DRUG ABUSE

A. Cellular mechanism of action for drugs of abuse (self-administered drugs)
   1. many drugs of abuse can act as agonists (either direct or indirect) at specific receptor sites in the brain

B. Examples
   1. stimulant drugs
      a. amphetamine/cocaine: indirect
   2. opiates
      a. morphine/heroin: direct
   3. hallucinogens
      a. LSD/psilocybin: direct
      b. marijuana: direct

C. Measuring reinforcing properties of a drug
   1. self-stimulation
      a. allowing animals to self-administer the drug
   2. place preference
      a. associating a particular environment with drug administration
      b. then testing to see if animal chooses that environment

D. The dopamine connection
   1. for many drugs, release of dopamine in the nucleus accumbens may make a significant contribution to rewarding (reinforcing) effect (ventral tegmentum to nucleus accumbens pathway)
      a. stimulant drugs
      b. opiates
      c. nicotine

E. Stimulant drugs
   1. both cocaine and amphetamine can inhibit catecholamine reuptake
      a. amphetamine can also stimulate catecholamine release
      b. so both can increase catecholamine concentration in the synaptic cleft
         1. which would include the nucleus accumbens area
c. keep in mind that other transmitters, such as serotonin, can also be affected in a manner similar to the catecholamines

2. evidence that dopamine could be important for reinforcement
   a. rats will self-administer stimulant drugs directly into the nucleus accumbens
      1. but not into the striatum
   b. low doses of dopamine receptor antagonists will initially increase the rate of lever pressing
      1. as animal tries to overcome the blockade
   c. and higher antagonist doses will decrease this lever pressing, since even increased lever pressing will not overcome the receptor blockade
d. $\alpha$ and $\beta$-blockers don’t have this effect
e. lesions of either the nucleus accumbens or ventral tegmental area with 6-hydroxydopamine will decrease lever pressing

3. acute stimulant drug risks
   a. hypertension, tachycardia, ventricular arrhythmias, seizure
   b. first three can be treated with propranolol
   c. and nitroprusside can also be used to lower blood pressure
      1. direct smooth muscle relaxant (produces nitric oxide)
d. seizures can be treated with diazepam (valium)

4. effects of chronic exposure
   a. cocaine and amphetamine psychosis
      1. mimics paranoid schizophrenia
   b. behavioral sensitization in animals
      1. more sensitive locomotor and stereotyped behavior response
c. craving in humans, even after abstinence from the drug
   1. drug treatment programs are aimed at reducing drug craving
      a. could behavioral sensitization in animals serve as a model for drug craving in humans?
      b. if so, could be used to test treatments for craving
   2. experimental approaches to reducing craving in humans
      a. direct dopamine agonists: bromocriptine
      b. opiate partial agonists: buprenorphine
      c. opiate antagonists: naltrexone
d. serotonin reuptake inhibitors: fluoxetine (Prozac):
      1. based on evidence that serotonin may antagonize reinforcing properties of stimulant drugs
   3. behavioral modification programs
      a. may include alternative positive reinforcements, such as vouchers for each negative urine drug test
F. Caffeine

1. Caffeine is a *methylxanthine*
   a. as is *theophylline*, a drug that has been used to treat asthma
   b. caffeine has been used medically as a respiratory stimulant in newborns who experience sleep apnea
   c. food sources
      1. caffeine: coffee, tea, chocolate and cola drinks
         a. cola drinks contain extracts of the *Cola acuminata* nut plus added caffeine
      2. theophylline: tea
      3. theobromine (a methylxanthine): chocolate

2. Caffeine is classified as a stimulant drug
   a. some behavioral similarities to the actions of amphetamine and cocaine
      1. stimulation of locomotor activity in rats
      2. production of *sensitization* (“reverse tolerance”) in rats following intermittent intraperitoneal administration
      3. anti-fatigue effects in humans
         a. e.g., *No Doz* tablets contain caffeine
         b. stimulatory effect in humans maintained with daily intermittent usage

