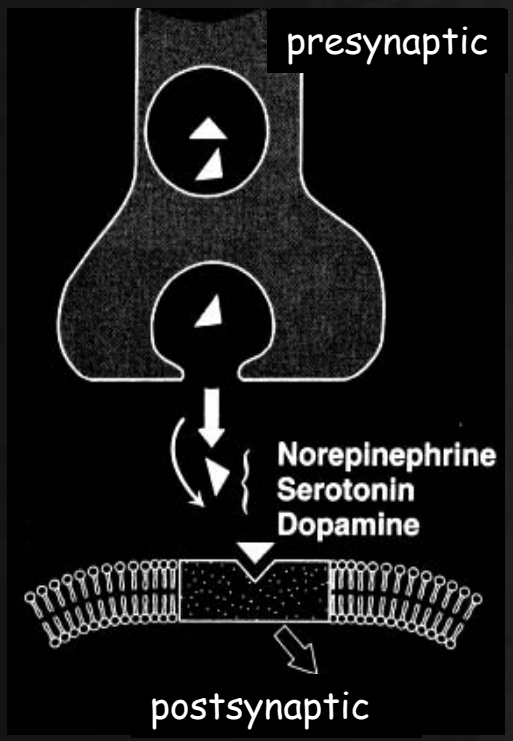
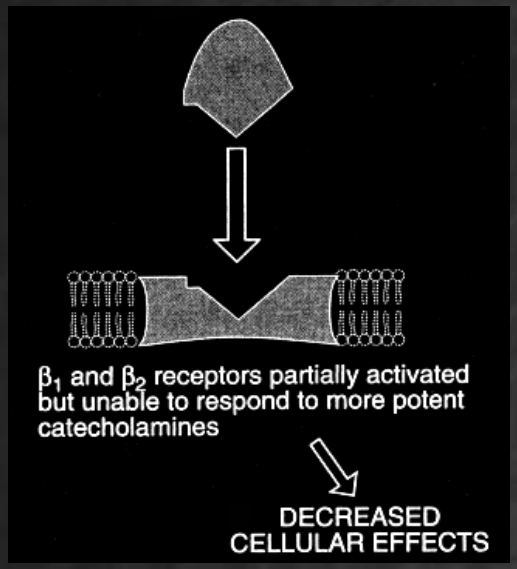


Neuron, basic properties:

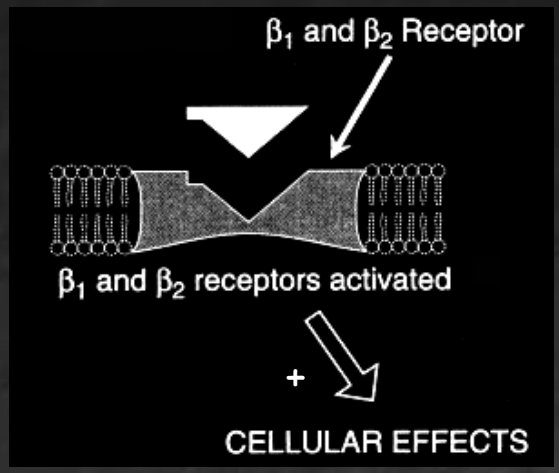




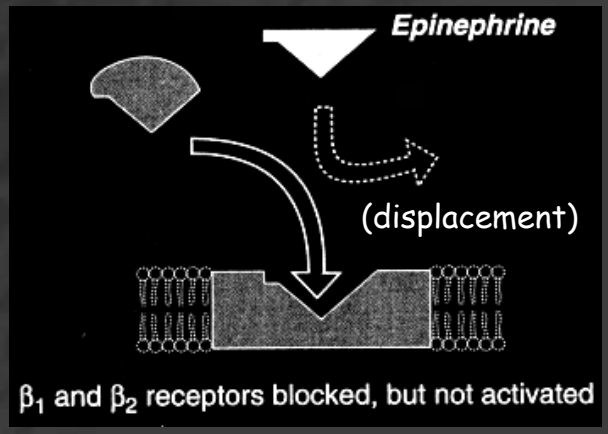
Partial agonist (LSD)



Agonist:



Antagonist (Naloxone)



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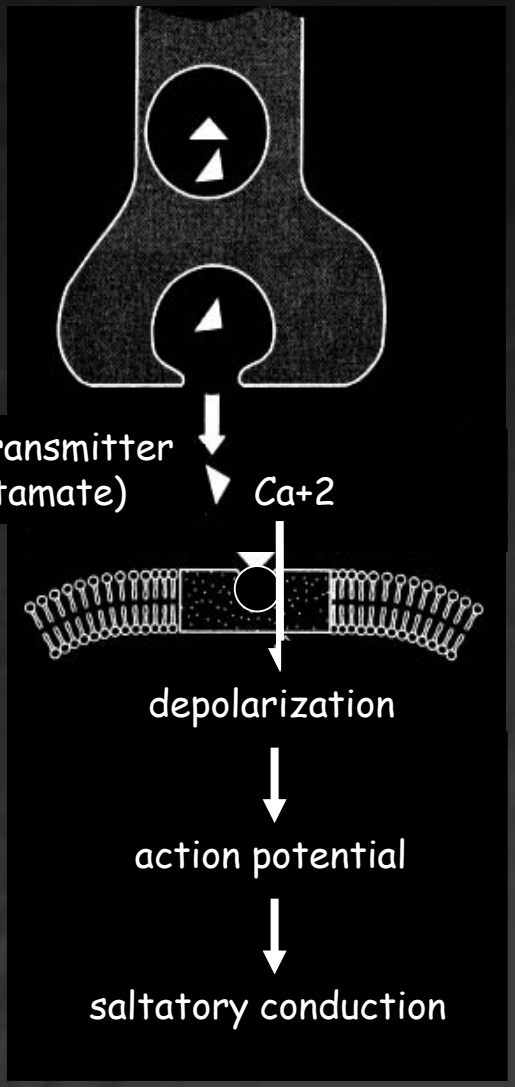

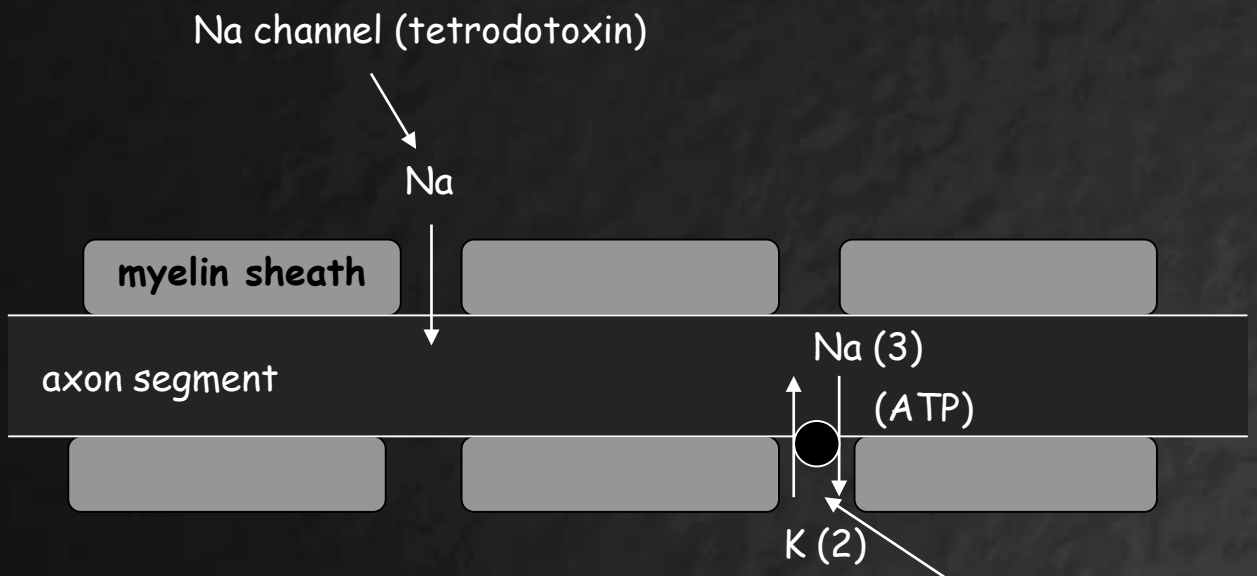

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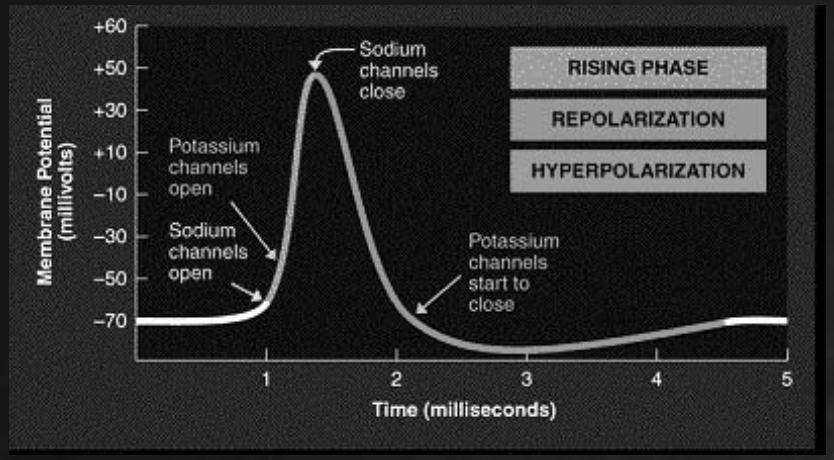

