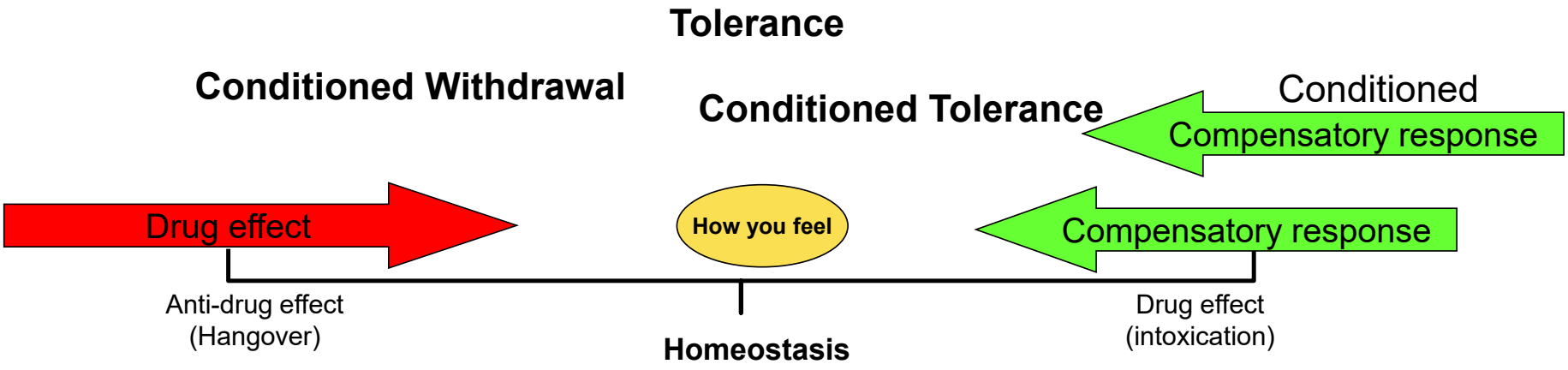
# Reward Circuits and Drug Addiction (II) Ch.4

- Basic Principles of Drug Action
  - Conditioned Withdrawal, Sensitization
- Drug Addiction- an overview
- Commonly Abused Drugs
  - Low Addictive Potential (marijuana)
  - High Addictive Potential (alcohol, nicotine, opiates)

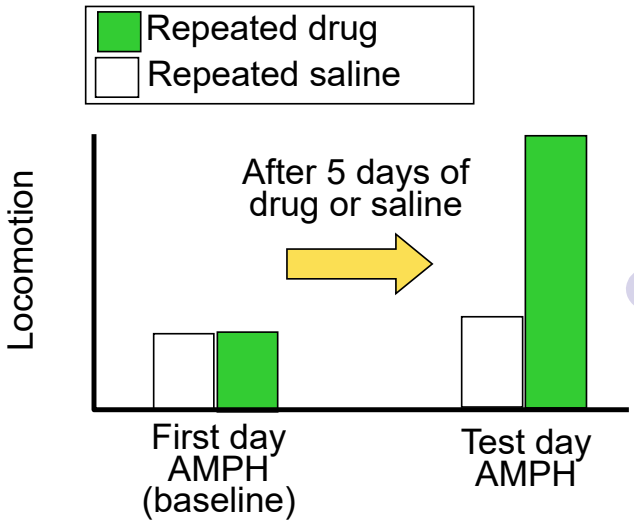
# Conditioned Withdrawal and Tolerance




- Brain gets conditioned to cues associated with drug taking. These cues trigger compensatory changes in body to prepare for more drug taking
  - **Go to drug context and then don't take drugs = conditioned withdrawal,** b/c there is no drug to counteract the compensatory changes which are usually opposite to those caused by drug
  - **Take drug in same context = conditioned tolerance** b/c body has prepared itself to counteract drug

# Principles of Drug Action (V)

- **Sensitization:** for some effects, repeated exposure ***increases*** sensitivity to behavioural effects of drugs




***Amphetamine (AMPH)-induced locomotion***. Classic effect involves 2 groups:

1) Gets low dose AMPH on Day 1 (test dose), then gets daily saline injections for 5 days

2) Gets test dose AMPH on Day 1, then gets AMPH repeatedly for 5 days.