3. Neuropharmacological actions of caffeine
   a. initial studies showed that caffeine can inhibit cAMP phosphodiesterase
      1. however, the concentrations needed to do this appear to be higher than those associated with stimulant effects following caffeine ingestion
   b. more recent studies have suggested that a major relevant action of caffeine is its ability to block *adenosine* receptors

4. Caffeine withdrawal
   a. headaches, drowsiness, fatigue, anxiety
   b. *avoidance* of withdrawal may contribute to motivation for chronic usage
   c. could *up-regulation* of adenosine receptors contribute to caffeine withdrawal?
      1. mild up-regulation of adenosine receptors in response to chronic caffeine has been observed in some rat brain areas (cortex and hippocampus)
      2. significance with regard to withdrawal has yet to be determined

5. Adenosine
   a. synthesis
      1. one significant route of formation in the brain: \(AMP \rightarrow adenosine\) via 5’-nucleotidase activity
      2. in the synaptic cleft, AMP can be formed from ATP and then produce adenosine in the cleft via nucleotidase activity
3. some of the ATP in the cleft can come from ATP released from synaptic vesicles via exocytosis

b. storage
   1. vesicular storage of adenosine has *not* been demonstrated
   2. suggests that adenosine in the cleft comes from soluble stores and/or that adenosine is formed in the cleft from AMP

c. release
   1. adenosine in the cleft increases after neuronal stimulation
      a. can be measured via *microdialysis*

d. receptor interaction
   1. $A_i \Rightarrow A_j$ subtypes
      a. all three subtypes are *G protein coupled*
   2. $A_1$: ↓ adenylyl cyclase activity, ↓$\text{Ca}^{++}$ entry, ↑ potassium permeability
      a. Q: does this profile suggest potential effects on NT release?
   3. $A_2$: ↑ adenylyl cyclase activity
   4. caffeine and theophylline block both $A_1$ and $A_2$

e. adenosine inactivation
   1. *reuptake* into neurons and glia a prime route of synaptic inactivation
      a. blocked by dipyridamole (DPR)
   2. can also be metabolized to inosine by *adenosine deaminase*

f. cellular effects of adenosine
   1. generally acts as an inhibitor of neuronal firing (in part via ↑ potassium permeability) and as an inhibitor of NT release (possibly via ↓$\text{Ca}^{++}$ entry)

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**G. Nicotine**

1. History
   a. *nicotine* was first isolated from leaves of tobacco in 1828
      1. unusual property in being a *liquid* natural alkaloid
   b. shown in 1889 that nicotine applied to rabbit ganglia would *stimulate* the post-ganglionic neuron
      1. first demonstration of what we refer to today as the *nicotinic* nature of the acetylcholine receptors on the post-ganglionic neurons
   c. tobacco was smoked predominantly in *pipes* until the late 1800s
      1. *cigarette* production started in late 1800s: cigarettes now account for about 90% of tobacco use
         a. average cigarette contains about $9 \text{ mg}$ of nicotine, which *delivers* about $1 \text{ mg}$ to the smoker per cigarette
      2. about 30% of the adult population (both men and women) are smokers
   d. cigarette smoking is considered the chief *avoidable* cause of death in the US
      1. contributing to about 1 in 5 deaths (about 450,000 people/year)
2. Pharmacological Properties
   a. *nicotine* appears to be the only *pharmacologically active* substance in tobacco smoke, apart from *carcinogenic tars* and *carbon monoxide*
   
