# Psych3 – The Biological Basis of Psychology

## Lecture 7

Primed for Addiction

# Lecture 7: Objectives

- Define addiction and dependence and contrast these two terms in terms of the presence of physical withdrawal.
- List the major classes of drugs of abuse and describe their general subjective and physiological effects when administered acutely, chronically and describe their withdrawal syndromes-which produce physical dependence?
- Define addictive liability and describe the factors that influence the addictive liability of drugs
- Describe the mechanisms of action of the stimulants: amphetamine, cocaine, MDMA (ecstacy), nicotine
- Describe the differences between the mechanisms of action of barbiturates and benzodiazepines and compare with the hypnotic drugs PCP and ketamine
- Explain how alcohol suppresses neurotransmission in your brain and describe the biochemical basis for concerns regarding interactions with other sedative/hypnotics drugs and with caffeine
- Describe the mechanism of action of opiate drugs and explain how substitution therapy using methadone and LAAM works in treating heroin/morphine addiction

# Lecture 7: Objectives

- Describe the mechanism of action of LSD, mescaline and MDMA
- Describe why MDMA + dancing can be deadly
- Describe the mechanism of action of cannabis and cannabis derivatives

# Definition of Addiction: basic terms

- **Drug Dependence**: **physiological dependence** produced by repeated drug-taking that is characterized by a **withdrawal syndrome** when drug is removed (e.g., alcohol, opiates)
- **Withdrawal syndrome**: **a set of physiological reactions that occur in response to removal of a drug** following repeated treatment; often (although not always), the reactions are opposite those produced by the drug itself
- **Addiction**: **psychological dependence** produced by repeated drug-taking that is characterized by obsessions and compulsive drug-seeking behaviors; results in a detrimental impairment in physical, mental or social functioning
- You can be dependent upon a drug, without being addicted to it (e.g., morphine for pain) or you can be addicted to a drug without being dependent upon it (e.g., cocaine & amphetamines)

# Addictive drugs affect the brain

- All drugs of abuse exert their psychoactive effects by acting as agonists or antagonists of receptors or transporters in the brain (i.e., **they have a site of action in the brain**)

- Certain classes of drugs of abuse have similar psychoactive effects because they have a very similar **mechanism of action** (how the drug interacts with a receptor to affect the body) e.g., sedative/hypnotic drugs

- Other classes of drugs of abuse have similar psychoactive effects that can be produced via different mechanisms of action (e.g., stimulant drugs)

- **Drugs of abuse are categorized based on the type of psychoactive effect they produce**

# Categories of drugs

- **Stimulants:** increase feelings of energy and well-being; produce sympathetic nervous system effects (**sympatomimetic**=mimic the activation of the sympathetic nervous system)
- **Depressants/Sedative/Hypnotics:** produce feelings of relaxation and a dream-like state (**anesthetic**=produce a dissociation from reality)
- **Narcotics/opiates:** produce a dream-like state and produce **analgesia** (reduction in pain)
- **Hallucinogens:** produce distortions of perception and alter a sense of reality
- **Cannabinoids:** produce feelings of well-being and sense of acuity (sharpness); can produce feelings of relaxation

# Pharmacological Principles of Addiction

- **Addictive liability (how addictive a drug is likely to be)** depends upon how quickly the drug enters/leaves the brain

- **Factors that influence how quickly a drug will enter/leave the brain:**

1) **Chemical structure:** How fatty is the drug? Does the drug look like nutrients that our brain uses?

   **Remember: the drug has to cross the BBB**; fattier drugs cross readily, drugs that look like nutrients our brain needs can sneak through transporters in the BBB

2) **Route of administration:** Is the drug entering directly into the blood stream or entering first into the stomach? High or low blood flow?

   FYI: routes of administration that increase the likelihood that a drug will enter the blood increase the addictive liability of the drug

Intravenous injection>smoking/snorting>sub-lingual>oral

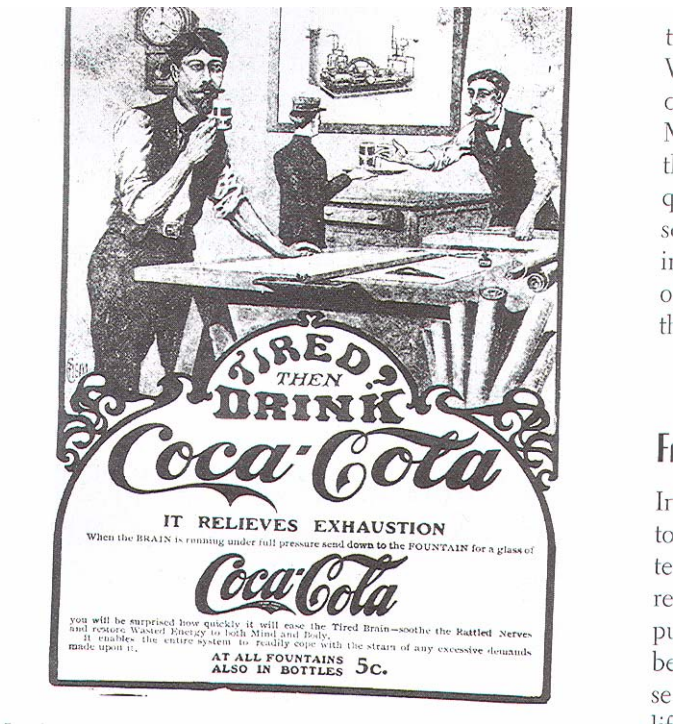
Lungs and nostrils have lots of blood capillaries

Lots of blood supply under the tongue

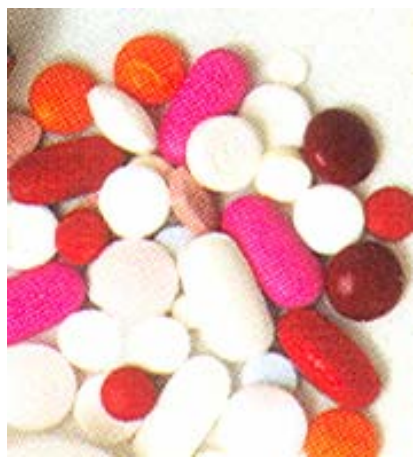
# Stimulant Drugs

- **Illicit (illegal) stimulants: cocaine, the amphetamines**

- **Licit (legal) stimulants: caffeine, nicotine, pseudoephedrine** (in allergy meds)
- **Prescribed and licit stimulants: Dexedrine (d-amphetamine), Adderall (d-amphetamine + amphetamine) and Ritalin (methylphenidate)**