On test day, both groups get same test dose of AMPH again

- After repeated exposure, locomotor response is much greater with the same dose of drug (the response has **sensitized).**
  - Locomotor effects of amphetamine caused by increase DA release
  - Drugs have multiple actions, some can develop tolerance while others sensitize in parallel.

➢ **ALL DRUGS OF ABUSE THAT HAVE ADDICTIVE POTENTIAL CAN PRODUCE SENSITIZATION to some of their effects**

# Addiction, What Is It?

- Many people take psychoactive drugs ***recreationally,*** but even if drug use is quite frequent, they can control their intake: heavy drug use does not necessarily mean the person is an addict.

- Three main factors we consider to qualify an individual as having a "substance use disorder"

➢ **1) *Habitual*** drug use that persists in spite of the adverse effects it has on health and social life
  - » May be viewed as a "chronically-relapsing disorder"

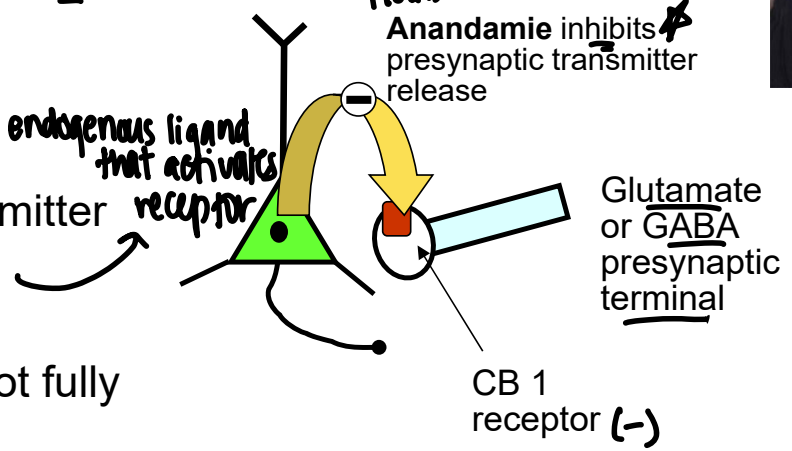
➢ **2) Drug seeking behaviour**: a disproportionate amount of time spent thinking about (craving) and acquiring the drug

➢ **3) Physical Dependence**: do they suffer from withdrawal from the drug
  - used 2 be the "gold standard" def
  - physical & emotional, can last up to a week
  - deal w/it w/ drugs
  - Can contribute to relapse in short term, but may not be a major factor contributing to long lasting effects of addiction.
  - Physical withdrawal last for a few days, but addiction can last a lifetime

- Three ways we can classify drugs as having a high addictive potential are
  - Common sense (do these drugs appear to be habit forming)
  - Whether animals will self administer the drug
  - Physical Dependence

# Marijuwannnanana (I)

- Low addictive potential: active ingredient is THC (Tetrahydrocannabinoid): from cannabis
  - receptors found all over brain (DA system, hippocampus, PFC, amygdala, accumbens.)
  - Receptors were found first, then neurotransmitter was discovered: **Anandamide,** acts as a retrograde messenger
  - Exact mechanisms for intoxicating effects not fully understood




- Withdrawal symptoms are uncommon, but can occur
- Technically defined as a hallucinogen, effects include:
  - **Lower, social doses:** ↑ sense of well-being, dreamy state, altered sensory perceptions, increased "munchies".
  - **Higher doses:** Sensory disturbances, emotional intensification, impaired motor, cognitive speech processes
    - In some instances, higher doses can produce transient psychotic symptoms (depersonalization, agitation, and paranoia)