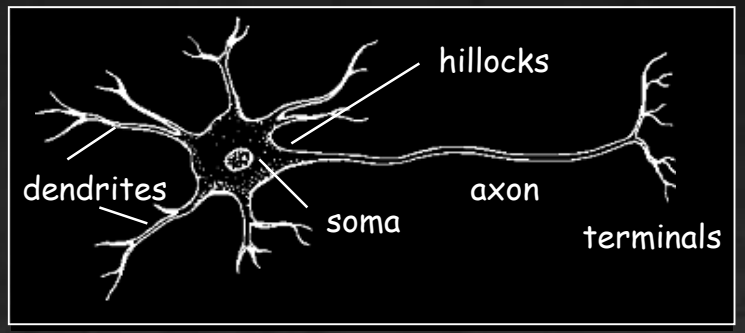

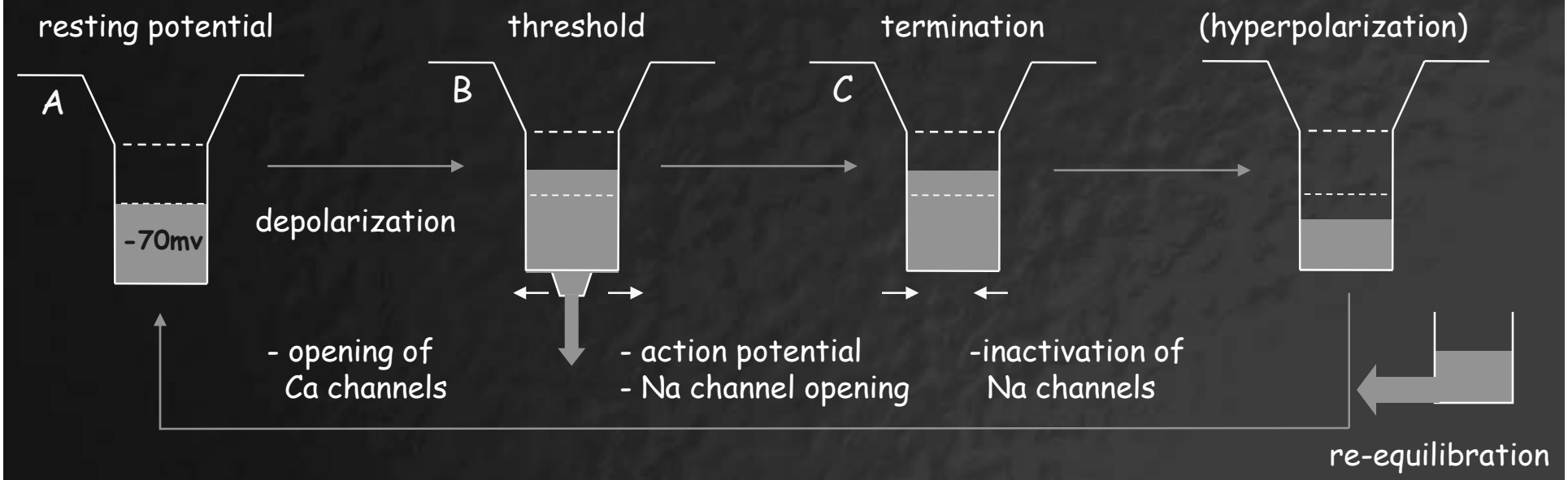

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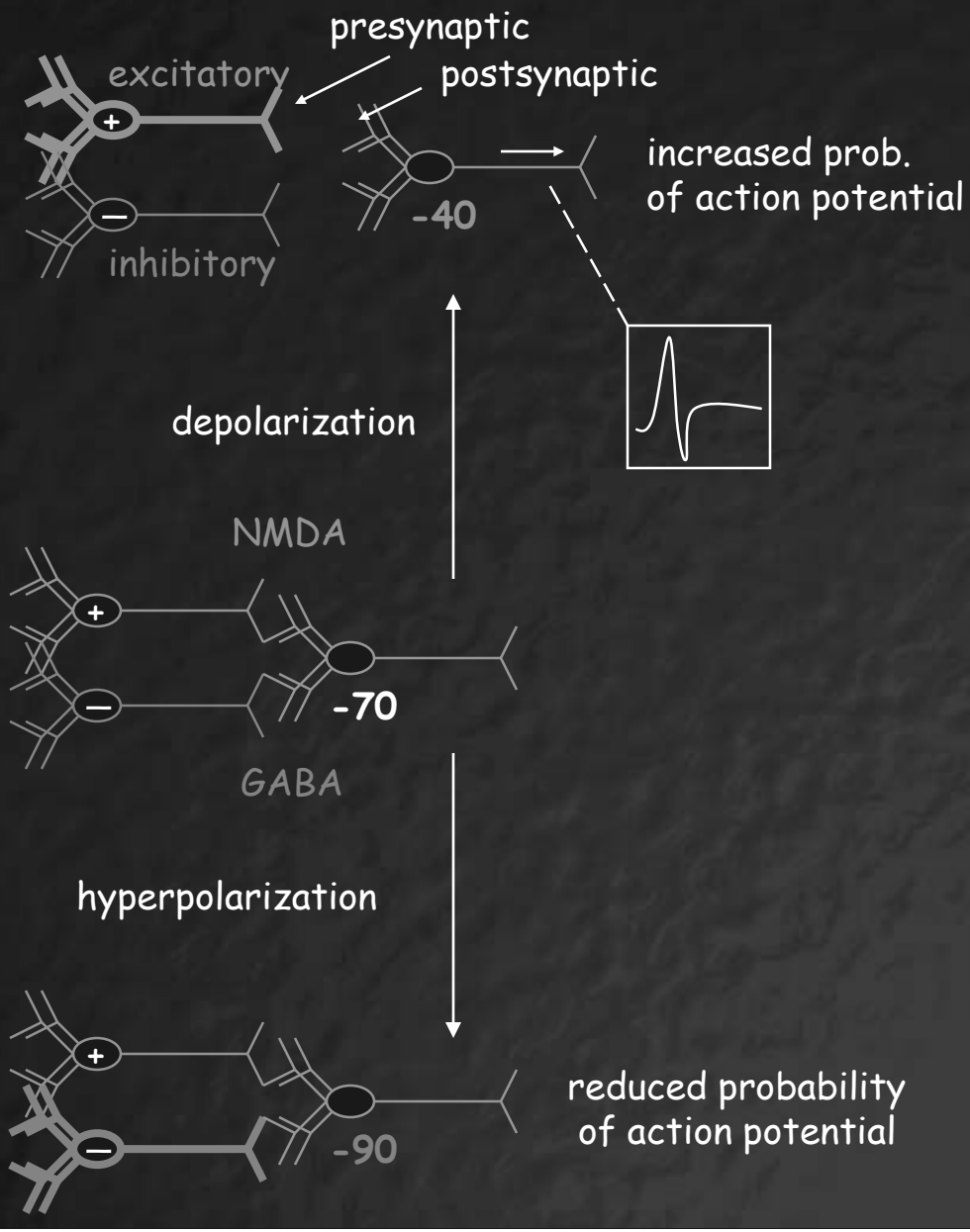

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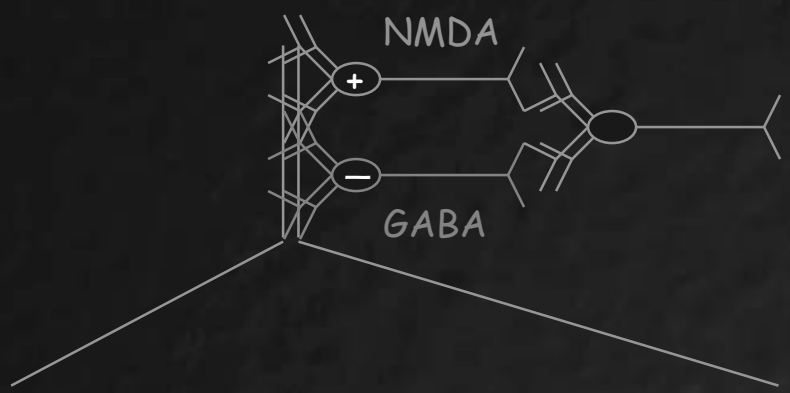

A – Ligand binding site
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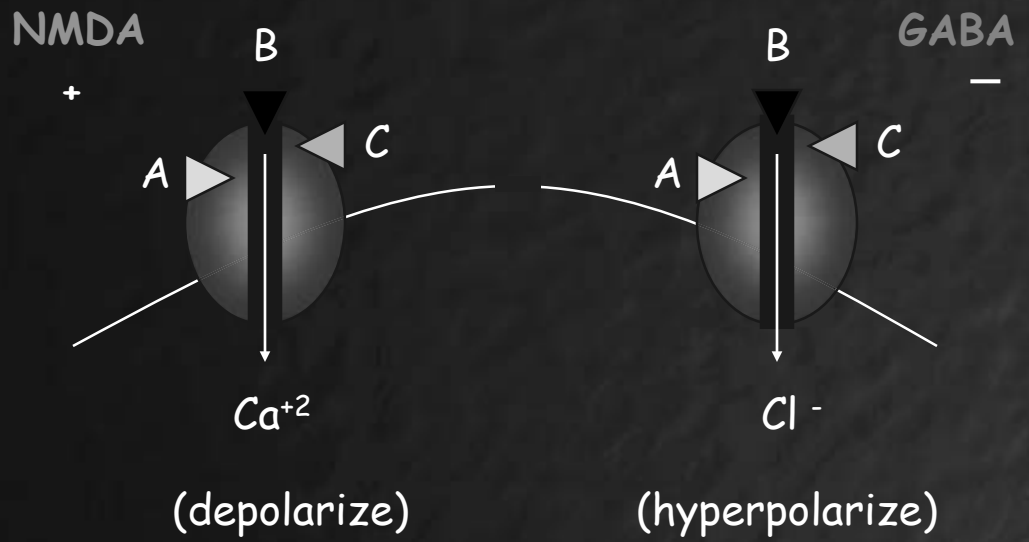
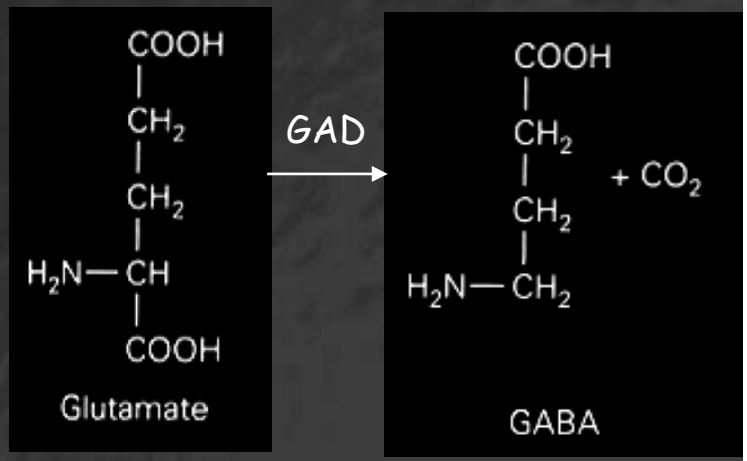
B - Channel binding site
(regulators, poisons, drugs)

C - Modifier / co-activator site
(co-agonists, drugs)





CNS stimulants:

Psychomotor group:

- excitement and euphoria
- reduction of fatigue, increased B.P.
- increased motor activity

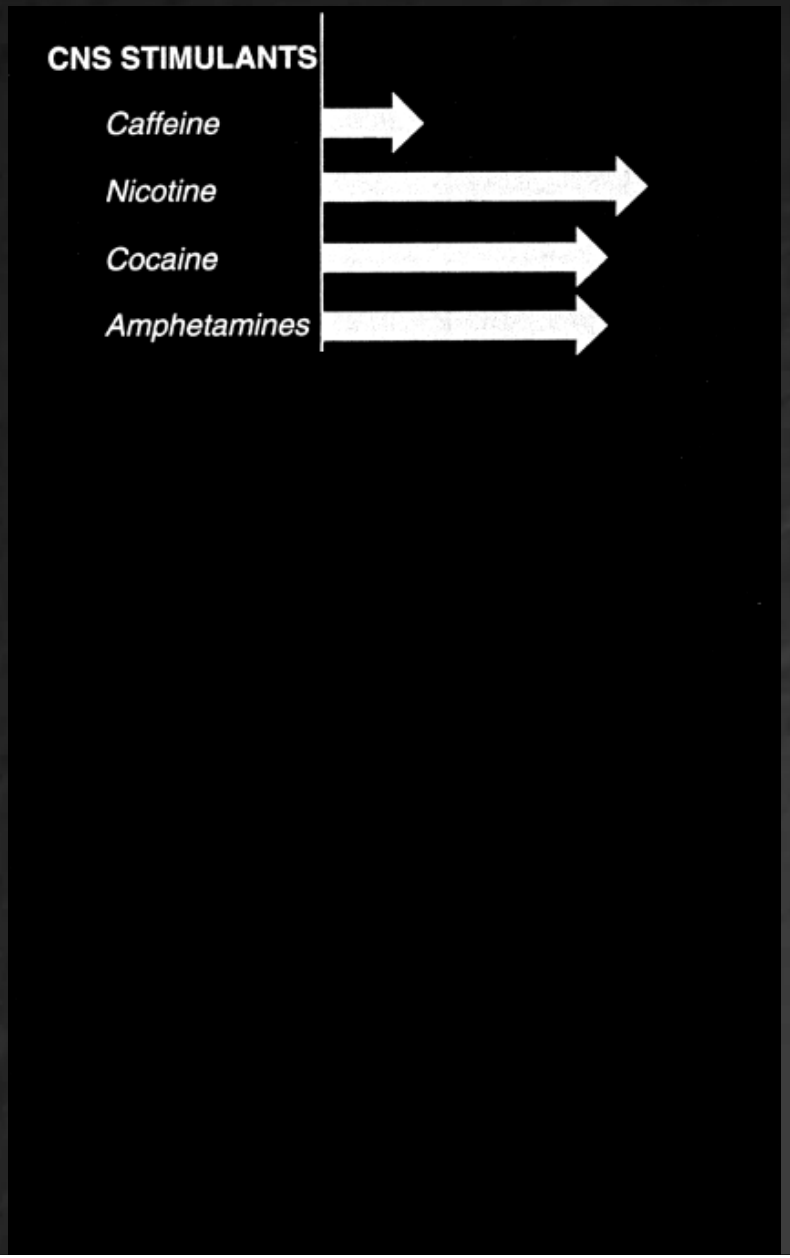
- caffeine, theophylline, theobromine
- nicotine
- cocaine
- amphetamines

Psychotomimetic drugs (hallucinogens):

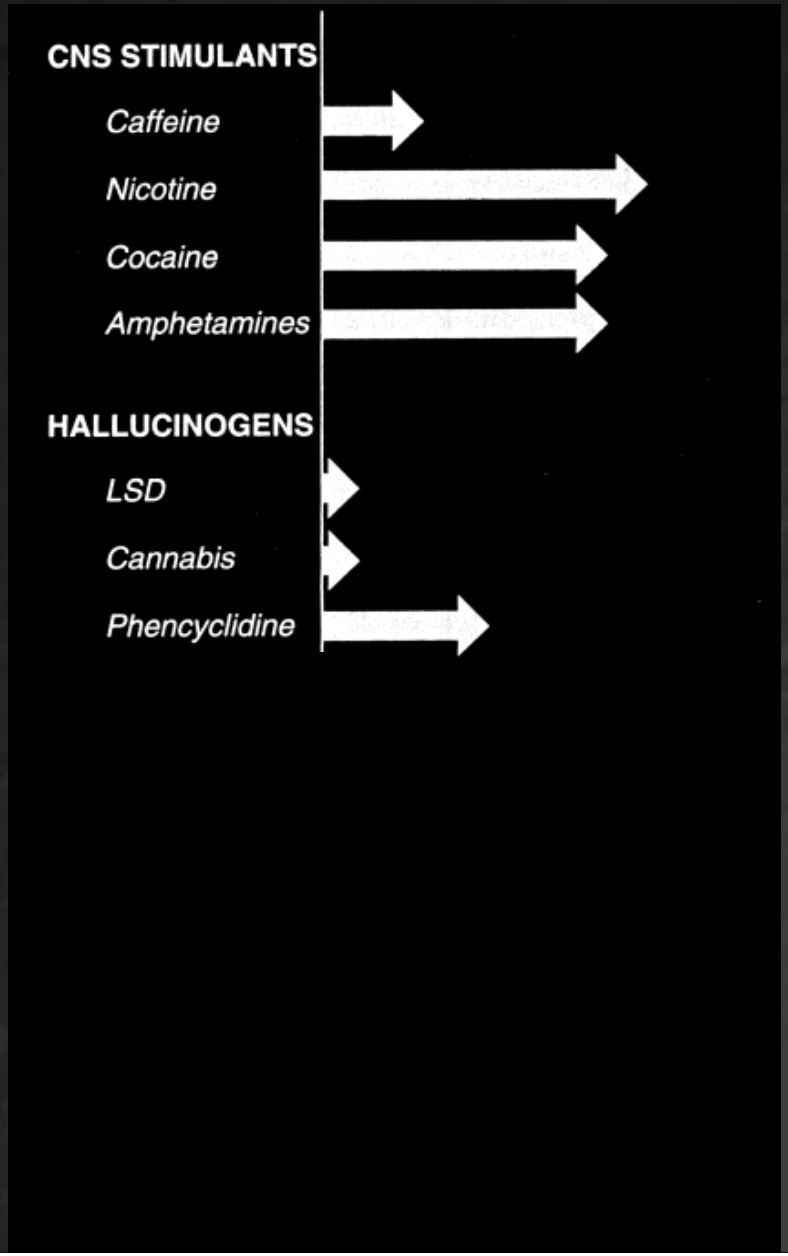
- changes in thought and mood
- few effects on brainstem / spinal cord

- lysergic acid diethylamide (LSD)
- Phenylcyclidine (PCP)
- Tetrahydrocannabinol (THC)