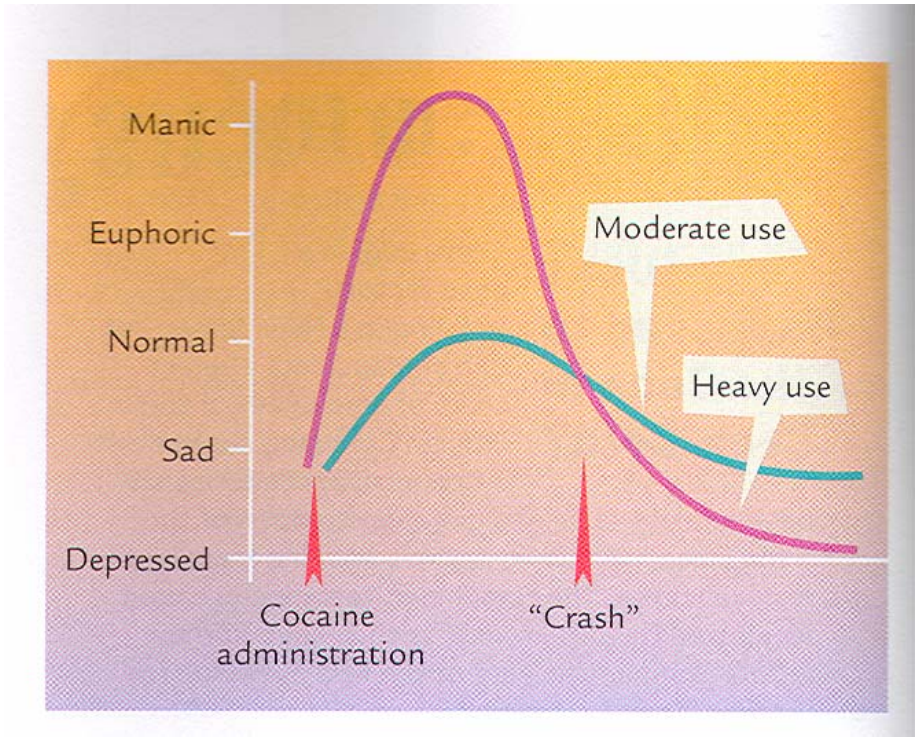



- **Acute (immediate) effects:** Increase feelings of energy and increase attention=sympthomimetic



# Stimulant Drugs

- **Effects of withdrawal:** tiredness, “crash”

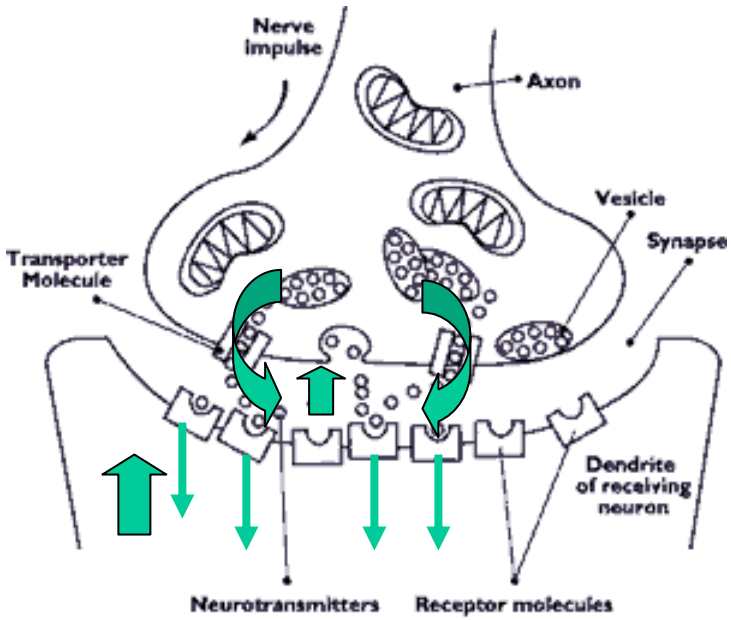



- **Chronic (long-term) effects:**
  - Tolerance to energizing effects
  - Sensitization of “crash” in withdrawal
  - Sensitization of psychotic effects and seizures
  - Cardiovascular problems due to over-stimulation of sympathetic nervous system

# Stimulant Drugs: Pharmacology

- **Amphetamines:** look like dopamine and norepinephrine; "reverse" the transporters of these neurotransmitters and elevate synaptic levels of dopamine and norepinephrine

**Amphetamines are indirect agonists** because they "reverse" the transporter



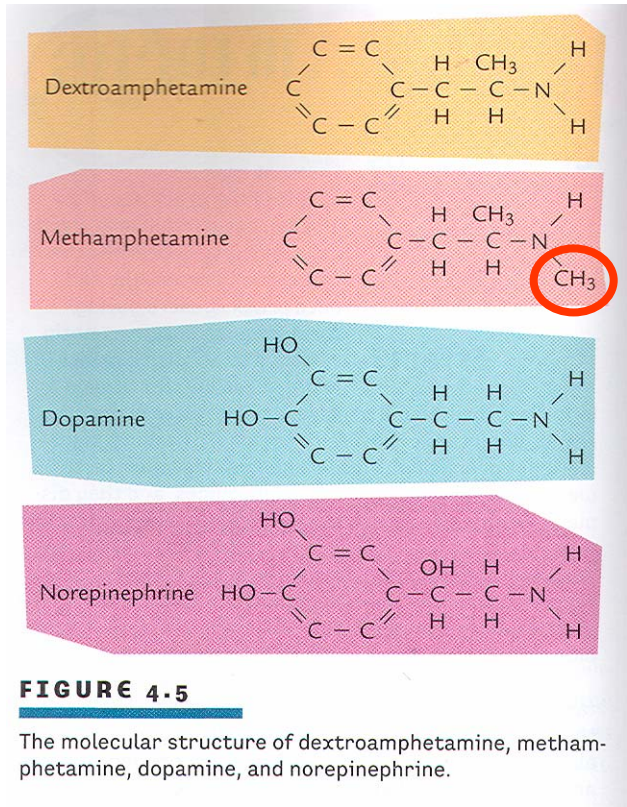




**FIGURE 4.5**

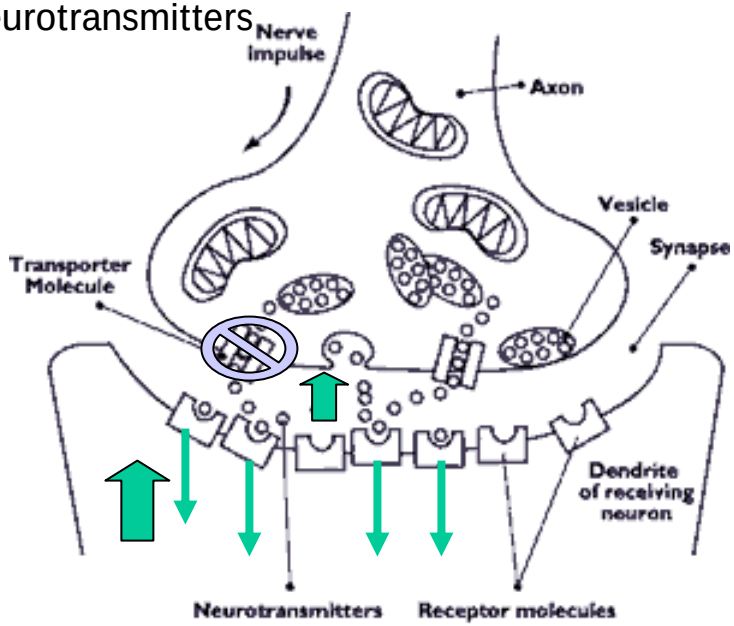
The molecular structure of dextroamphetamine, methamphetamine, dopamine, and norepinephrine.