   1. acute effects of smoking can be *mimicked* by nicotine administration, and can be *blocked* by nicotinic receptor antagonists, such as *mecamylamine*
      a. an antagonist which works in both the periphery and CNS
   b. effect on ganglia is usually initial excitation followed by depression (desensitization)
      1. same is true for effects on the adrenal medulla
         a. initial release of catecholamines, followed by inhibition of release
   2. and also for the neuromuscular junction
      a. high concentrations can produce neuromuscular paralysis
   c. initial effects can produce an ↑ in blood pressure due to *cardiac stimulation*, *release of catecholamines* from the adrenal medulla, and *stimulation of carotid receptors* which signal for an ↑ in sympathetic activity
      1. cardiac and vasoconstrictive effects of nicotine make smokers a *higher risk group for cardiovascular disease and stroke*
   d. can also produce an ↑ in stomach *acid secretion* which may contribute to the formation of peptic *ulcers*
   e. first experience with smoking can produce nausea and vomiting, possibly via activation of sensory receptors in the stomach
   f. many of the peripheral effects decrease with continued usage
   g. toxicity
      1. can be *fatal* with administration of 60 mg of nicotine
      2. most overdosages come about either via *children* eating cigarettes or because of exposure to *nicotine-containing insecticides*
         a. in the latter case, nicotine *absorption through the skin* allows for a buildup in the body
   3. death can ensue following *convulsions and respiratory paralysis*

3. Pharmacokinetics
   a. *rapid* entry into the brain occurs following smoking
      1. within *10 seconds*
   b. half-life (*t_1/2*) of about 2 *hours* in the blood
      1. *liver* is major metabolic organ
   c. nicotine *is transmitted in the milk* of nursing mothers who smoke

4. CNS Receptors and Behavioral Effects of Nicotine
   a. brain nicotinic receptors, although differing somewhat in structure compared to the peripheral receptors, still show an *excitatory* action when occupied by nicotinic agonists, including the *naturally occurring agonist, acetylcholine*
   b. many nicotinic receptors in the brain are located *pre-synaptically*
      1. when occupied by acetylcholine, they can help ↑ transmitter release
   c. at post-synaptic sites, may *potentiate* the effects of other *excitatory* inputs, such as those mediated by *glutamate* receptors, including *NMDA* receptors
      1. may have implications with regard to *learning and memory*
d. high concentration of receptors found in the ventral tegmentum, nucleus accumbens, substantia nigra pars compacta and striatum
e. ventral tegmental area (VTA) is a dopamine cell body area that terminates in the nucleus accumbens
  1. this pathway has been implicated in influencing locomotor activity and in contributing to drug reinforcement properties
  2. microdialysis studies have shown an increase in extracellular dopamine in the accumbens following peripheral nicotine administration in the rat
  3. nicotine effects are likely due to stimulation of nicotinic receptors on VTA cell bodies
    a. nicotinic agonists added directly to the VTA increase locomotor activity
    b. nicotine self-administration is inhibited by administration of a nicotinic antagonist directly into the VTA

5. Nicotine and Addiction
   a. is nicotine addictive?
      1. Stedman’s Medical Dictionary definition of addiction
         a. habitual psychological and physiological dependence on a substance or practice which is beyond voluntary control
      b. drugs which are addictive can usually be shown to have positive reinforcing effects in controlled studies
      c. lever pressing to obtain nicotine has been observed in rat and primate studies
         1. at higher unit dosages, the number of lever presses falls off
         a. probably representing the obtainment of a desired blood level of nicotine with fewer presses needed at the higher dosages
      d. human studies have also indicated lever pressing responses for nicotine
         1. this lever pressing was abolished when saline was substituted for nicotine
   e. these observations indicate that nicotine is a positive reinforcer
      1. shows the potential for nicotine to be classified as addictive
   f. in humans, studies have indicated a correlation between “pleasurable feelings” from smoking and plasma nicotine levels
      1. with 5 ng/ml representing a low plasma level and 23 ng/ml a high level
         a. this high level represents a plasma concentration of about 0.14 μM
   g. smokers given a nicotinic antagonist that works in the CNS (mecamylamine) increased the amount of smoking, apparently in an attempt to overcome the nicotinic blockade in the CNS
      1. this result was not obtained if the subjects were given a nicotinic antagonist that only worked in the periphery (pentolinium)
   h. a similar sort of finding can be observed when comparing smokers who use regular cigarettes versus those who use cigarettes low in nicotine and tar
      1. those using the low nicotine/tar cigarettes will smoke more cigarettes, puff harder and deeper, and smoke more of the cigarette
      2. this leads to similar plasma nicotine concentrations to those found in subjects smoking higher nicotine cigarettes
6. Nicotine and Withdrawal
   a. abstinence symptoms include
      1. severe craving for nicotine, irritability, anxiety, difficulty concentrating, 
         insomnia, increased appetite and weight gain
   b. symptoms begin about 24 hours post-abstinence, peak at between 36-72 hours 
      and then gradually decline
   c. avoidance of withdrawal does not explain smoking relapse, however, since 
      most relapses occur after withdrawal symptoms have declined