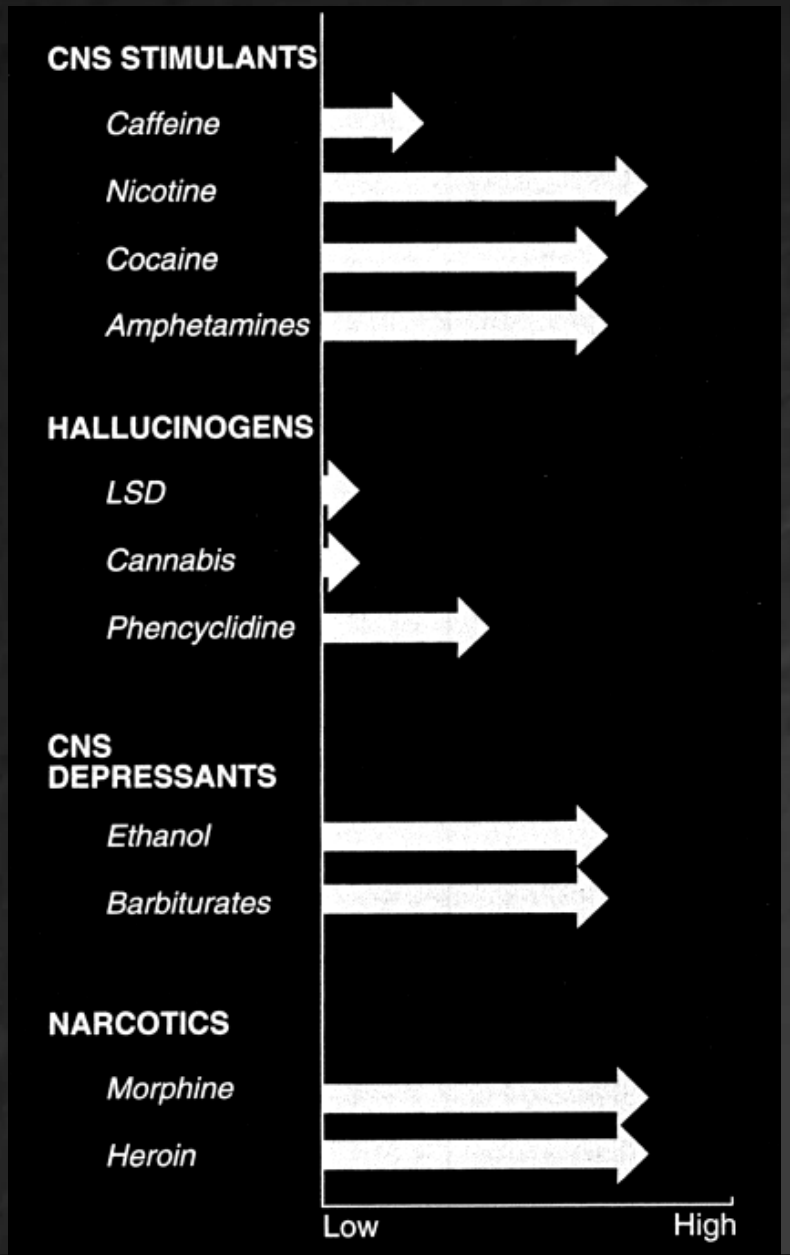
Potential for dependency:



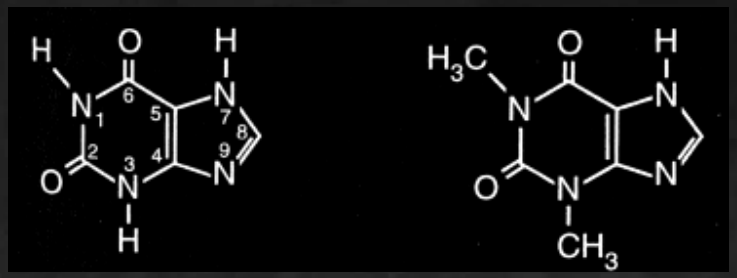
Potential for dependency:



Potential for dependency:



Psychomotor agents, Methylxanthines:



(caffeine, theophylline, theobromine)
(coffee 1,3,7 : tea 1,3 : coca 3,7)

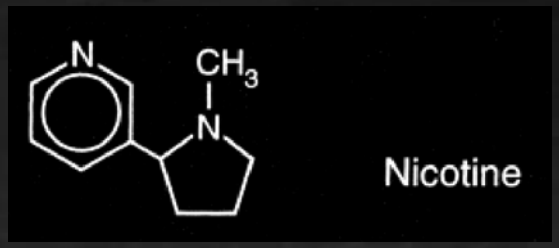
Actions:

- inhibits phosphodiesterase, leading to increased cAMP / cGMP
- increased intracellular calcium, increased cardiac contractility
- smooth muscle ⟶ vasodilator (except cerebral vessels)
- methylxanthines also block adenosine receptors
- theophylline inhibits prostaglandins (smooth muscle), mild diuretics
- stimulate gastric HCl secretion (contraindicated for peptic ulcers)
- individual clearance rates can vary widely

Pharmacology:

- cross CNS and placental barriers, secreted in milk
- 1-200 mg (1-2 cups coffee) - reduction of fatigue, increased alertness
- 1500 mg - anxiety, tremors, arrhythmia
- metabolized in the liver (CYP system -3-demethylation, 8-hyroxylation)

Psychomotor agents, Nicotine:



Actions:

- stimulates sympathetic ganglia / adrenal medulla
- increased blood pressure, heart rate, vasoconstriction
- potent, fast acting poison (insecticide), pregnancy-reduced birth weight

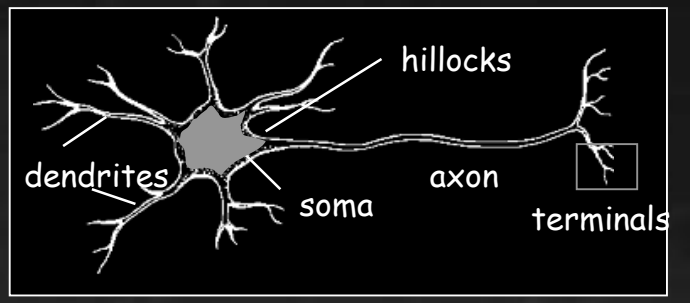
CNS:

- reward, arousal, relaxation, enhanced attention / reaction time
- sympathetic stim. < parasympathetic stim. < parasympathetic blockade
- respiratory paralysis (high dose)

Pharmacology:

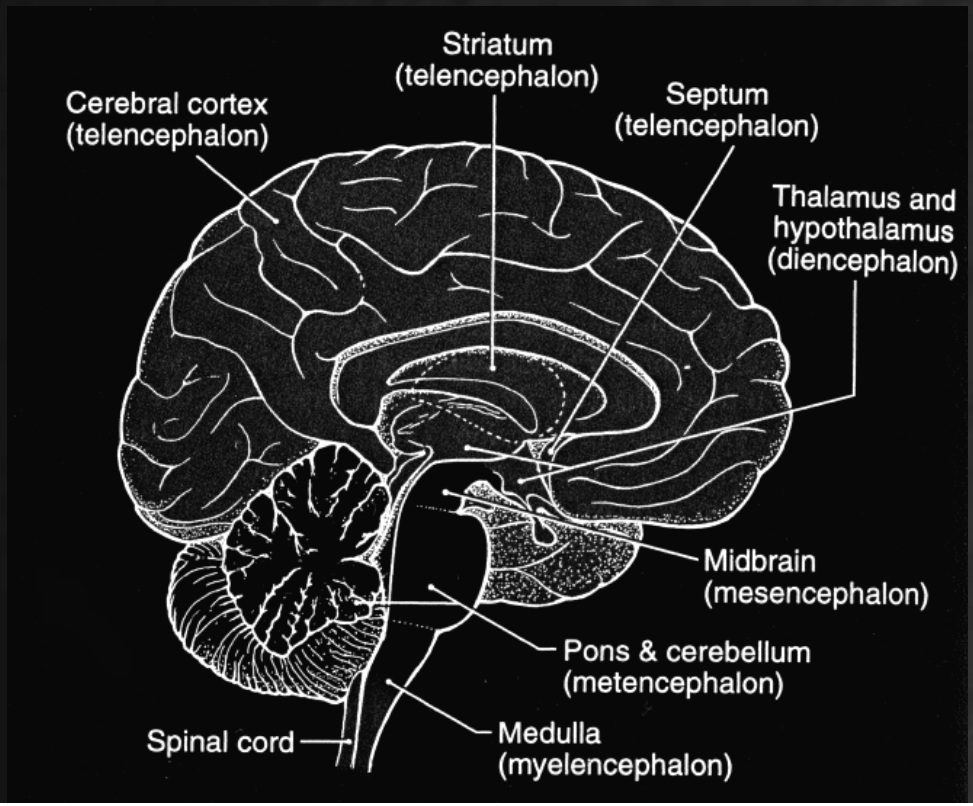
- alkaloid, crosses CNS and placental barriers easily, secreted in milk
- 1 cigarette contains 6-8 mg nicotine, 90% absorbed
- acute lethal dose (~60 mg), tolerance to acute effects occurs quickly
- most inactivated 2-4 hrs (lungs/liver), major metabolite - cotinine, N'-oxide

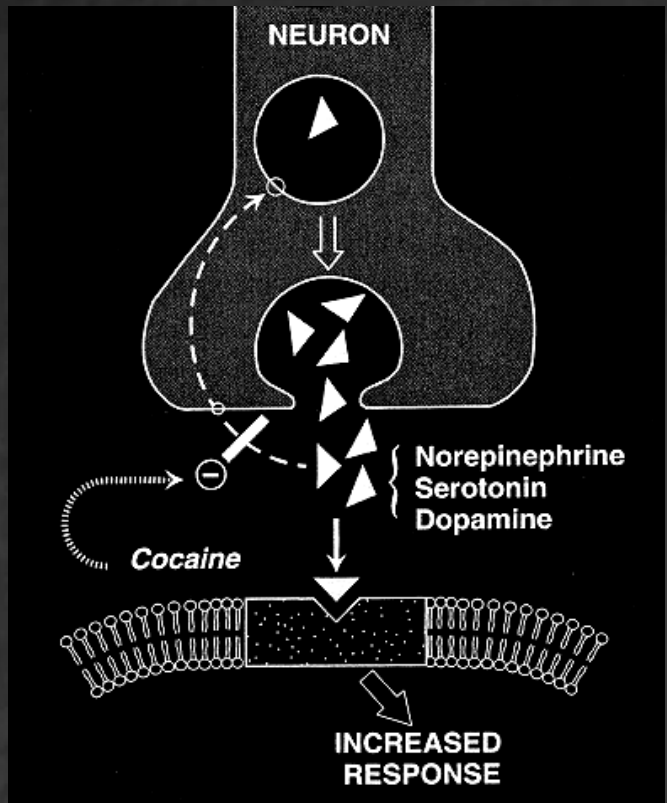
Psychomotor agents, Cocaine:



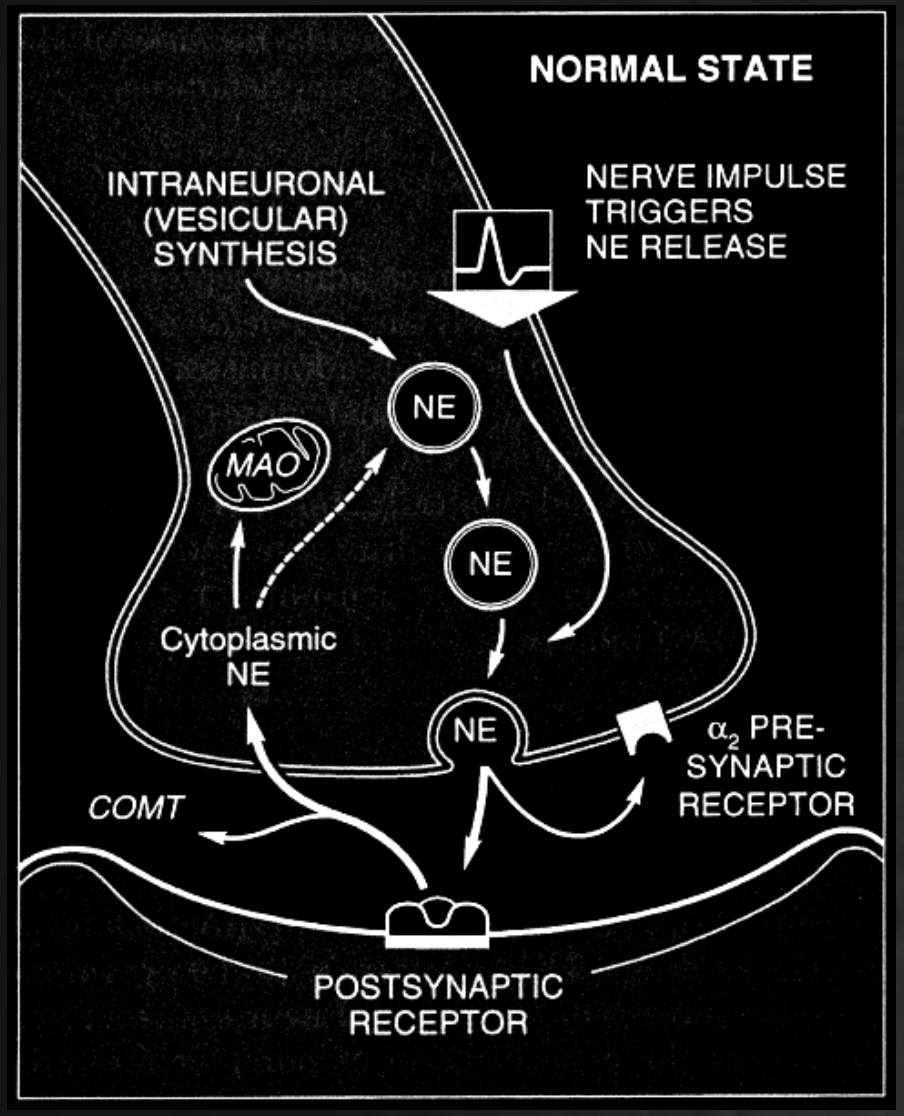
Actions:

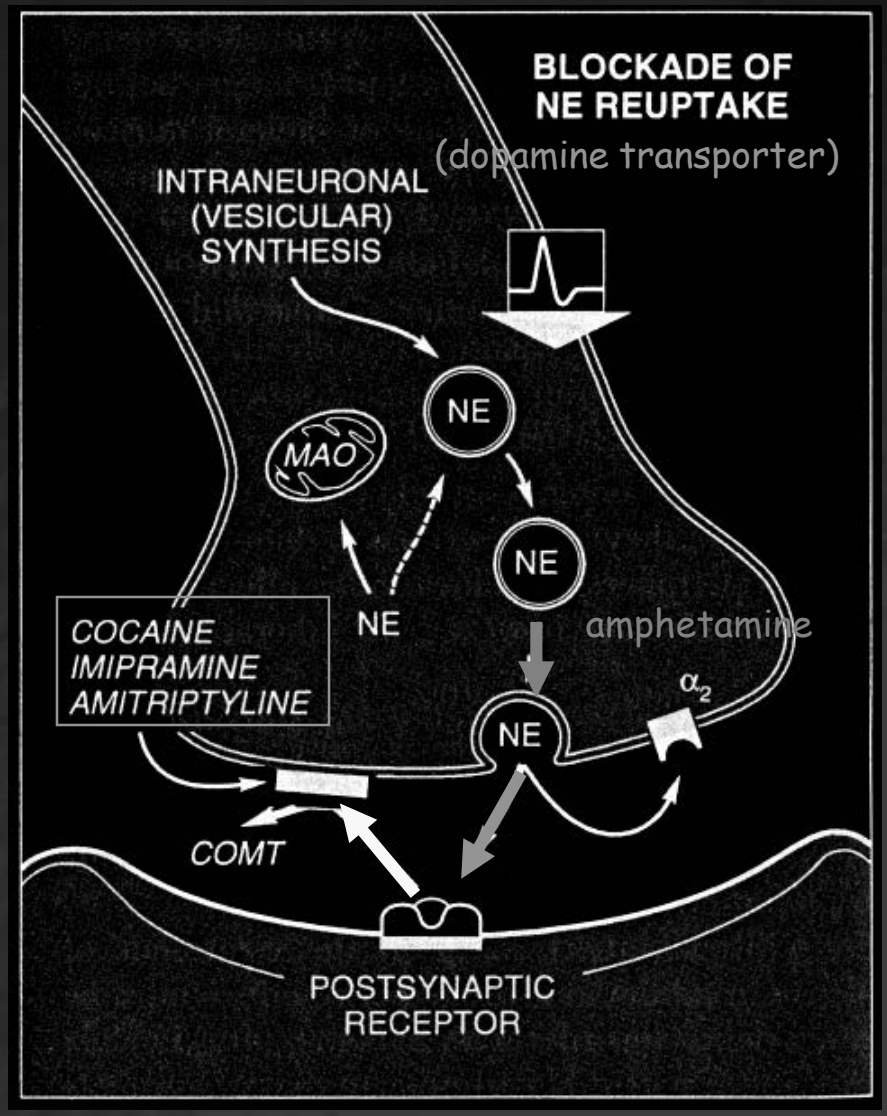
- CNS: stimulation of cortex and brainstem
- initial exposure - intense euphoria due to cortical stimulation (limbic)
- chronic intake depletes dopamine, leading to mood "cycling" / addiction
- blocks presynaptic re-uptake of norepinephrine, serotonin and dopamine



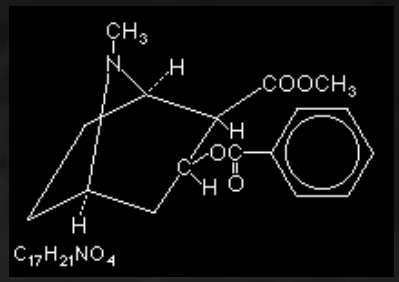


Psychomotor agents, Cocaine:





Psychomotor agents, Cocaine:



CNS:

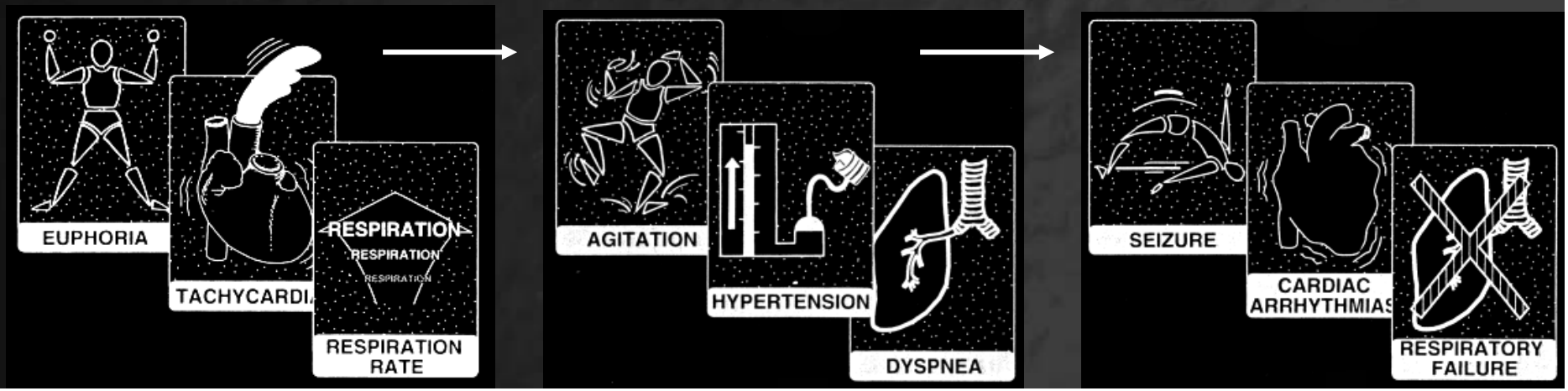
- feeling of enhanced mental awareness, euphoria ⟶ delusions, paranoia
- chronic use depletes dopamine reserves (euphoria / depression)

PNS:

- potentiation of norepinephrine ("fright or flight" actions)
- associated tachycardia - arrhythmia, hypertension, pupil dilation, vasoconstriction (necrosis of nasal septum)

Pharmacology:

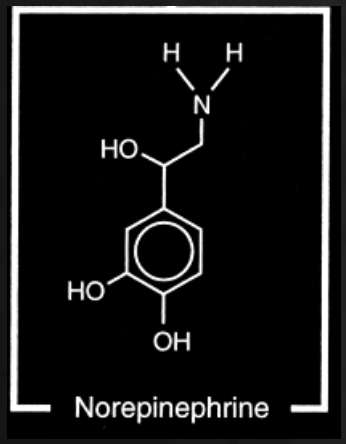
- similar to amphetamine, shorter duration than amphetamine
- used as local anesthetic (voltage-dependent sodium channels)

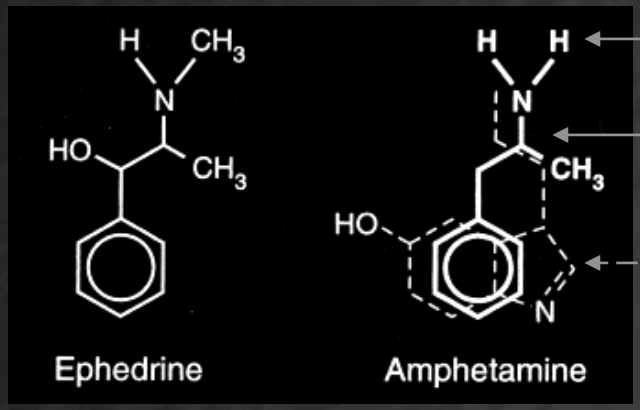


Psychomotor agents, Amphetamines:

Actions:

- similar to cocaine elevated levels of catecholamines are elevated in the synaptic cleft. However the mechanism differs.
- In the case of amphetamines, NT levels are elevated through increased release from intracellular stores. Amphetamines also inhibit MAO which degrades these neurotransmitters, further increasing NT levels.
- enhances alertness, reduces appetite / fatigue, insomnia (dopamine)
- methamphetamine - higher ratio of CNS to peripheral (amphetamine)
- medically used to combat depression, narcolepsy, appetite control

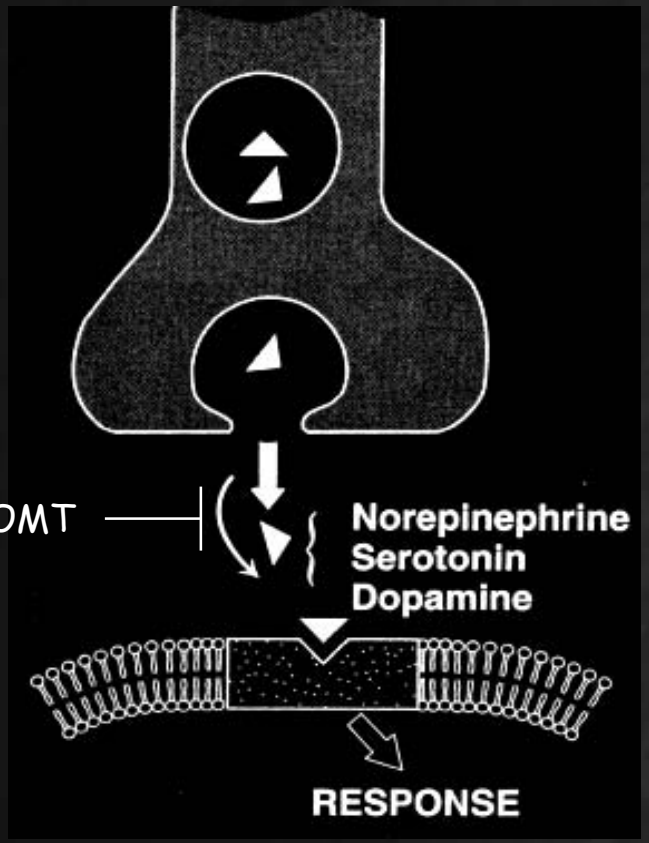


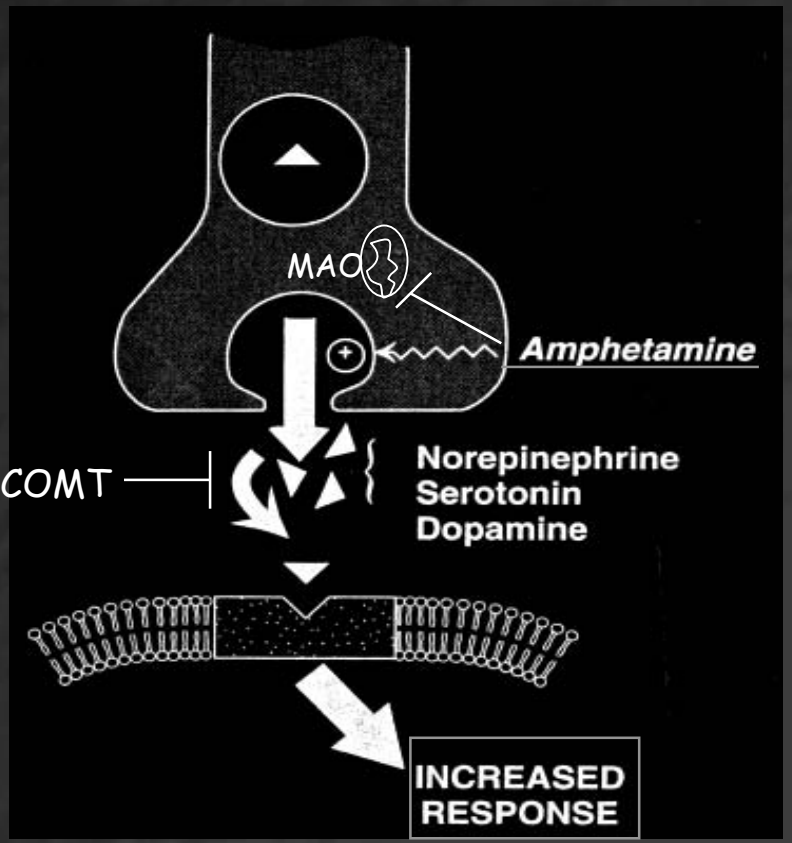


Amphetamines, mode of action:

Additional:

- elevates blood pressure (vasoconstrictor)
- produces sedation in children (basis for amphetamine-like drug Ritalin)
- enhanced neural stimulation via elevated catecholamines levels ⟶ excitotoxicity
- hallucinations tend to be auditory and tactile in nature, strong paranoid component

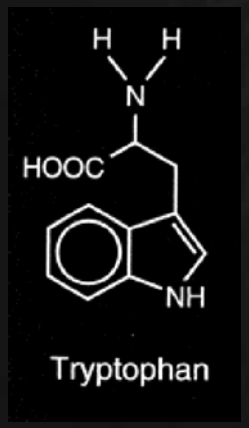




Psychotomimetics, LSD:

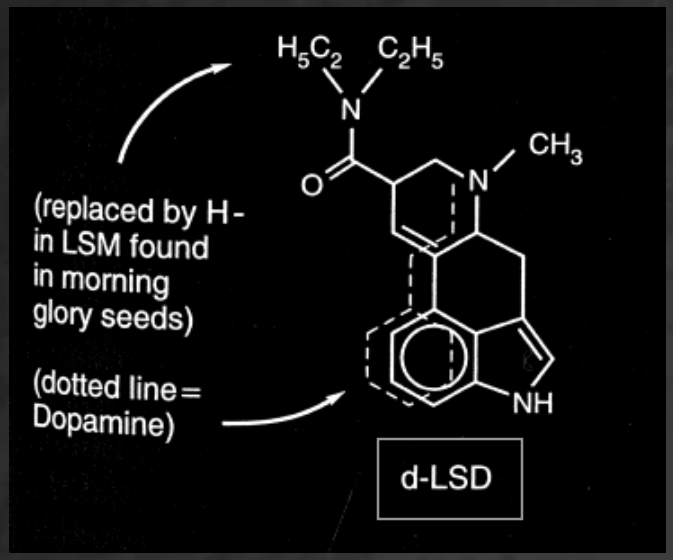
Actions:

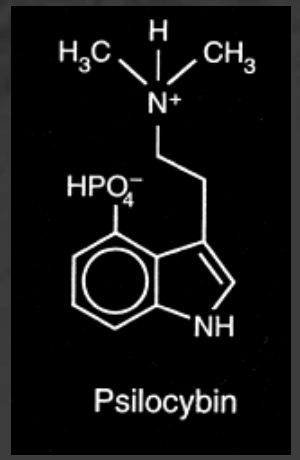
- exhibits serotonin agonist activity (midbrain - presynaptic receptors)
- activation of sympathetic neurons - pupillary dilation, increased BP / temp.
- hallucinations, mood alterations, occasional long-term psychotic changes
- adverse reactions - hyperreflexia, nausea, muscular weakness
- hallucinations tend to be visual in nature, potent (adult dose can be 2ug/kg)
- Haloperidol and other neuroleptics used to block effects of LSD.