- **FYI: Methamphetamine:** the addition of the methyl group makes methamphetamine an indirect agonist at serotonin transporters also

# Stimulant Drugs: Pharmacology

- **Cocaine:** blocks the reuptake of dopamine, norepinephrine and serotonin and elevates synaptic levels of these neurotransmitters

**Cocaine is an indirect agonist** at dopamine, norephinephrine and serotonin synapses because it blocks the reuptake of these neurotransmitters



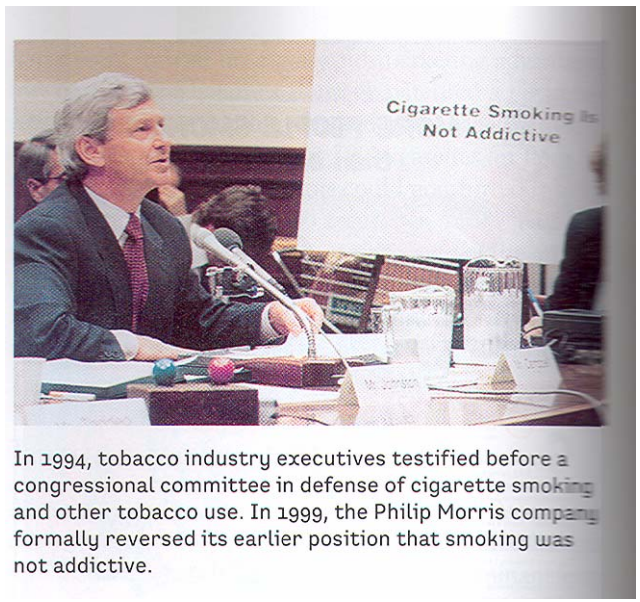

- Like amphetamines, cocaine can interact with different transporters= **indirect agonist**

- Relative Affinities:

  serotonin transporter>dopamine transporter>norepinephrine transporter

# Stimulant Drugs: Pharmacology

- **Nicotine:** an agonist at **nicotinic acetylcholine (ACh) receptors**
- Nicotinic ACh receptors are **ionotropic receptors** that are stimulated by endogenous ACh or nicotine-like drugs
- **Nicotine is very fatty and crosses the BBB very readily**; addiction made worse by the fact that it is inhaled


In 1994, tobacco industry executives testified before a congressional committee in defense of cigarette smoking and other tobacco use. In 1999, the Philip Morris company formally reversed its earlier position that smoking was not addictive.

- Nicotine itself may also be responsible for the numerous health hazards associated with smoking

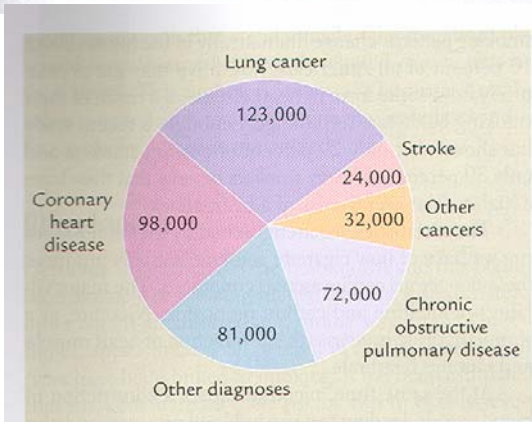



**FIGURE 11.1**

The distribution of approximately 430,000 U.S. deaths attributed each year to cigarette smoking.

*Source:* Centers for Disease Control and Prevention (1999, March 3). *Morbidity and Mortality Weekly Report.* Atlanta: Centers for Disease Control and Prevention.

# Depressants/Sedative/Hypnotics

- **Illicit drugs: PCP (angel dust), GHB (gamma hydroxybutyrate), Rohypnol (flunitrazepam)**
- **Licit (legal) drugs: alcohol**
- **Prescribed and licit d/s/h's: barbiturates, benzodiazepines, ketamine (veterinary anesthesia=Special K)**
- **Acute (immediate) effects:**
  Increase feelings of relaxation, reduce anxiety (**anxiolytic**), produce sleepiness (sedation), can produce a dissociation from reality (hypnotic-type drugs)

➔common action is to depress the CNS

➔good for reducing muscle spasms, seizures and anxiety

➔bad for reducing breathing and cardiac function

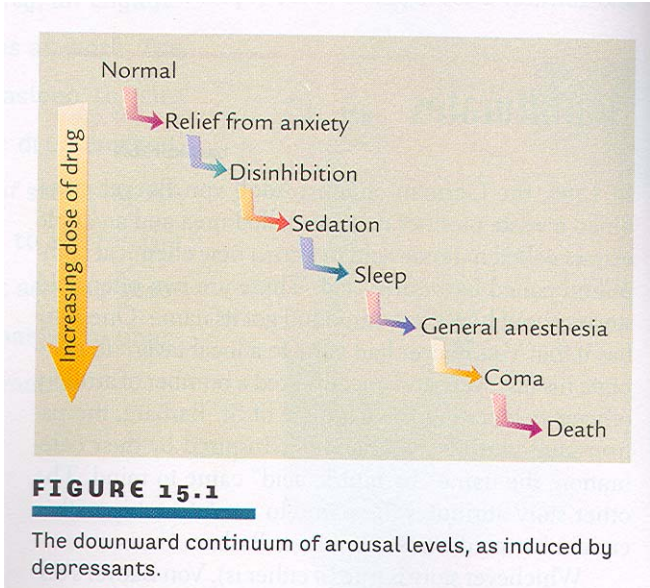



**FIGURE 15.1**

The downward continuum of arousal levels, as induced by depressants.