7. Nicotine Cessation Strategies
   a. giving a nicotinic receptor blocker such as mecamylamine
      1. ↓ nicotinic responses but not successful in smoking cessation efforts
   b. Nicorette
      1. chewing gum containing nicotine
      2. considered a much safer way to administer nicotine compared to 
         smoking
      3. can help relieve some of the withdrawal symptoms
      4. some success in maintaining smoking abstinence, especially when 
         combined with counseling
         a. 70% greater abstinence rate compared to placebo
   c. Nicoderm
      1. transdermal skin patch delivery system
      2. applied once a day
      3. produces a more stable level of nicotine compared to chewing gum
      4. 2-3x greater abstinence rate compared to placebo
         a. abstinence rate with the patch is about 30%

H. Alcohol

1. Pharmacological Properties
   a. CNS
      1. although some may view alcohol as a stimulant (loosening up social 
         interactions, etc.), pharmacologically it is classified as a CNS depressant 
      2. any “stimulant” action probably results from depression of inhibitory 
         controls
      3. memory and concentration are among the first processes to be 
         negatively affected
      4. behavioral inhibitions decrease, sometimes accompanied by 
         uncontrolled mood swings and emotional outbursts
      5. sensory and motor disturbances occur
         a. studies have been carried out to try to determine the relationship 
            between blood alcohol levels and probability of being involved in 
            a car accident
            1. up to 0.05%: no significant increase
            2. at 0.08%: 4x greater probability
            3. at 0.15%: 25x greater probability
      6. % of subjects showing gross intoxication (of speech, gait, etc.) when 
         blood alcohol is between 0.05 and 0.10%: 30% of subjects
a. when level is > 0.15%: 90% of subjects
7. at higher alcohol levels, loss of consciousness occurs (at a blood level of about 0.30%) accompanied by respiratory depression (at about 0.45%)
a. at these concentrations the effect of alcohol can be fatal
8. chronic effects of heavy alcoholic usage
   a. memory loss, sleep disturbances, seizures
   b. associated nutritional deficits can produce a condition known as Korsakoff’s psychosis, characterized by confusion, memory loss and confabulation (a good word to look up in a Medical Dictionary!)

b. GI tract
   1. alcohol stimulates gastric acid secretion
      a. therefore can be dangerous in patients with a gastric ulcer
   2. high alcohol content drinks (40% alcohol) can cause a direct irritation of the gastric mucosa and may produce gastric inflammation

c. liver
   1. excessive long-term ethanol consumption produces damage to the liver
   2. fat accumulation in the liver progresses to hepatitis (inflammation of the liver) and then to cirrhosis, which is characterized by damage to hepatic cells and replacement of the hepatic cells by fibroblasts (fibrosis)
      a. part of this may be due to release of fatty acids and fatty acid oxidation

d. cardiovascular
   1. ethanol produces centrally mediated cutaneous vasodilation
      a. can make you feel warm, but you are actually loosing body heat
   2. studies suggest that mild drinking can reduce incidence of coronary heart disease
      a. in plasma HDL (high density lipoprotein) levels a contribution? 1. can help remove cholesterol from the circulation

e. diuretic
   1. ethanol secretion of antidiuretic hormone from the posterior pituitary
      a. therefore diuresis (urination) is ↑