Tryptophan

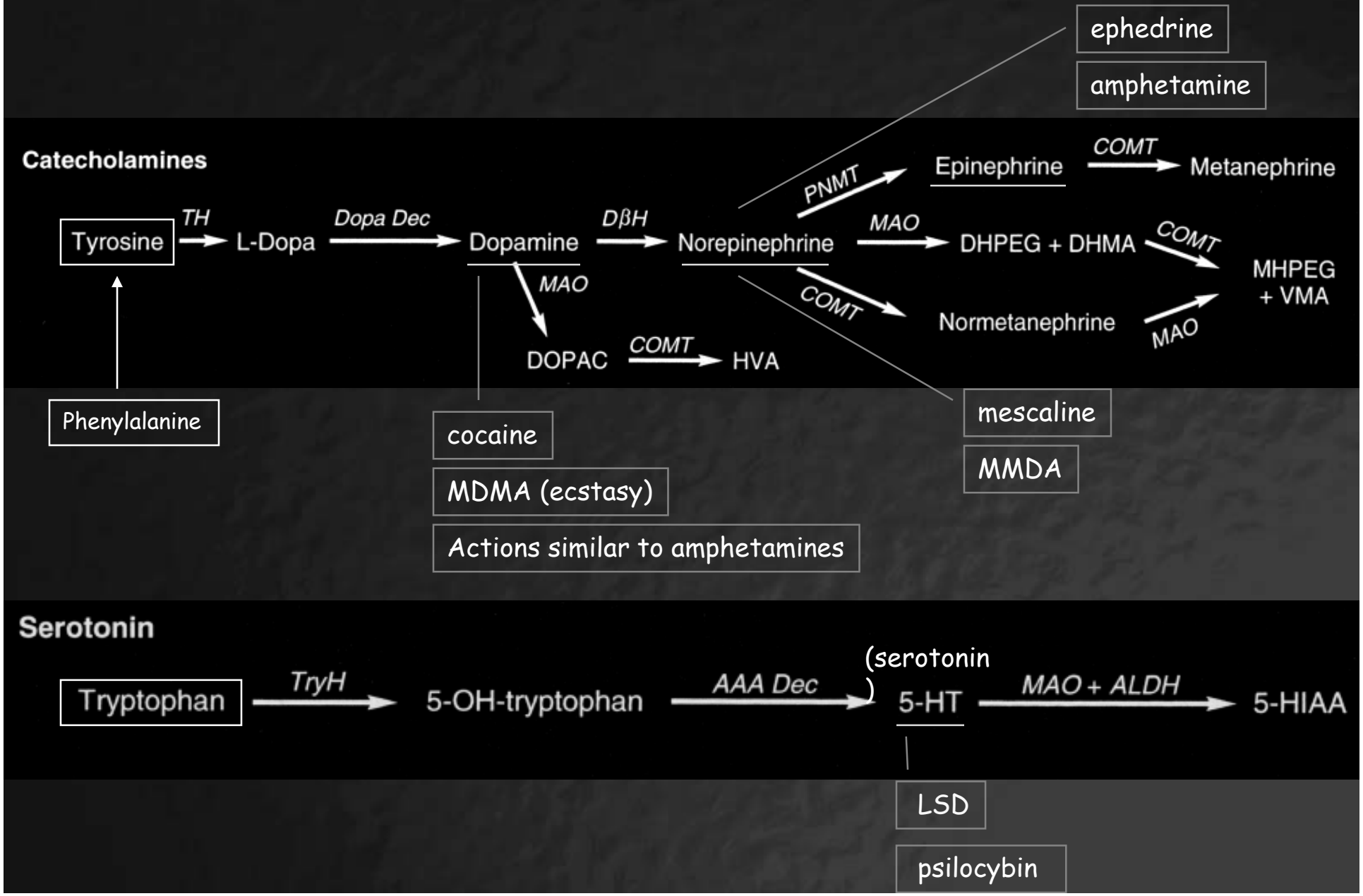
Serotonin
(5-OH-Tryptamine)



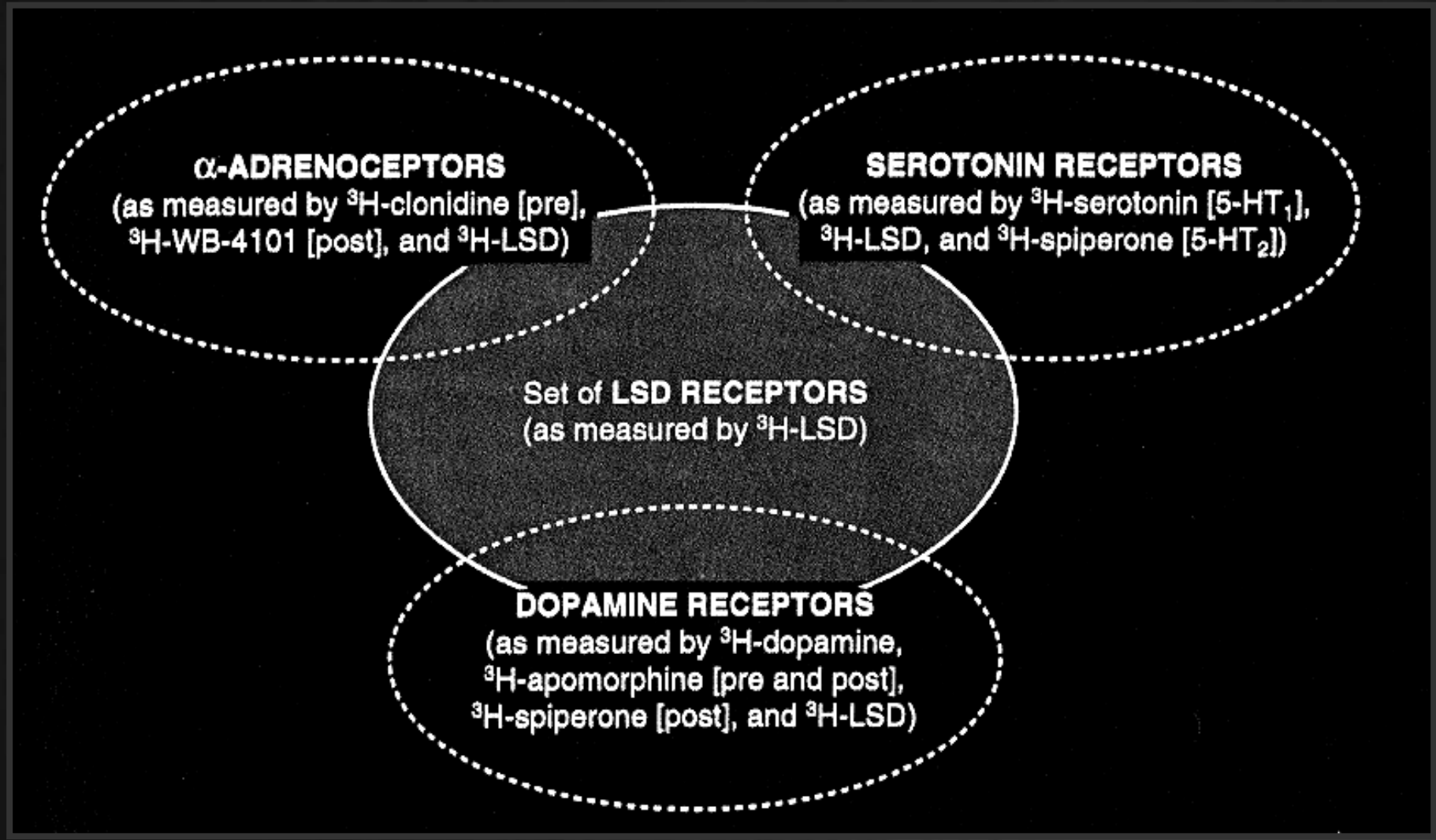


Psilocybin

Relationships among AA / NT / drugs:



Psychotomimetics, LSD:



Psychotomimetics, Phenylcyclidine:

Actions:

- anesthetic / analgesic properties
- tachycardia, hypertension, hyperthermia, increase in muscle tone
- bizarre repetitive movements (stereotypy), ataxia, dysarthria

CNS:

- excitement / agitation rapidly alternating with euphoria / depression
- individuals can exhibit schizophrenic symptoms (also animal models)
- potential long-term impairment of learning / memory (NMDA receptors)
- indirectly enhances dopamine and serotonin levels in the CNS

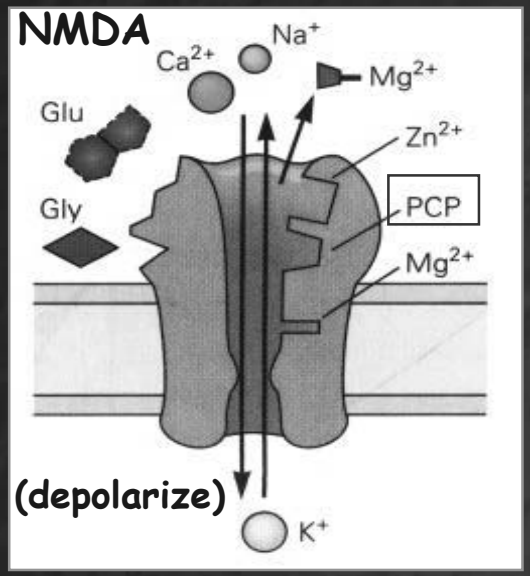
Pharmacology:

- structurally related to the anesthetic ketamine and MK-801
- open channel, non-competitive blocker of NMDA type glutamate receptors (non-competitive NMDA antagonist)
- highly lipid soluble, allowing persistent accumulation in the brain

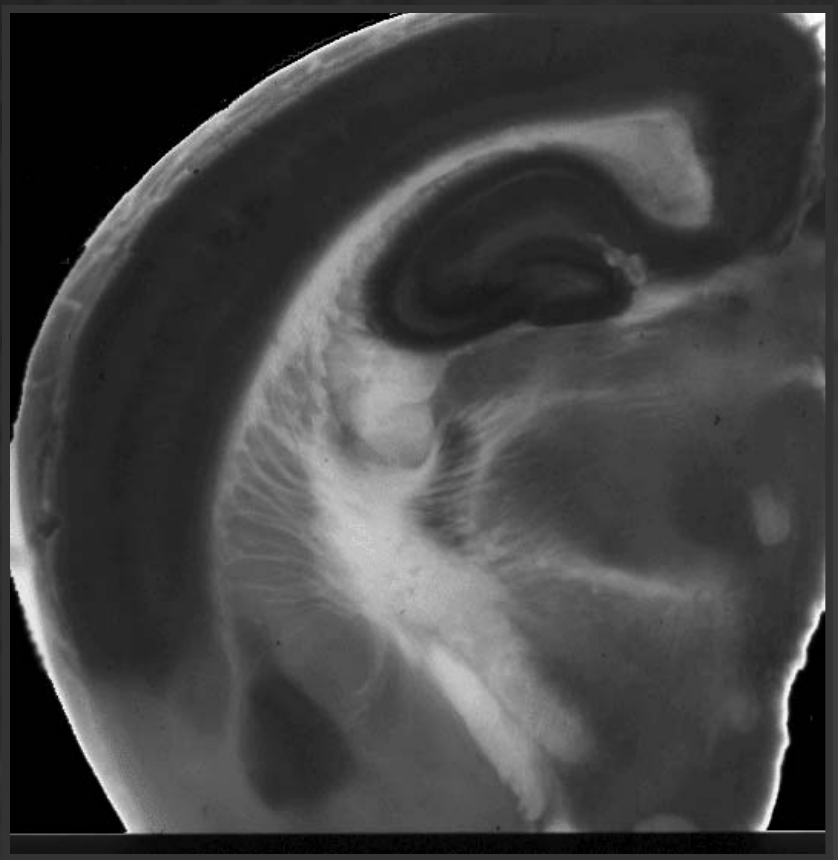
Psychotomimetics, Phenylcyclidine:

Actions:

- blockade of NMDA channels by PCP (or more selective antagonists such as MK-801) induce / exacerbate psychotic symptoms in patients
- interestingly, several drugs which enhance current flow through NMDA receptors exhibit anti-psychotic properties. Drugs which bind to dopamine D2-class receptors also exhibit anti-psychotic actions (dopamine antagonists such as clozapine)
- overall, results suggest that drugs which act directly or indirectly to affect dopamine release can have profound effects on mood / thought



Anxiolytics and Antidepressants



Antidepressants and mood stabilizing agents:

Anxiolytics:

Benzodiazepines:

Barbituates:

- (phenobarbital, pentobarbital, secobarbitol, thiopental)

Non-barbituate sedatives:

- (ethanol, chloral hydrate, antihistamines)

Anti-depressants:

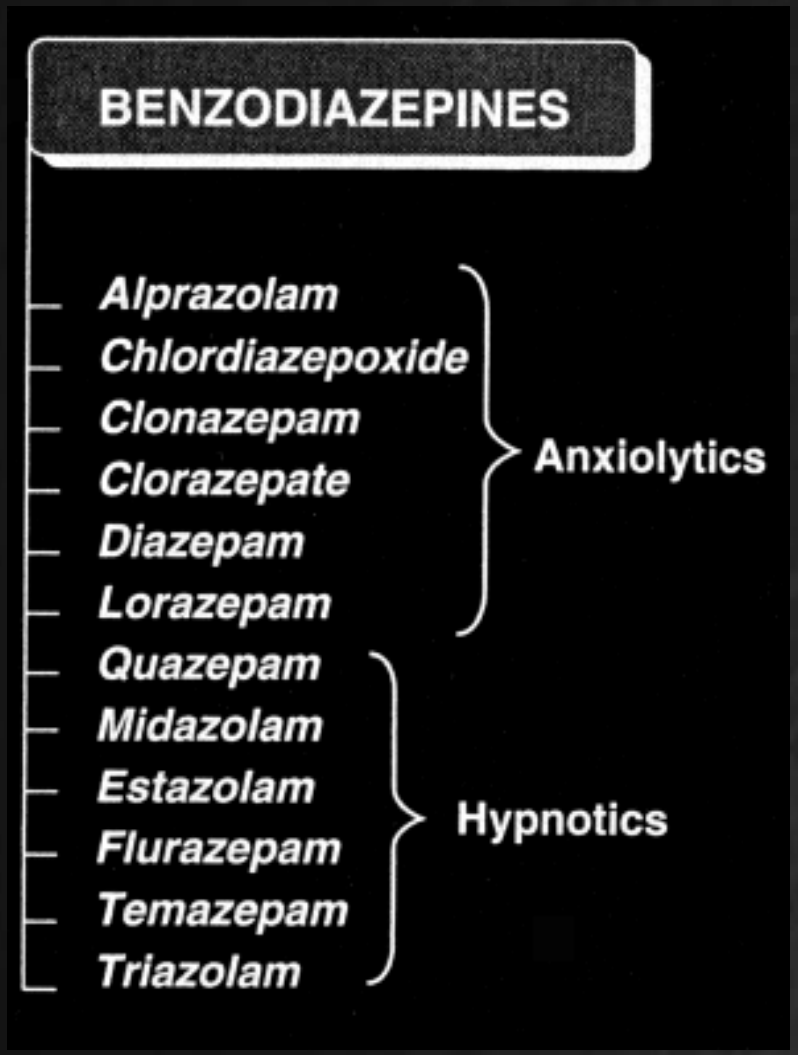
Tricyclic/polycyclic antidepressants

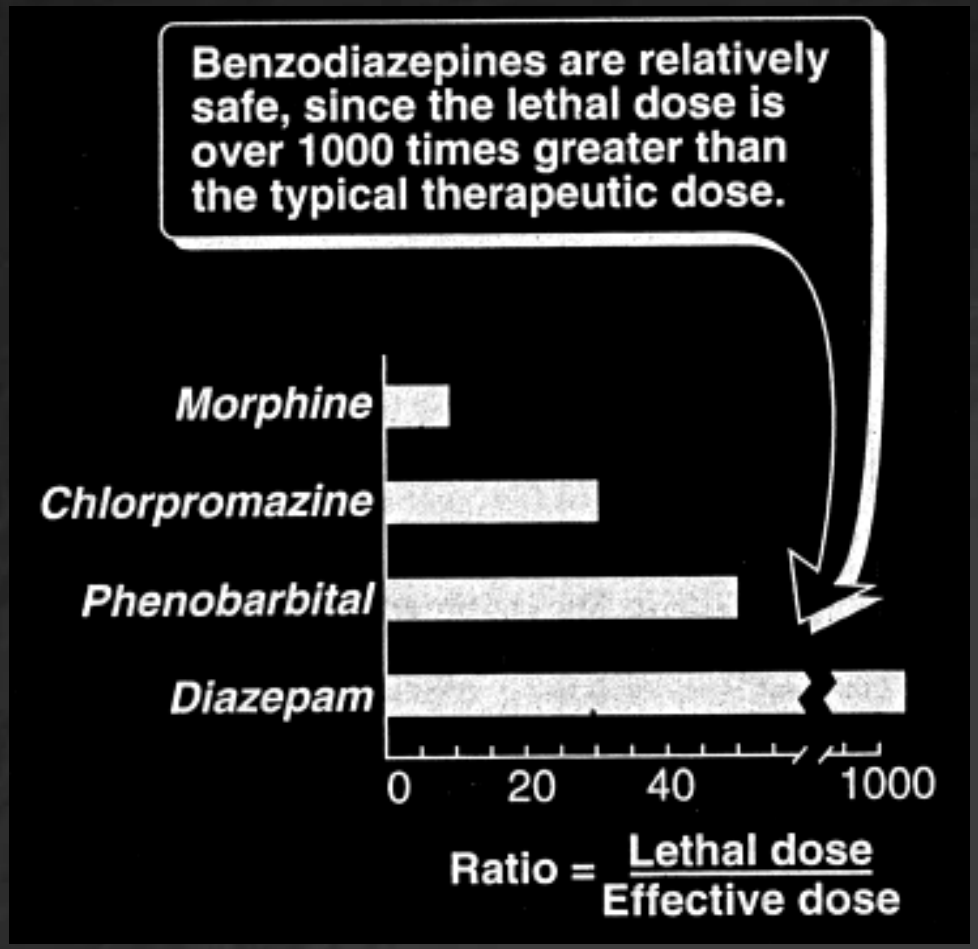
Serotonin selective re-uptake inhibitors

Monoamine oxidase (MAO) inhibitors

Drugs to treat mania: (lithium)

Anxiolytics, Benzodiazepines:





Anxiolytics, Benzodiazepines:

Actions:

- thought to reduce anxiety by selectively inhibiting limbic circuits
- no anti-psychotic activity, no effects on autonomic nervous system
- some sedative properties, hypnosis at higher levels
- anticonvulsant activities
- muscle relaxants, reduce spasticity - presynaptic inhibition on spinal cord
- used therapeutically to treat anxiety, depression, seizures, muscle spasm

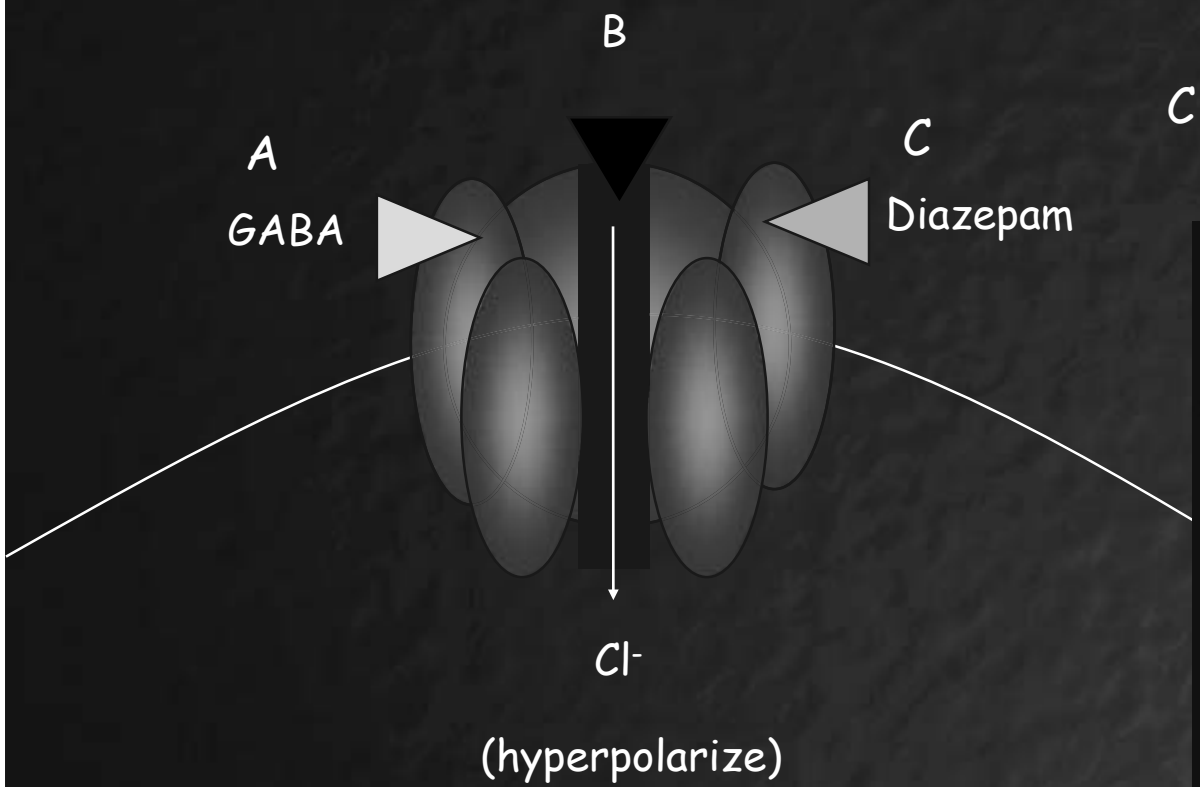
Pharmacology:

- half-lives of benzodiazepines vary tremendously, this is a key component governing their therapeutic use

Benzodiazepines:

- highest density of binding sites: cerebral cortex, amygdala (limbic), hippocampus, hypothalamus
- diazepam (antagonist - flumazenil)

Anxiolytics, Benzodiazepines:



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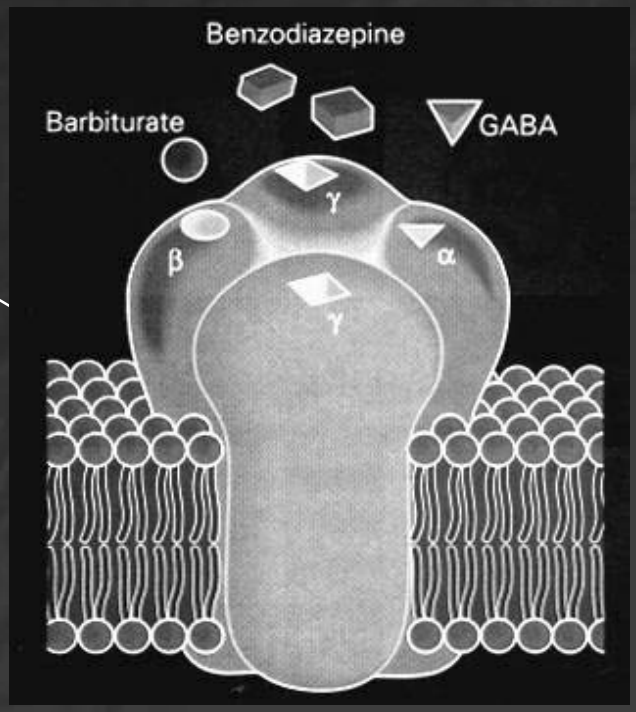
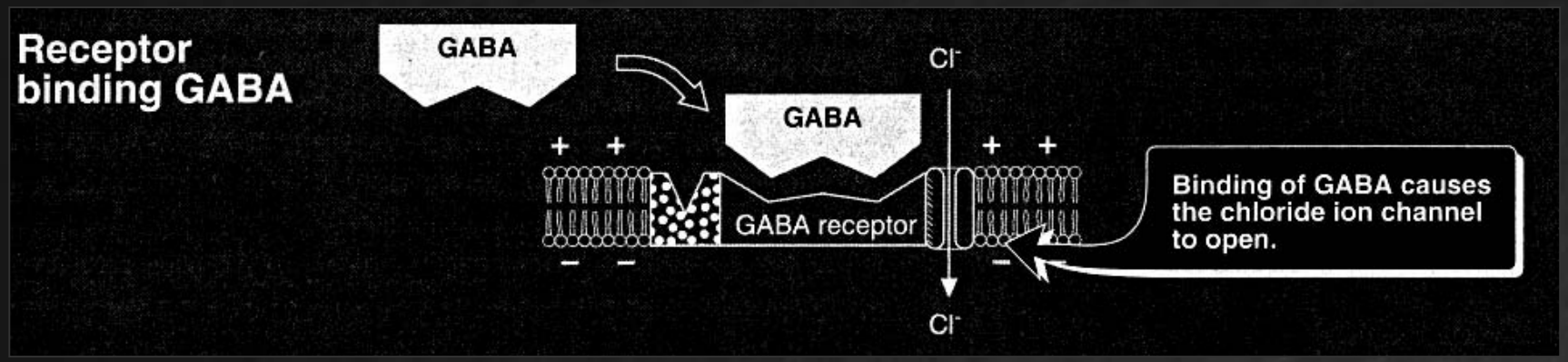
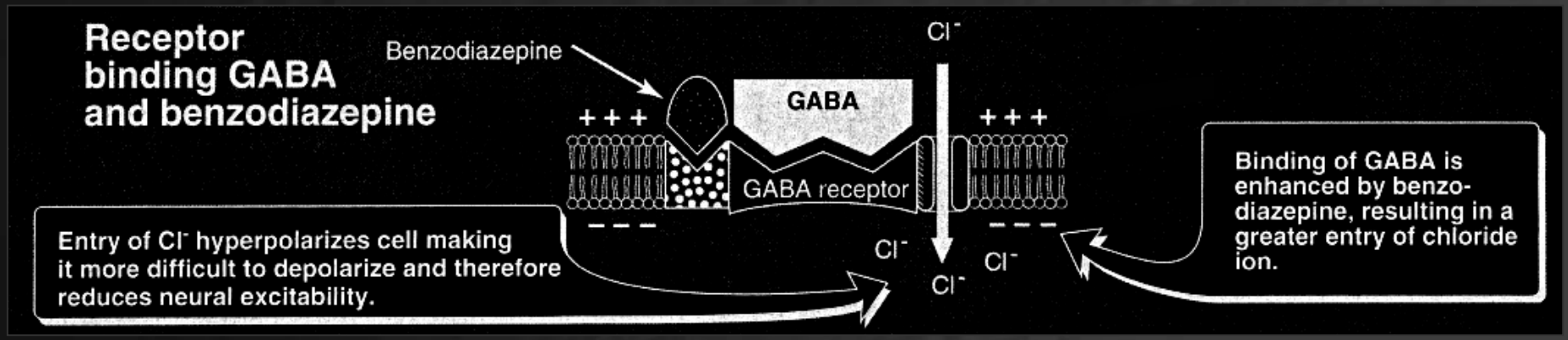
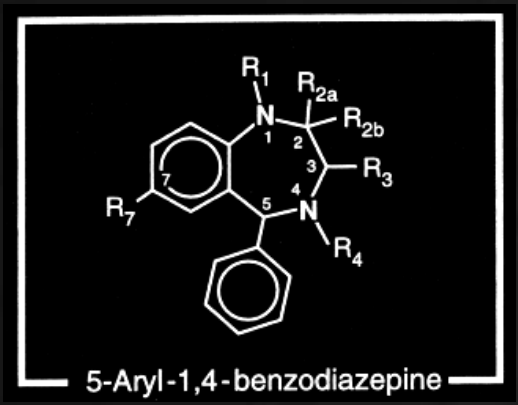