# Depressant/Sedative/Hypnotic Drugs

- **Effects of withdrawal:** anxiety, difficulty sleeping, “shakes”, nausea and vomiting, perspiration, convulsions, fever, increased heart-rate, hallucinations➔physical dependence

- **Chronic (long-term) effects:**
  - Tolerance to sedative/depressant effects
  - Development of physical dependence
  - Sensitization of CNS excitability upon withdrawal
  - Sensitization of psychotic effects

  ➔**death upon withdrawal**

# Depressant/Sedative/Hypnotic Drugs: Pharmacology

- **Barbiturates:** co-agonists at the GABA A receptor
  - Facilitate GABA binding and increase the duration of channel opening

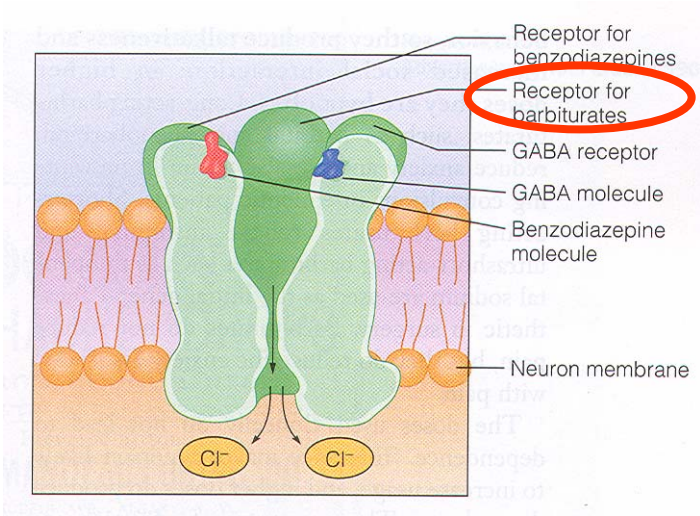



**Table 15.1**

**Major barbiturates**

| GENERIC NAME | BRAND NAME | DURATION OF ACTION | RELATIVE POTENTIAL FOR ABUSE |
|---|---|---|---|
| phenobarbital | generic* | long | low |
| mephobarbital | Mebaral | long | low |
| butalbarbital | Pheniline Forte** | intermediate | moderate |
| amobarbital | Amytal | intermediate | high |
| secobarbital and amobarbital | Tuinal | short, intermediate | high |
| pentobarbital | Nembutal | short | high |
| secobarbital | Seconal | short | high |

- **Notice how the abuse liability of barbiturates relates to the duration of action of the drug**

# Depressant/Sedative/Hypnotic Drugs: Pharmacology

- **Benzodiazepines:** co-agonists at the GABA A receptor
  - Facilitate GABA binding and increase the probability of the channel opening

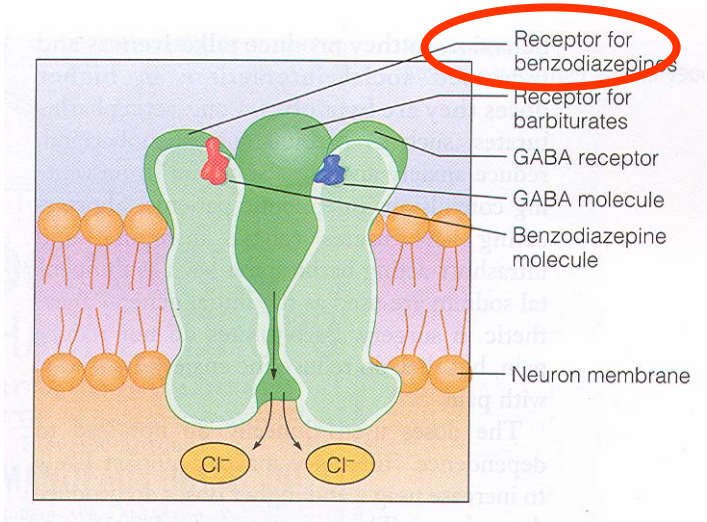



**TABLE 15.3**

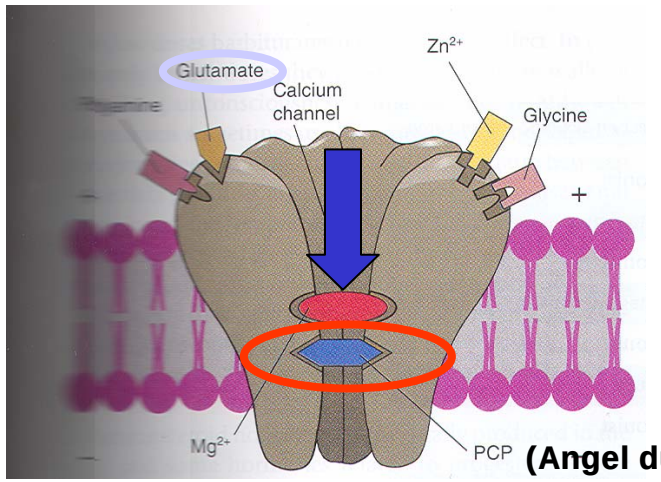
**The leading benzodiazepines on the market**

| TRADE NAME | GENERIC NAME | ELIMINATION HALF-LIFE (in hours) |
|---|---|---|
| **Long-acting benzodiazepines** | | |
| Valium | diazepam | 20–100 |
| Librium | chlordiazepoxide | 8–100 |
| Limbitrol | chlordiazepoxide and amitriptyline (an antidepressant) | 8–100 |
| Dalmane | flurazepam | 70–160 |
| Tranxene | clorazepate | 50–100 |
| **Intermediate-acting benzodiazepines** | | |
| Ativan | lorazepam | 10–24 |
| Klonopin | clonazepam | 18–50 |
| Restoril | temazepam | 8–35 |
| ProSom | estazolam | 13–35 |
| **Short-acting benzodiazepines** | | |
| Versed | midazolam | 2–5 |
| Halcion | triazolam | 2–5 |
| Xanax | alprazolam | 11–18 |

- Benzodiazepines are categorized based on their duration of action (how long they act on the receptor)
- Long-acting benzos can build up in the blood→over-dosing
- Rohypnol (date-rape drug) is a long-acting benzo that is now banned by the FDA

# Depressant/Sedative/Hypnotic Drugs: Pharmacology

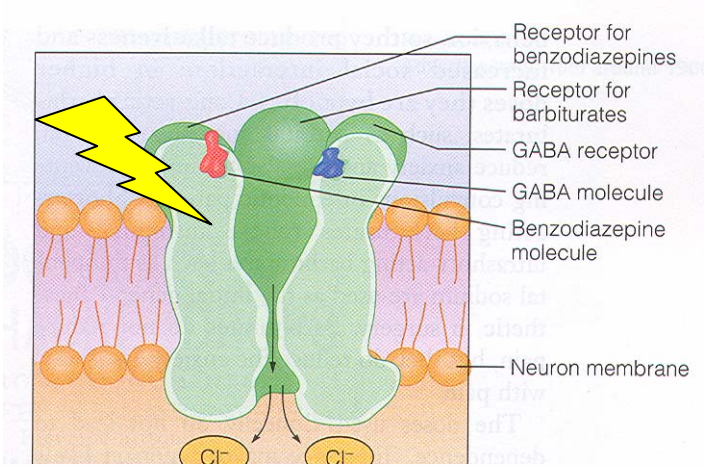
- **Dissociative anesthetics:** typically non-competitive antagonists at NMDA receptors (including PCP, ketamine)
  - Physically block the ionotropic NMDA receptor and prevent effects of glutamate