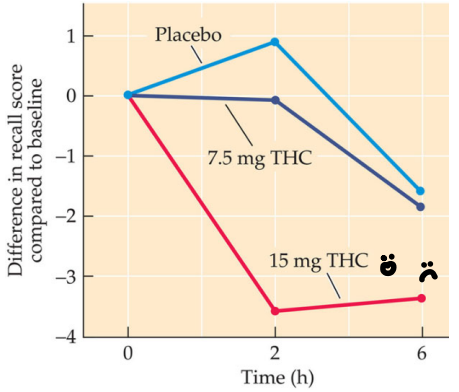
Nancy Regan commercial

war on drugs :( gateway drug :(

honk shoooo zzzzzz me fighting demons to stay awake rn

# Marijuana (II)

- **Acute marijuana** affects cognitive functions and psychomotor performance.
  - Impaired performance for a variety of verbal, spatial, time estimation, and reaction-time tasks.
  - Cannabinoids appear to interfere with all aspects of memory processing.
- **Basically, if you're stoned, don't expect to do well on cognitively-challenging tasks**




mem test recall diff words ↓ all aspects of memory

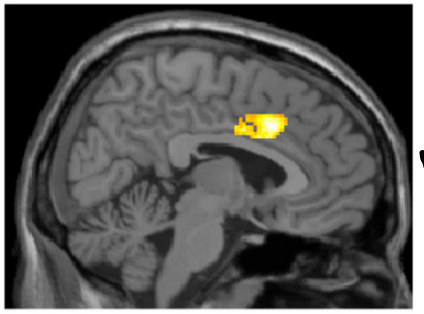
**Health Effects with Chronic use:** No reports of overdose. basically impossible

- Smoking may damage lungs; reduce testosterone levels in men; Animal studies suggest it may impair immune resistance

**Imaging studies:** chronic use associated with some brain abnormalities

- Associated with reduced activation in prefrontal/amygdala regions in response to emotional faces- deficits in appropriately judging emotional and affective cues?

Areas of increased activation in controls > chronic marijuana users in response to angry faces



not as good @ recognizing angry faces

Recent studies suggest a link between marijuana use & schizophrenia

- Marijuana may precipitate development of psychosis in **young** individuals at risk of developing schizophrenia i have a story about this...

THC has a number of **medicinal effects** (anti-nausea, analgesia, appetite stimulant, potential antidepressant properties)

- Drug companies developing compounds that stimulate cannabinoid receptors for treatment of a number of disorders

did u know cancer patients use this ☆

# Alcohol (I)

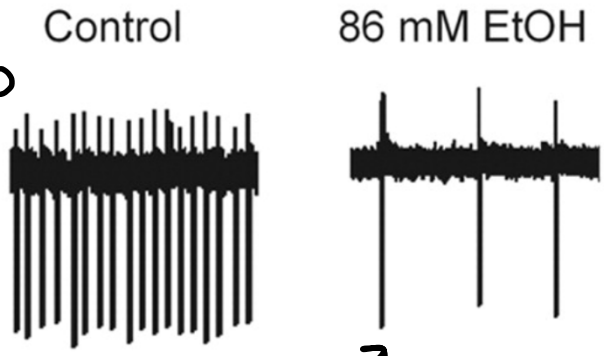

- High addictive potential: Oldest of the recreationally-used/abused drug
- 2/3 of population consumes, 10% become addicted
  - Biphasic action: lower doses = disinhibition, euphoria, relaxation.
  - With increasing amounts, slurred speech, disrupted motor co-ordination, sedation, coma, death

most ppl cant get there

- Depresses neural firing in multiple ways.
  - Acts as a positive modulator GABA receptors (like benzodiazepines) but IS not an agonist
  - Reduces functioning of NMDA glutamate receptors
  - Blocks $Ca^{2+}$ and other ion channels in neurons
  - Disrupts second messenger systems

(+) allosteric modulator → make receptor stronger (sleep lectures)

Neural firing before and after alcohol



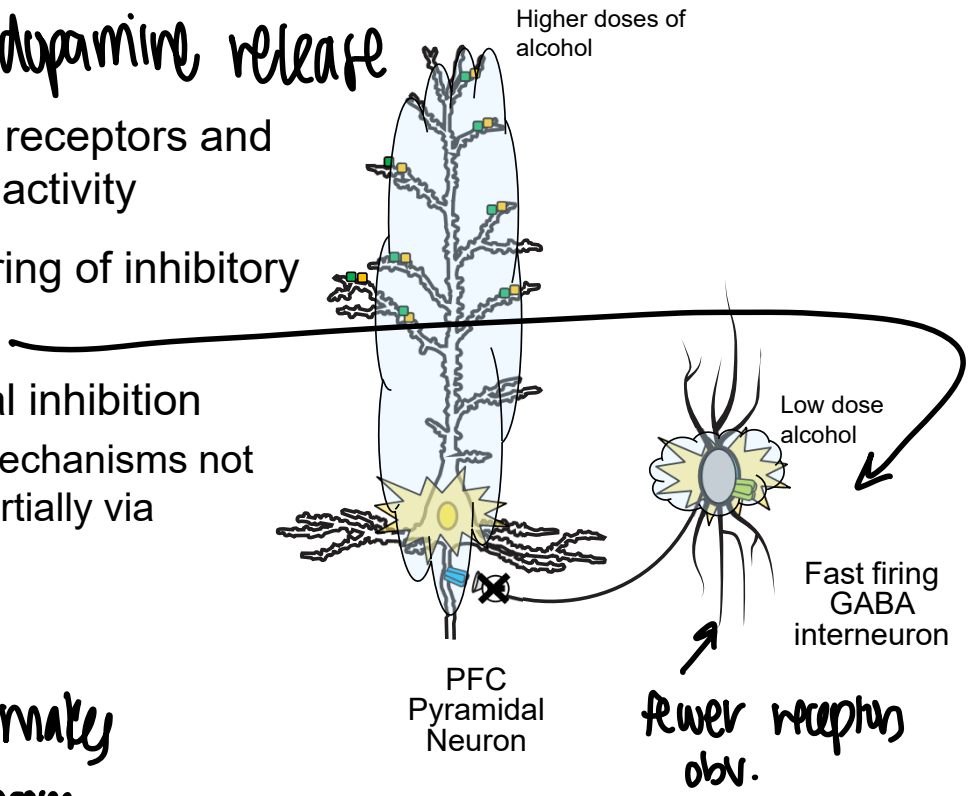

thats kind of a big difference

"pharmacology.....
like nothing else in life.....
size matters"

# Alcohol (II)

dopamine release

- **Alcohol:** facilitates activity at GABA receptors and reduces glutamate-NMDA mediated activity
- Low doses preferentially suppress firing of inhibitory interneurons, can ***dis-***inhibit cortex
- Higher doses causes broader cortical inhibition
  - Alcohol increases DA release, but mechanisms not completely understood (mediated partially via interactions with opioid system)




fewer receptors obv.

taking out sm neurons bit, makes brain more excitable → boom

ofc someone asked abt SSRI's ↑ alcohol LOLL

# Alcohol (III) – Hangovers and Withdrawal


- Many effects of classic "hangover" are due to increased levels of *acetaldehyde* (alcohol metabolite) or other forms of acute toxicity
  - Headaches, nausea, and abdominal cramps
  - Acetaldehyde can be excreted through sweat (exercise)
- Dehydration and electrolyte/vitamin imbalance (via frequent urination) also contributes to hangover
  - Sports drinks/vitamins before bed can help offset
- Hangover is also associated with reduced opioid activity
  - Fatty/spicy foods can increase opioid release
- Others hangover effects due to direct effects of alcohol or **withdrawal**
  - sleepiness (*suppression of REM sleep*) , ↑ sensitivity to bright lights/loud noises, anxiety, high blood pressure, rapid heart rate/breathing, sweating, vomiting.
  - Some of these effects may be offset by taking more alcohol
- **Alcoholics** (i.e.: those that are physically dependent) have much more severe withdrawal ***(can be lethal)***
- ***Delirium tremens*** (DTs) can last 2-4 days. Can include hallucinations, delusions, confusion, hyperthermia, convulsions/seizures, unstable blood pressure etc.

Not on exam

# Nicotine (I)

- High addictive potential: from tobacco
- Stimulates *nicotinic **acetylcholine** receptors,* ↑ neural activity
  - Nicotinic receptors reside on DA neurons, main pathway that underlies the reinforcing/addictive properties of the drug

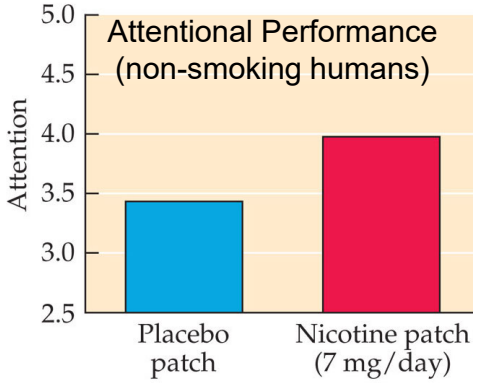
- **Effects in non-smokers**: nausea, vomiting, coughing, sweating, abdominal cramps, dizziness, flushing, diarrhea.
- **Effects in smokers:** less hungry, more alert, more relaxed
  - Over time, many of the aversive effects of nicotine develop tolerance, whereas some of the "rewarding" effects may sensitize.

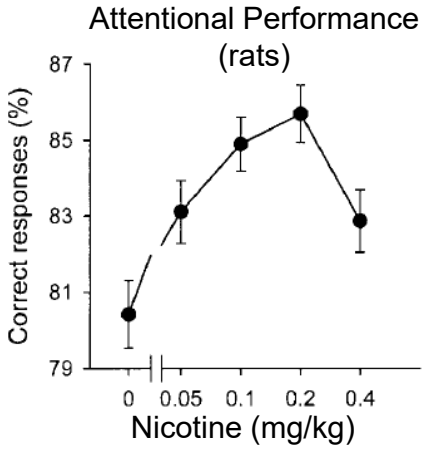
- Withdrawal: irritability, anxiety, restlessness, constipation, difficulty sleeping, concentration, increased appetite.

- **Addictive properties** of nicotine linked to route of administration
  - Inhalation of tobacco smoke caused rapid/pulsatile increase in nicotine in blood/brain
  - Nicotine therapies (ie: nicotine patch) causes gradual, sustained increases in blood/brain levels of the drug- not as reinforcing.

# Nicotine (II)

- About 70% of people who experiment with smoking become addicted.
  - Compare vs alcohol (10%) or heroin (30%).
- ~ 20% of all attempts to quit are successful for <2 years
- Multiple health hazards with chronic use (primarily from the smoke)
- Its not ALL bad: ***nicotine*** has been shown to:
  - Improve **attention**/cognition in normal subjects (both smokers AND non-smokers)
  - Also improves cognition in individuals with Alzheimer's or schizophrenia
  - Decrease risk of Parkinson's
- Drugs are being developed to produce beneficial effects of nicotinic stimulation



# Opiates (I)

- High addictive potential; originally used ~ 4000 B.C.
  - In order of potency; fentanyl > heroin > morphine>methadone >codeine
  - The rush: when taken I.V., initial wave of intense abdominal orgasmic pleasure that evolves to serene drowsy euphoria
  - First rush entices the user to do more, tolerance builds up, higher doses needed to get similar effect; never as good as 1st rush

- Act as agonists for "endogenous opioid" receptors
  - **Enkephalin and endorphin** are 2 common endogenous opioid peptides- generally ***inhibit*** neural activity
  - Endogenous opioids mediate numerous functions (analgesia, emotional regulation, sensory/motor integration)
  - Receptors in the accumbens mediate pleasurable aspects of natural rewards (e.g.; sweet/fatty tastes)
  - Opioid receptors are on GABA neurons in the VTA. Activating these receptors inhibit GABA neurons, disinhibits dopamine neurons