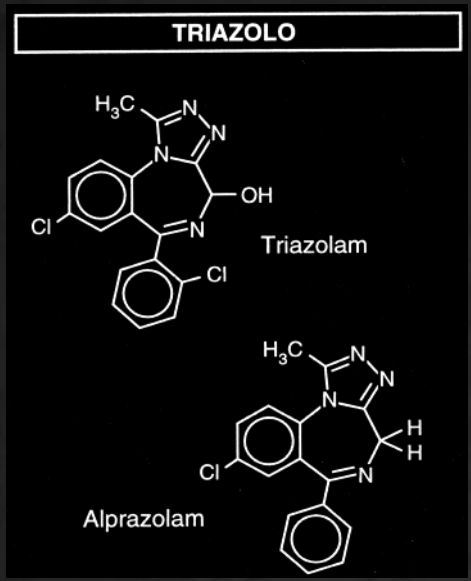
Anxiolytics, Benzodiazepines:

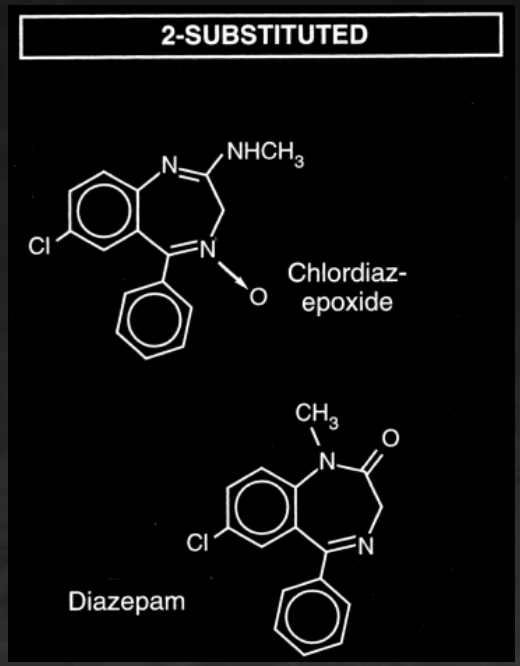


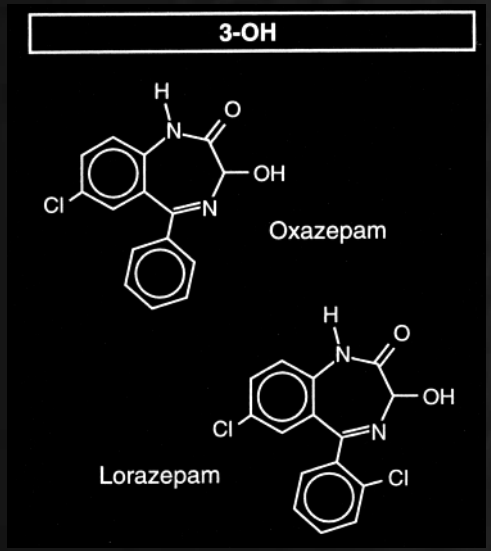


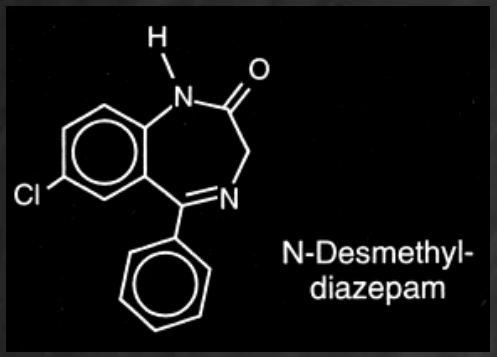
Anxiolytics, Benzodiazepines:

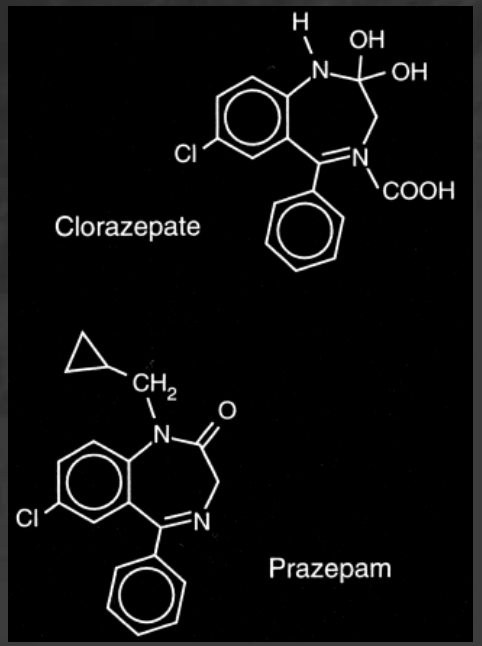




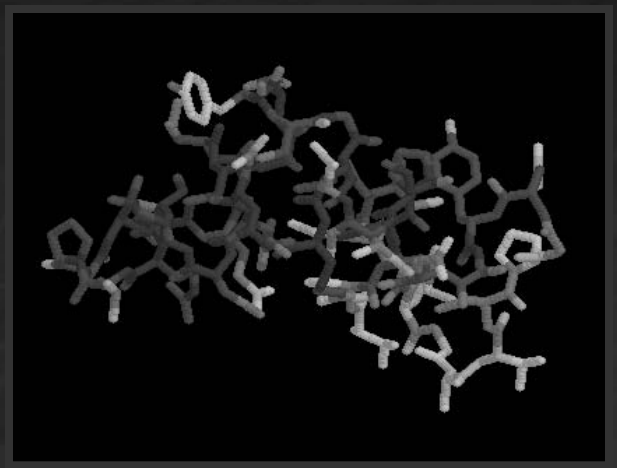








Antidepressants



Antidepressants, Tri- poly-cyclics (TCA's):

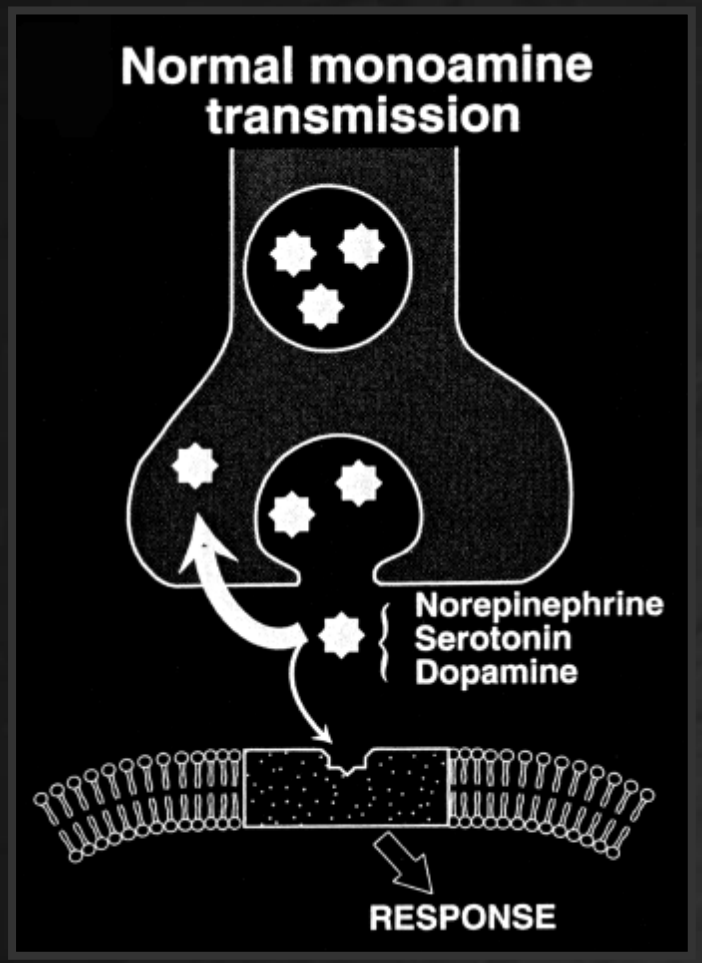
Actions:

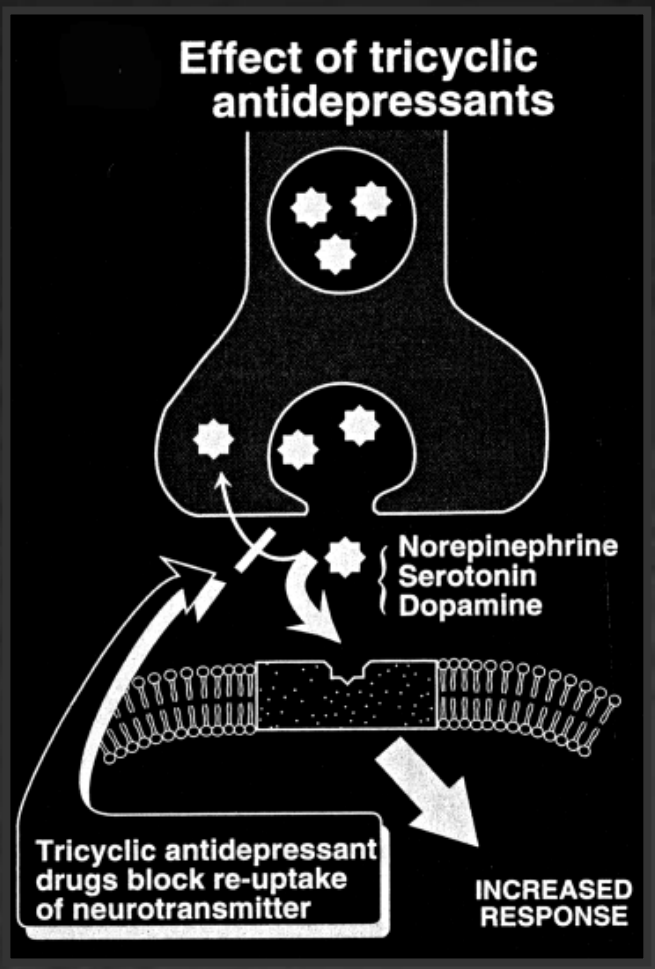
- used to treat severe major depression chronic pain and panic disorders
- elevates mood, improves alertness, reduced morbid preoccupation
- TCA's typically do not exhibit these effects in normal individuals
- mood elevation is slow in onset (2 weeks +), however effects are persistent
- tolerance to anti-cholinergic and autonomic effects usually develops
- physical and psychological dependence can occur

Adverse effects:

- cholinergic: blurred vision, xerostomia, constipation, urinary retention
- narrow therapeutic window (5-6) creates significant potential for overdose
- cardiac over-stimulation can be life threatening
- orthostatic hypotension (fainting), reflex tachycardia (elderly)
- sedation (first several weeks)

TCA's, mechanisms of action:

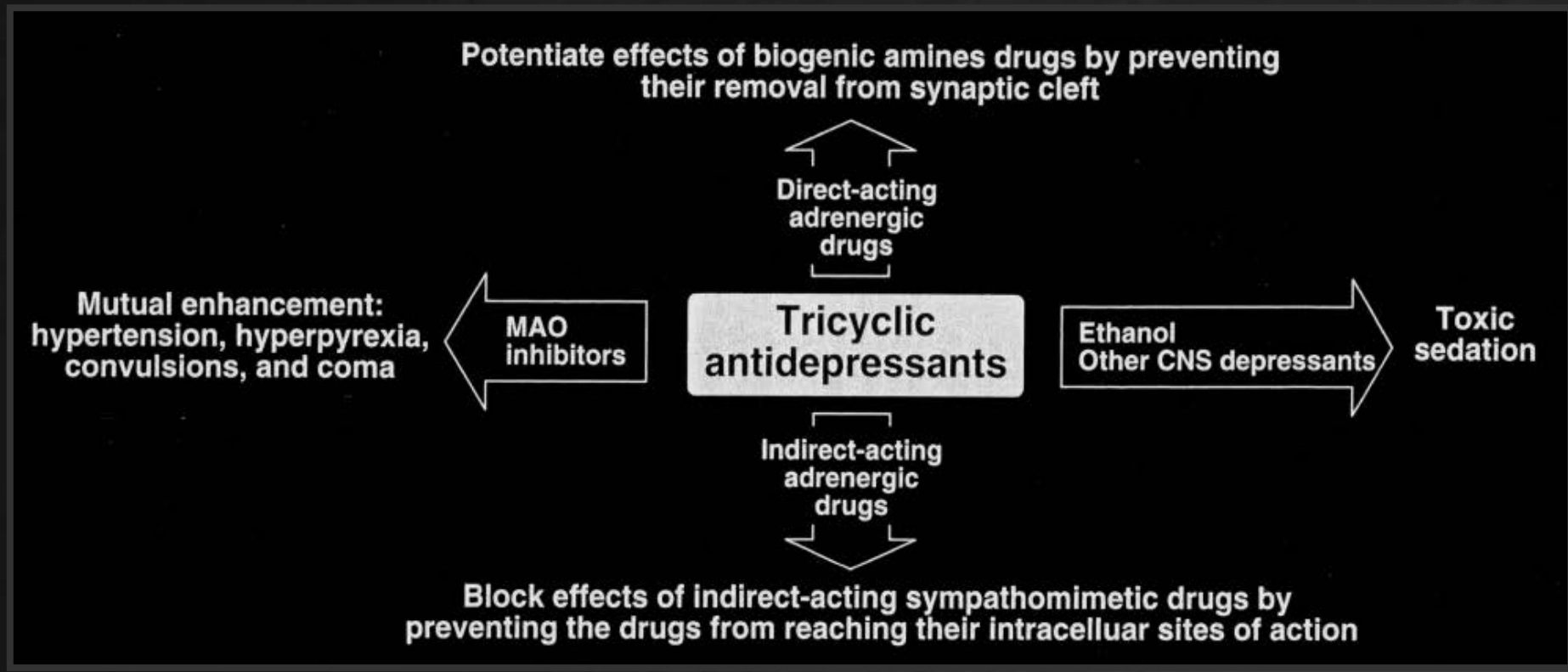




Notes:

- the events depicted only represent the initial actions of TCA's
- TCA's also inhibit alpha-adrenergic, histamine and muscarinic receptors