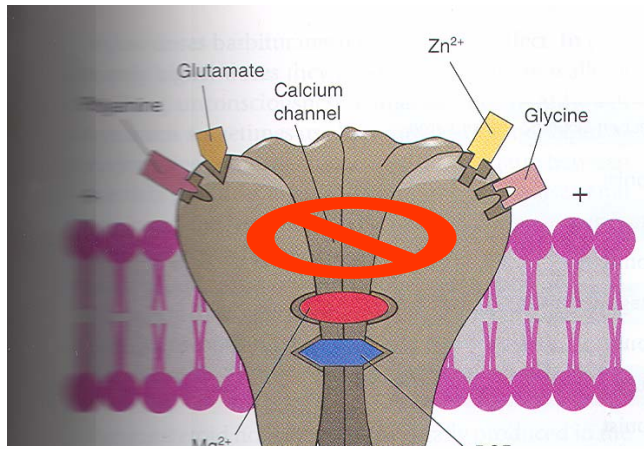



- Dissociative anesthetics typically do not produce sedation but rather produce **a dissociation from reality** which is why ketamine is used in veterinary medicine and drugs like PCP and ketamine are abused

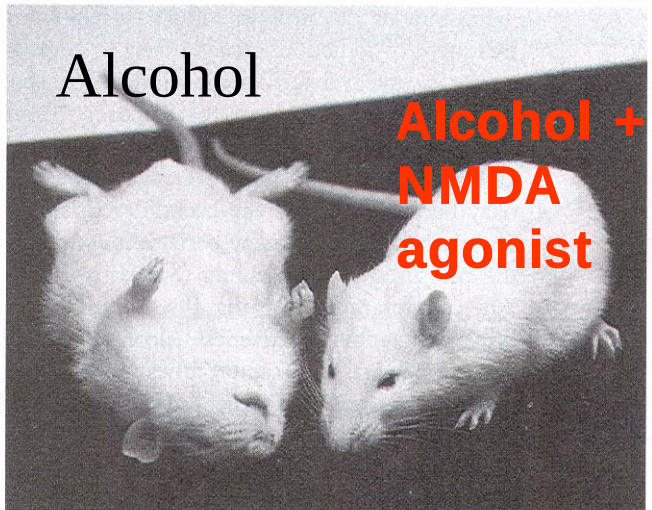
# Depressant/Sedative/Hypnotic Drugs: Pharmacology

- **Alcohol:** the double-whammy
  - Co-agonist at GABA A receptors
  - Non-competitive antagonist at NMDA glutamate receptors







# Drinking & other drugs: important interactions

- **Alcohol + caffeine: "to sober up"**
  - Alcohol withdrawal→CNS hyperactivity
  - Caffeine→CNS hyperactivity
  - 1 + 1 = synergistic hyperactivity→seizures, brain damage or death
- **Alcohol + barbiturates/benzo's:**
  - Alcohol→CNS depressant
  - Barbiturates/benzo's→CNS depressant
  - 1 + 1 = synergistic depression→death

  - Alcohol withdrawal→CNS hyperactivity
  - Barbiturate/benzodiazepine withdrawal→CNS hyperactivity
  - 1 + 1 = synergistic hyperactivity→seizures, brain damage or death

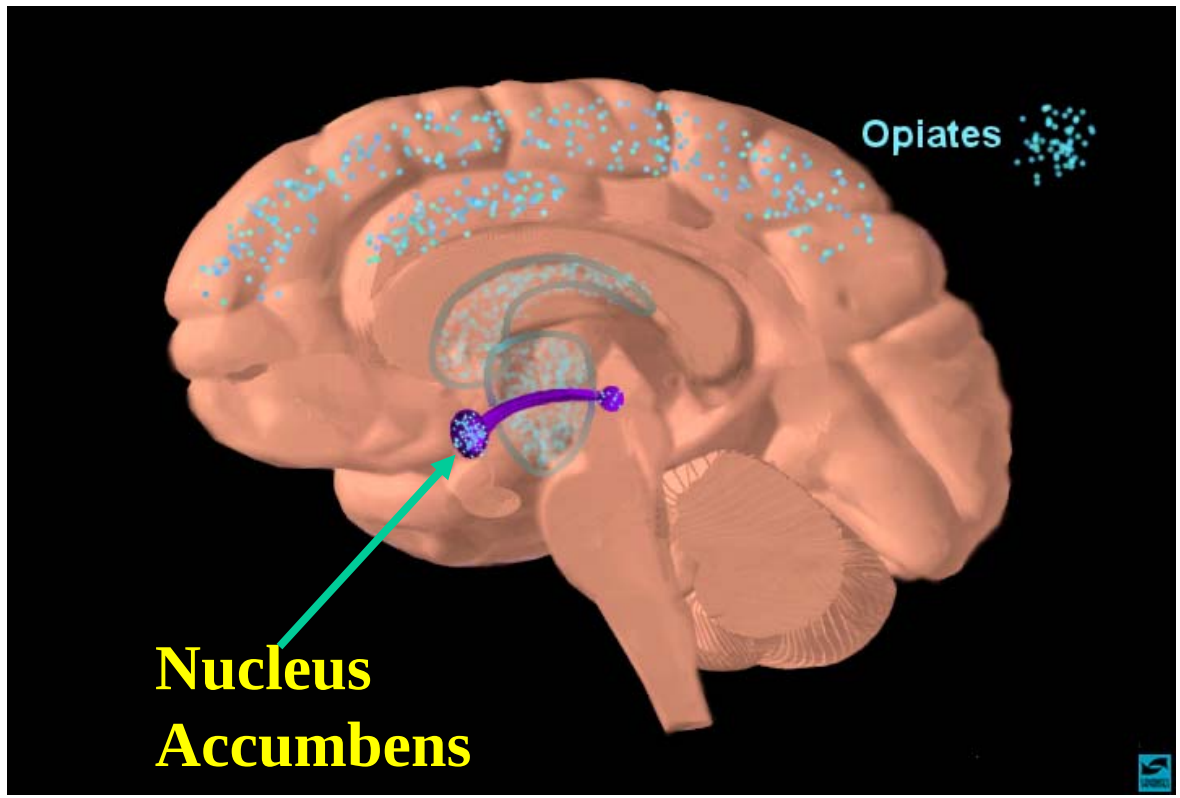
# Narcotics/Opiates


- **Illicit drugs: heroin**

- **Prescribed and licit narcotics: morphine, codeine, methadone, LAAM, meperidine (Demerol), propoxyphene (Darvocet), oxycodone (OxyContin)**

- **Acute (immediate) effects:** Increase feelings of relaxation, reduce pain, euphoria

➔common action is to depress the CNS



# Narcotic/Opiates

**TABLE 5.1**

**Symptoms of administering heroin and of withdrawing heroin**

| ADMINISTERING | WITHDRAWING |
|---|---|
| Lowered body temperature | Elevated body temperature |
| Decreased blood pressure | Increased blood pressure |
| Skin flushed and warm | Piloerection (gooseflesh) |
| Pupillary constriction | Tearing, runny nose |
| Constipation | Diarrhea |
| Respiratory depression | Yawning, panting, sneezing |
| Decreased sex drive | Spontaneous ejaculations and orgasms |
| Muscular relaxation | Restlessness, involuntary twitching and kicking movements* |
| Nodding, stupor | Insomnia |
| Analgesia | Pain and irritability |
| Euphoria and calm | Depression and anxiety |

- **Withdrawal effects:**
  - Similar to sedative drugs but without death (think Trainspotting)
- **Chronic (long-term) effects:**
  - Tolerance to euphoric and analgesic effects
  - Development of physical dependence
  - Sensitization of some CNS excitability upon withdrawal

# Narcotic/Opiates: Pharmacology

- All narcotic/opiate drugs are derived from opium

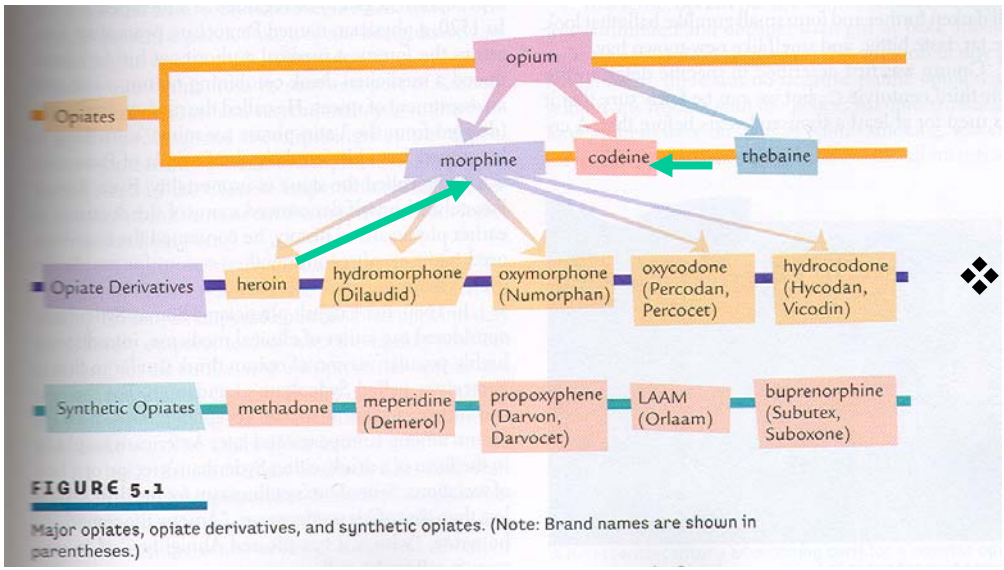



FIGURE 5.1

Major opiates, opiate derivatives, and synthetic opiates. (Note: Brand names are shown in parentheses.)

A young harvester tends to his crop of opium poppies in the rugged mountains of Colombia.

- **Common mechanism of action: Agonists at mu (for morphine) opiate receptors** (metabotropic receptors that are normally stimulated by endorphins (endogenous pain killers-kicked in during sex by the way)

- **Addictive liability depends upon the duration of action of the opiate**
  - **Heroin = super-fast**
  - **Morphine=fast**
  - **Methadone=slower**
  - **LAAM=super-slow**

FYI: codeine and heroin are converted to morphine in your brain

# Hallucinogens

- **Illicit drugs: LSD (lyseric acid diethylamide), psilocybin, mescaline, MDMA (ecstasy) and derivatives**

- **Acute (immediate) effects:** distortions of perceptions, synethesia (intermingling of senses), dissociations from reality, anxiety

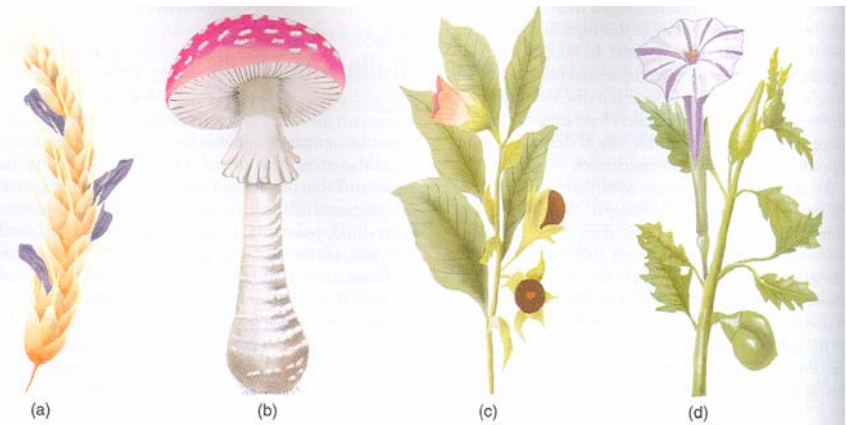
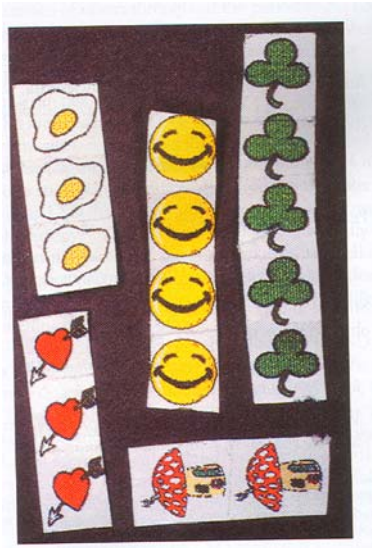



**FIGURE 6.1**

Botanical sources for four hallucinogenic drugs: (a) *Claviceps tulasne* (ergot), (b) *Amanita muscaria* (ibotenic acid), (c) *Atropa belladonna* (atropine), (d) *Datura stramonium*, called jimsonweed (atropine, scopolamine, and hyoscyamine). They are shown the same size, when in actuality they are not.



The peyote cactus, source of mescaline.

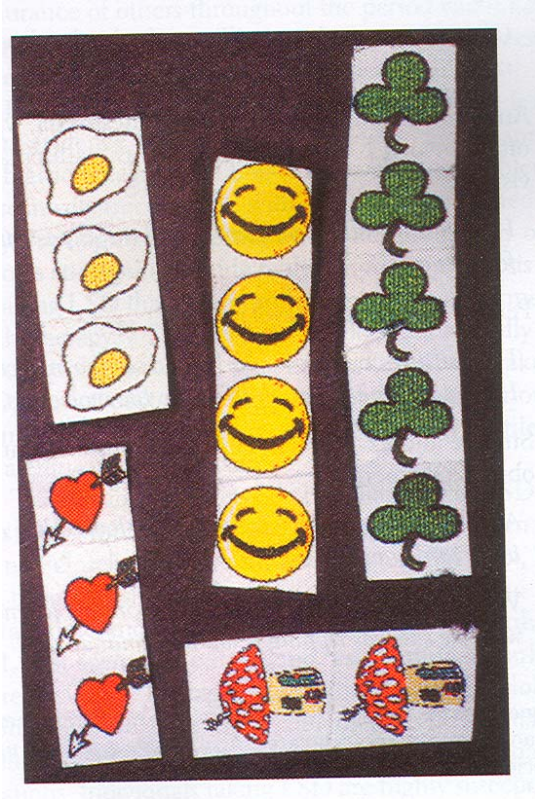
*Psilocybe mexicana* mushrooms, the source of psilocybin.

# Hallucinogens

- **Withdrawal effects:**
  - Do not produce any well-defined physical withdrawal syndrome
  - **Hallucinogen Persisting Perception Disorder = flashbacks =** Re-experiencing of the effects of the drug long after the drug has been eliminated from the body (occurs only with LSD)

- **Chronic (long-term) effects:**
  - With LSD, frequency or severity of flashbacks sensitize
  - With MDMA-Damage to serotonin neurons????

# Hallucinogens: Pharmacology



- **LSD and psilocybin (magic mushrooms):** act as an **agonist at serotonin 5-HT2A receptors**

- Both fatty so they cross BBB readily
- Because LSD is administered sublingually, enters blood stream quickly

- LSD has a much higher affinity for the 5-HT2A receptor than does psilocybin so is a more potent hallucinogen
  - i.e., you need to take way more psilocybin to get the same hallucingoenic effect as LSD

*Psilocybe mexicana* mushrooms, the source of psilocybin.

# Hallucinogens: Pharmacology

- **Mescaline:** derived from the peyote cactus

- Resembles norephinephrine BUT acts as an **agonist at serotonin 5-HT2A receptors**

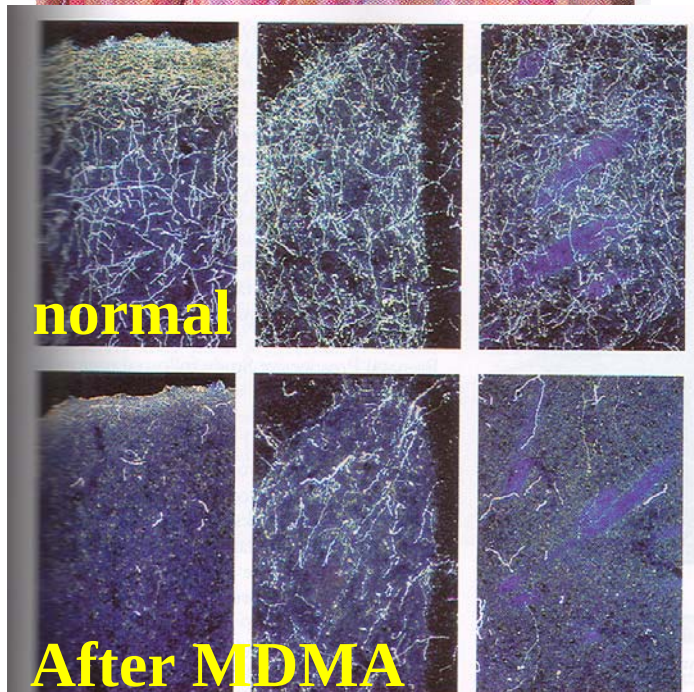
The peyote cactus, source of mescaline.

# Hallucinogens: Pharmacology

- **MDMA (ecstasy):** amphetamine derivative that has pronounced **indirect agonist effects on serotonin and norephinephrine transporters**

- Can be classified as a stimulant due to its effects on motor activity and sympathetic nervous system function➔strong sympathomimetic effects➔heat exhaustion & stroke acutely

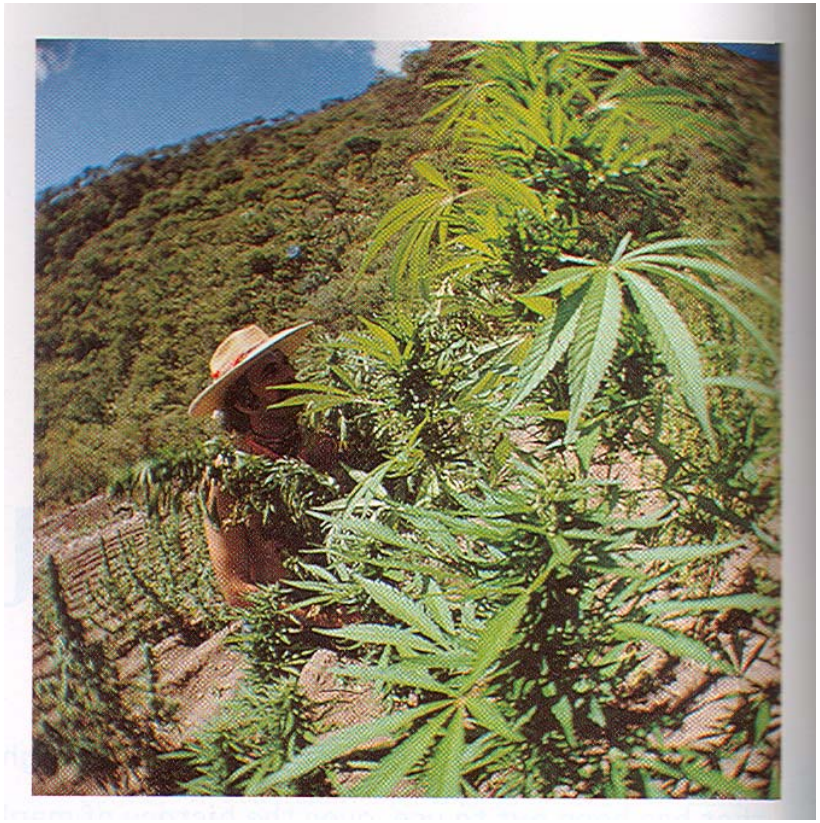
- Can be classified as a hallucinogen as often perception is heightened or altered (due to effects upon serotonin system-chronic use kills serotonin neurons???)



# Cannabinoids

- **Illicit drugs: hashish, marijuana, sinsemilla**

- **Acute (immediate) effects:** increase in heart-rate, anxiety, dilation of blood vessels (blood-shot eyes), impotence, euphoria and dream-like state, increased perception of sight and sound, loss of sense of time, increased appetite



# Cannabinoids

- **Withdrawal effects:**
  - Irritability, stomach pain, anxiety and loss of appetite but considerably more mild than those of heroin or alcohol

- **Chronic (long-term) effects:**
  - Similar if not worse health issues as reported for cigarette smoking
  - **Amotivational syndrome:** blasé attitude, lack of motivation or caring
  - Cognitive impairments sensitize!!!

**TABLE 7.1**

**A comparison of the components of marijuana and tobacco smoke**

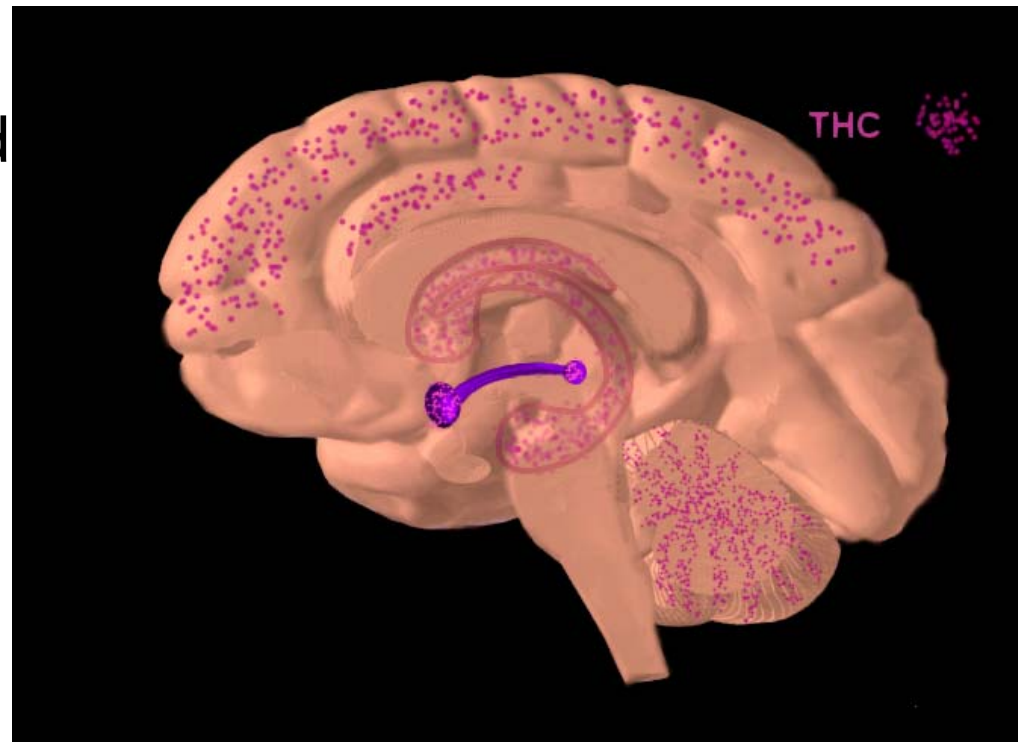
| COMPONENT | MARIJUANA | TOBACCO |
|---|---|---|
| Carbon monoxide (mg) | 17.6 | 20.2 |
| Carbon dioxide (mg) | 57.3 | 65.0 |
| Ammonia (micrograms) | 228.0 | 178.0 |
| Acetaldehyde (micrograms) | 1,200.0 | 980.0 |
| Acetone (micrograms)* | 443.0 | 578.0 |
| Benzene (micrograms)* | 76.0 | 67.0 |
| Toluene (micrograms)* | 112.0 | 108.0 |
| THC (tetrahydrocannabinol) (micrograms) | 820.0 | — |
| Nicotine (micrograms) | — | 2,850.0 |
| Napthalene (nanograms) | 3,000.0 | 1,200.0 |

*See Chapter 13 for information about the health risks of inhaling some of these chemicals.

# Hallucinogens: Pharmacology

- **Cannabinoids:** all contain varying amounts of delta-9-tetrahydrocannabinoid (**THC**) which acts as an **agonist at cannabinoid (CB1) receptors**

- **Cannabinoid receptors:** were actually identified BECAUSE marijuana altered the brain➔there had to be something binding THC



# Drugs of abuse act on neurotransmission

**Table 2.1 Some Representative Neurotransmitters**

| Neurotransmitter | Functions | |
|---|---|---|
| Acetylcholine | Transmitter at muscles; in brain, involved in learning, etc. | Nicotine |
| **Monoamines** | | |
| Serotonin | Involved in mood, sleep, and arousal, and in aggression, depression, obsessive-compulsive disorder, and alcoholism. | LSD, mescaline, cocaine, MDMA, methamphet. |
| Dopamine | Contributes to movement control and promotes reinforcing effects of abused drugs, food, and sex; involved in schizophrenia and Parkinson's disease. | Cocaine/amphetamines |
| Norepinephrine | A hormone released during stress. Functions as a neurotransmitter in the brain to increase arousal and attentiveness to events in the environment; involved in depression. | Cocaine/amphetamines |
| Epinephrine | A stress hormone related to norepinephrine; plays a minor role as a neurotransmitter in the brain. | MDMA |
| **Amino Acids** | | |
| Glutamate | The principal excitatory neurotransmitter in the brain and spinal cord. Vitally involved in learning, and implicated in schizophrenia. | Alcohol, PCP, ketamine |
| Gamma-aminobutyric acid (GABA) | The predominant inhibitory neurotransmitter. Its receptors respond to alcohol and the class of tranquilizers called benzodiazepines. Deficiency in GABA or receptors is one cause of epilepsy. | Barbiturates, benzo's, alcohol |
| Glycine | Inhibitory transmitter in the spinal cord and lower brain. The poison strychnine causes convulsions and death by affecting glycine activity. | |
| **Peptides** | | |
| Endorphins | Neuromodulators that reduce pain and enhance reinforcement. | Heroin, morphine and other opiates |
| Substance P | Transmitter in neurons sensitive to pain. | |
| Neuropeptide Y | Initiates eating and produces metabolic shifts. | |
| **Gas** | | |
| Nitric oxide | Along with carbon monoxide, one of two known gaseous transmitters. Controls intestinal muscles, dilates blood vessels in the brain, and may participate in learning. Can serve as a retrograde transmitter, allowing the postsynaptic neuron to influence the presynaptic neuron's release of neurotransmitter. | |