f. fetal development
   1. heavy use of alcohol during pregnancy can harm fetal development
      a. referred to as fetal alcohol syndrome (FAS)
   2. abnormal facial development (wide-set eyes), retarded growth, retarded mental development
   3. sometimes also with congenital cardiac abnormalities
   4. found to occur in 19% of births with mothers who drink an average of the equivalent of 4 glasses of wine per day during pregnancy
   5. may have greatest effects if large ethanol consumption occurs early in pregnancy
   6. dose-response relationship not known
a. it has been suggested that there may be a “threshold” intake that is necessary for this effect, and that it is only a problem with the heavy alcohol usage such as that indicated above

7. mechanism unknown
a. both ethanol and its metabolite, acetaldehyde, inhibit cell division in culture

3. Pharmacokinetics
a. if considered as a drug, we can say that the amount of ethanol consumed is much larger than for most other drugs
1. a 6 oz. glass of wine with a 10% alcohol content represents about 17 g of alcohol
   a. a similar sedating effect can be achieved with 5 mg of diazepam (Valium), indicating that diazepam is about 3400x more potent than alcohol
2. another way to look at potency is to calculate the molar concentration of ethanol required in the blood to produce CNS effects
   a. for a 0.10% blood concentrations, this would equate to a concentration of 22 mM
      1. a much higher concentration for drug effect compared to most other drugs
   a. many other drugs are effective in the μM range
b. one consequence of this need for a high level of alcohol in the blood is that metabolism of the alcohol can become saturated
   1. the metabolism of most drugs follows a first-order kinetic paradigm, whereby the rate of metabolism is proportional to the concentration of the drug
   2. but the alcohol concentration is high enough so that its metabolism follows zero-order kinetics
      a. this means that the rate of metabolism is not proportional to the alcohol concentration
      b. you simply metabolize a certain steady amount of alcohol per time, independent of alcohol concentration
         1. about 10 ml of alcohol/hr
      c. this continues until the alcohol levels drop down far enough so that you go back to first-order kinetics of metabolism
      d. this saturation of metabolism is due primarily to the supply of NAD⁺ needed for alcohol metabolism not being able to keep up with demand
   c. ethanol is readily absorbed from the stomach and even more readily absorbed from the duodenum (upper part of small intestine)
      1. therefore conditions which alter emptying of stomach contents can alter the rate of alcohol absorption
         a. if food is present in the stomach, this will delay transfer to the intestine
         b. therefore drinking on an empty stomach (faster transfer to the intestine) will result in a faster CNS effect of the alcohol
d. ethanol is metabolized primarily in the liver via alcohol dehydrogenase to acetaldehyde

1. liver microsomal enzymes may also play a role in ethanol oxidation
   a. and ethanol may interfere with the metabolism of other drugs that use this system
   b. one example is diazepam (valium), so that a combination of ethanol and valium would lead to a greater plasma concentration of valium than normal
      1. this is one reason patients have to be careful about combining valium with alcohol
      2. this combination could lead to coma and respiratory arrest

4. Molecular Basis for Ethanol Action
   a. in many brain areas, alcohol potentiates GABA-mediated \( \uparrow \) in Cl⁻ permeability
      1. this will potentiate neuronal firing inhibition
         a. this can occur at a 5 mM ethanol concentration
         b. similar to the effect of benzodiazepines
            1. of interest that a benzodiazepine derivative, RO 15-4513, can block the effect of ethanol on Cl⁻ permeability, and can also block the ataxic effects of ethanol

5. Tolerance
   a. metabolic and cellular
      1. metabolic: increased ability to metabolize alcohol
      2. cellular: less effect at the cellular level

6. Withdrawal
   a. more serious medical consequences compared to opiate withdrawal
      1. anxiety, nausea, cramps, tremors, hallucinations, seizures
   b. patient should be under medical supervision
      1. withdrawal symptoms lessened with benzodiazepines (Librium, Valium) treatment

7. Pharmacological Treatments of Alcoholism
   a. disulfiram (Antabuse) to bring on a sick feeling when alcohol is consumed
      1. disulfiram effect lasts for about 10 days
      2. calcium carbamide (Abstem) inhibition of aldehyde dehydrogenase lasts for a shorter period of time (1 day)
   b. naltrexone
      1. opiate antagonist with a longer half-life than naloxone
      2. its use in humans based in part on animal studies
         a. in rats bred to prefer alcohol, naloxone diminished this preference
            1. Q: implications of this finding?
      3. relapse rate reported to be \( \downarrow \) in human clinical trials testing naltrexone
I. HALLUCINOGENIC DRUGS

1. MARIJUANA

   a. the most widely used illicit drug in the United States
   b. active ingredients (cannabinoids) isolated from the Cannabis sativa plant
      1. THC (??-tetrahydrocannabinol) is one of the main psychoactive components
   c. routes of administration
      1. smoking
      2. oral
         a. produces more variable plasma concentration compared to smoking
   d. psychoactive drug behavioral effects
      1. in general, psychoactive drug effects can vary according to dose, setting, mental state, and past experiences with the drug
   e. marijuana behavioral effects
      1. calmness, relaxation, dream-like state
      2. increased hunger and thirst
      3. disinhibition
      4. lightheadedness
      5. slowing sensation of time passage
      6. enhanced visual, auditory and tactile sensations
      7. in some cases: anxiety, panic and/or paranoid states may be produced
      8. impaired short-term memory
      9. impaired problem solving
         a. especially with problems involving sequential steps
      10. cognitive test impairment may be less in those with more extensive prior experience with marijuana usage
         a. cognitive tolerance or learning how to overcome deficits in processing?
      11. impaired performance in simulated and actual automobile driving evaluations
      12. psychomotor (e.g. response time) decrements for up to 8 hours post-smoking
   f. physiological effects
      1.↑ heart rate (tachycardia)
         a. possibly due to ? cardiac vagal input
      2. redening of the conjunctiva in the eyes
      3. analgesia
         1. especially in tests of neuropathic (nerve damage)-induced pain
      4. lung pathology has been reported in Rhesus monkeys after one year of
daily smoking

g. tolerance and withdrawal
   1. for humans smoking one cigarette/day
      a. tolerance developed to heart stimulatory effect
      b. but not to subjective high
   2. withdrawal symptoms found in rats exposed to daily THC treatment,
      followed by administration of a THC receptor antagonist (SR 141716A)
      a. wet-dog body shakes, head shakes, biting and chewing

h. medicinal usage
   1. anti-emetic and anti-nausea for patients on chemotherapy (anti-cancer),
      for whom other agents do not work well
      a. other agents include ondansetron (a 5-HT3 receptor blocker)
      b. THC (Marinol) and nabilone (an analog: Cesamet) are
         cannabinoids that are used
      c. oral administration and rectal (THC) to avoid first-pass
         hepatic metabolism
   2. appetite stimulant in anorexic AIDS patients
      a. Marinol
   3. other possible uses
      a. analgesic
      b. glaucoma to reduce intraocular pressure
      c. antispasmodic
         1. some benefit reported for multiple sclerosis patients

i. animal studies
   1. reinforcing properties of THC?
      a. most studies are negative on this
      b. place-preference studies have even suggested aversive
         properties
   2. motor immobility (catalepsy) can be produced

j. cellular mechanisms of action
   1. THC is an agonist at CB1 receptors in the brain
      a. G-protein coupled receptor
      b. another form found in the spleen and macrophages is
designated as CB2
   2. high receptor concentration found in substantia nigra, striatum and
cerebellum
      a. related to motor effects?
   3. receptors also found in the hippocampus and frontal cortex
      a. related to cognitive effects?
   4. very low density found in brainstem cardiac and respiratory control
centers
      a. related to relative safety (in terms of lack of lethality) of
         cannabinoids?
   5. overall density of cannabinoid receptors is as high or higher than any
      other G protein-coupled receptor in the brain

k. effects of receptor stimulation
a. ? of adenylyl cyclase activity
b. inhibition of voltage-gated calcium channels
   1. if this occurs on nerve terminals, it can produce
      inhibition of transmitter release
c. receptors can down-regulate with chronic THC exposure
   1. could contribute to tolerance
l. endogenous cannabinoids
   1. previous discovery of opiate receptors led to discovery of endogenous
      opioid peptides (enkephalins, endorphins, etc.)
   2. with the discovery of cannabinoid receptors, we can ask: do
      endogenous cannabinoids also exist?
      a. an arachidonic acid-related compound has been found with
         cannabinoid-like properties
      1. named anandamide
         a. ananda is a Sanskrit word for bliss
         b. so it can help to know other languages if you
            discover a new compound and get to name it!!
      b. additional arachidonic acid-related compounds with cannabinoid
         properties have also been found
         1. suggesting a “family” of endogenous cannabinoids?
   3. role of these compounds in normal neuronal functioning currently being
      examined

2. PHENCYCLIDINE (PCP)

a. medically, PCP has been classified as a “dissociative anesthetic”
   1. subjects are dissociated from their environment without losing
      consciousness
b. routes of administration
   1. oral, intranasal, added to cigarettes for smoking, iv or im
      (intramuscular)
c. behavioral effects
   1. altered body image: e.g., feeling distant from limbs
   2. feelings of floating
   3. dreamlike state
   4. impaired ability to concentrate
   5. muscle incoordination (ataxia)
   6. can mimic schizophrenic behavioral symptoms
      a. paranoid, withdrawn, hallucinatory
      b. because of this, an evaluation of its pharmacological properties
         has led to alternatives to the dopamine theory of schizophrenia
         1. or at least to an extension of this theory
   7. neurotoxicity?
      a. still an open issue for human subjects
   8. it is self-administered in rats and rhesus monkeys
      a. predictive of drug abuse potential in humans
d. pharmacological actions
   1. antagonist at the NMDA receptor
      a. blocking the channel, rather than the glutamate binding site

3. **LSD (D-LYSERGIC ACID DIETHYLAMIDE)**

   a. first synthesized as a derivative of ergot alkaloids
   b. psychoactive properties discovered *accidentally* by Albert Hofmann in the early 1940s
      1. later took 250 µg to test LSD action: resulted in a major trip!
         a. visual distortions, dilated pupils, more intense visual response to colors, feeling outside of the body, dreamlike state, feelings similar to being drunk
      c. an additional effect that has been reported: *synesthesia*
         1. mixed sensations: hearing colors, seeing smells, etc.
   d. “bad trips” can also be experienced
      1. panic, confusion, paranoia
   e. “flashbacks” mimicking drug experiences when not on the drug, can also occur
   f. model for schizophrenia?
      1. possibly not as good as some others
      2. schizophrenics given amphetamine, cocaine or PCP report that these drugs make them feel *similar* to their schizophrenic episodes, but that this doesn’t happen with LSD
   g. pharmacological properties
      1. LSD resembles *serotonin* in structure
      2. specific binding of LSD to rat brain membranes is displaced by serotonin, and *vice versa*
         a. suggests that LSD can bind to serotonin receptors
      3. importance of 5-HT$_{2A}$ receptors suggested by behavioral studies in cats
         a. LSD produces limb flicking, head shaking, abortive grooming and constant eye movements
         b. these effects are blocked by 5-HT$_{2A}$ receptor antagonists, such as *ritanserin*
         c. could this type of receptor blockade be of clinical significance with regard to the anti-schizophrenic actions of clozapine and risperidone?
            1. these drugs block 5-HT$_{2A}$ receptors, *in addition* to blocking dopamine receptors
      4. cross reactivity of LSD with psilocybin, one of the active ingredients found in “magic mushrooms”
         a. psilocybin also resembles serotonin (and LSD) in structure