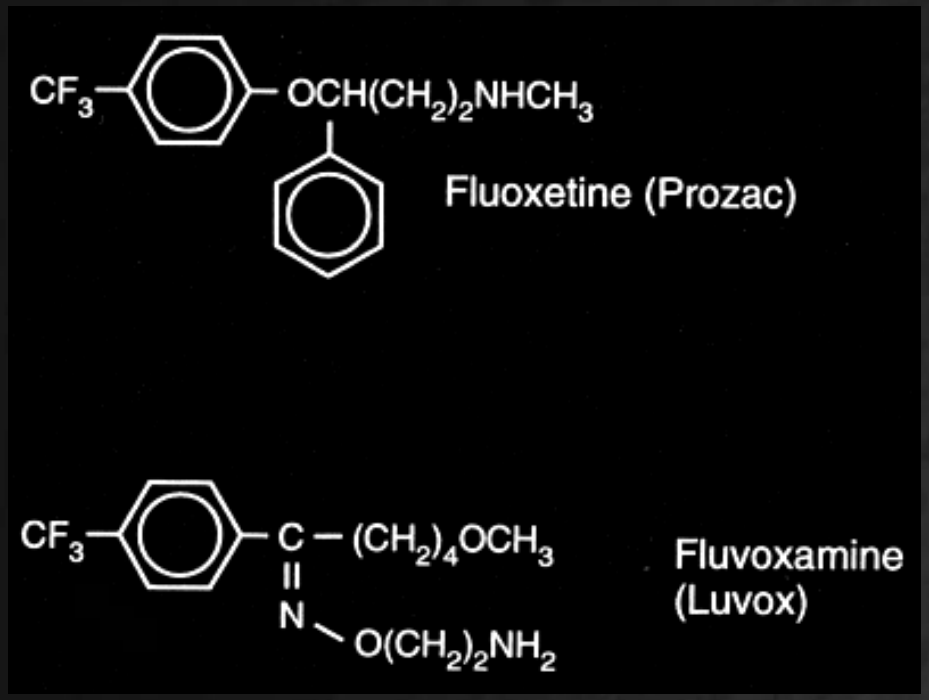
TCA's, interactions:

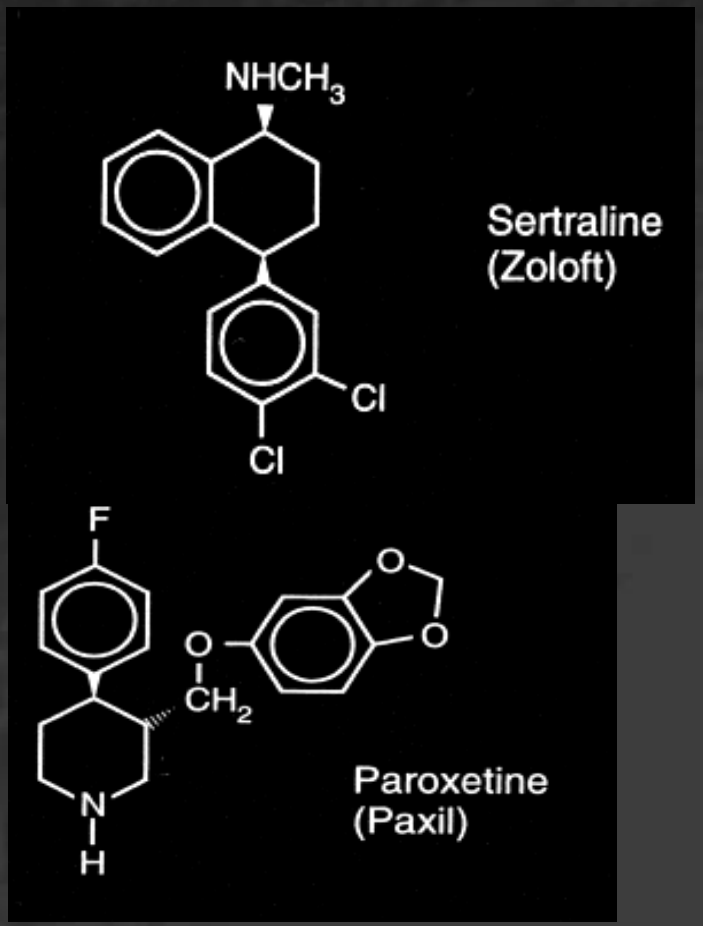


Serotonin selective re-uptake inhibitors:

Actions:

- used to treat major depression, bulimia, obsessive-compulsive disorders
- fewer side effects (TCA's - cholinergic, hypotension, weight gain)





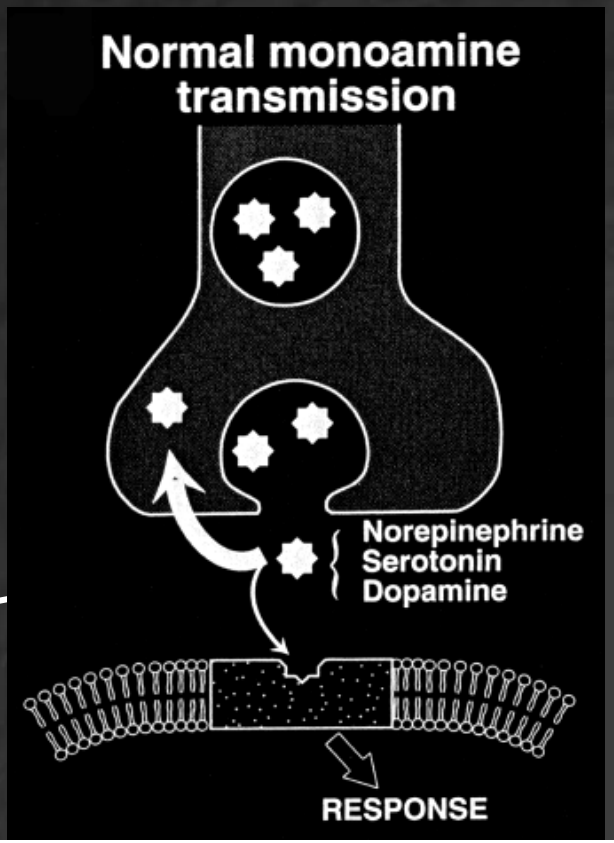
Serotonin selective re-uptake inhibitors:

Adverse effects:

- sexual dysfunction, nausea, anxiety, insomnia
- fluoxetine inhibits P-450 enzyme responsible for metabolizing TCA's, neuroleptic drugs and others (some individuals lack P-450 enzyme responsible for metabolizing fluoxetine and thus eliminate it very slowly)

Non-specific:
Cocaine
Amphetamines
LSD
TCA's

Specific:
SSRI's



Antidepressants, MAO inhibitors:

Actions:

- originally discovered through actions of iproniazid (derivative of anti-tubercular drug isoniazid). Used to treat "atypical depression"
- two MAO isoforms: MAO-A (mitochondrial localization - preferred substrates serotonin, norepinephrine) and MAO-B (extracellular localization – preferred substrate – phenylethylamine)
- MAO-A inhibition most important for anti-depressant effects (slow onset)

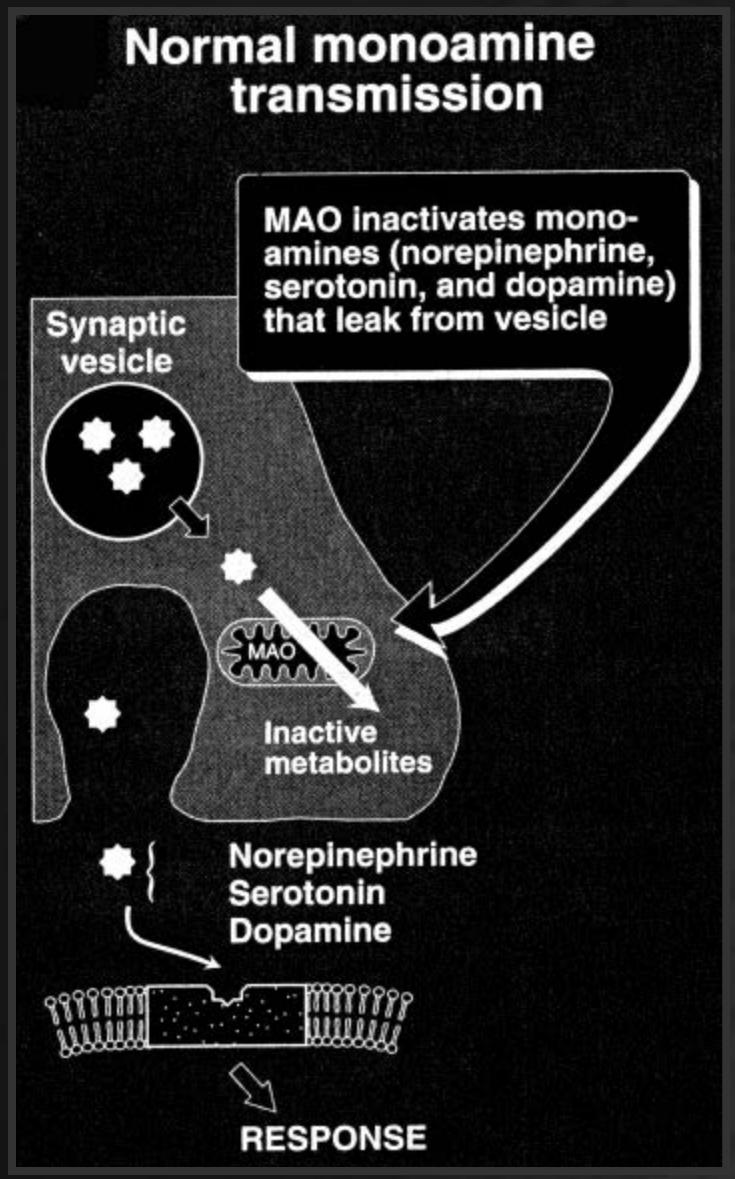
CNS:

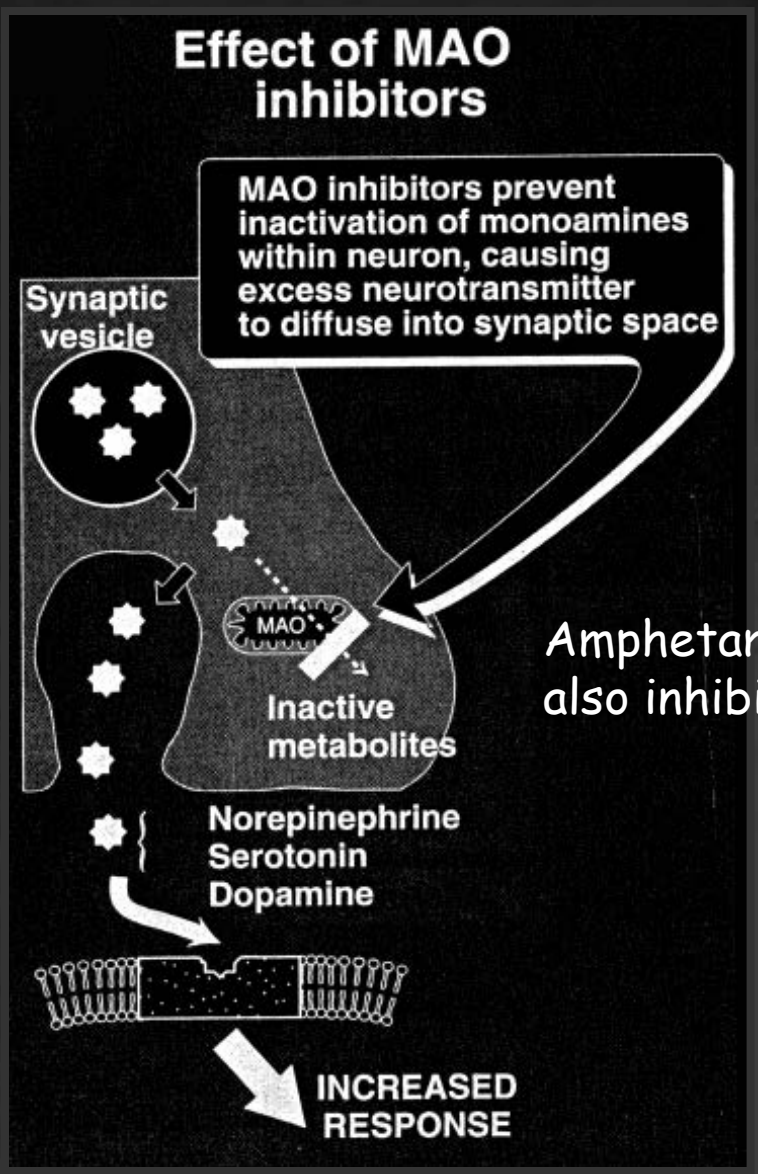
- inhibition of MAO-A results in elevation in 5-HT, NE, and DA levels
- elevation of 5-HT may indirect result of elevating NE

Adverse effects:

-MAOI's largely relegated to secondary role due to propensity to induce serious hypertensive reactions in patients ingesting foods high in tyramine (fava beans). Second/third generation anti-depressants more widely used.
- insomnia, depression of blood pressure, symptoms similar to TCA's

Antidepressants, MAO inhibitors:

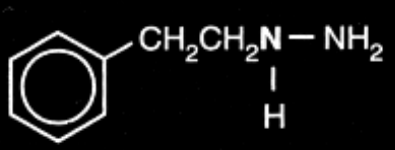




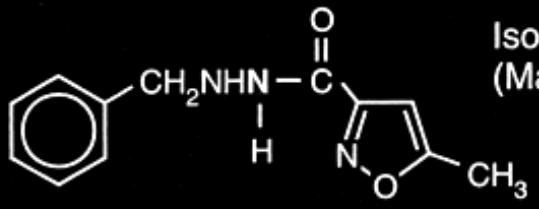
Amphetamines also inhibit MAO

MAO inhibitors:

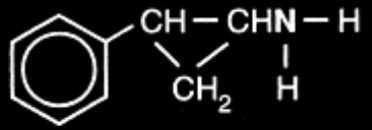
IRREVERSIBLE



Phenelzine
(Nardil)

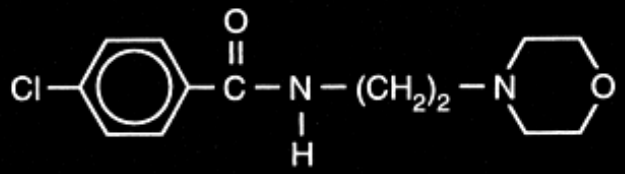


Isocarboxazid
(Marplan)



Tranylcypromine
(Parnate)

REVERSIBLE



Moclobemide
(Aurorix)

Antidepressants, overview: