PSYCHEDELIC DRUGS (p.1)

1. Terminology
   “hallucinogens” – induce hallucinations, although sensory distortions are more common
   “psychotomimetics” – to mimic psychotic states, although truly most drugs in this class do not do so
   “phantasticums” or “psychedelics” – alter sensory perception
   (Julien uses “psychedelics”)
   alterations in perception, cognition, and mood, in presence of otherwise clear ability to sense
   may increase sensory awareness, increase clarity, decrease control over what is sensed/experienced
   “self-A” may feel a passive observer of what “self-B” is experiencing
   often accompanied by a sense of profound meaningfulness, of divine or cosmic importance (limbic system?)

   these drugs can be classified by what NT they mimic:
   anti-ACh, agonists for NE, 5HT, or glutamate (See p. 332, Table 12.1 in Julien, 9th Ed.)

2. The Anti-ACh Psychedelics
   e.g. scopolamine (classified as an ACh blocker)
   high affinity, no efficacy
   plant product: Belladonna or “deadly nightshade” (Atropa belladonna)
   Datura stramonium (jimson weed, stinkweed)
   Mandragora officinarum (mandrake plant)
   pupillary dilation (2nd to atropine)
PSYCHEDELIC DRUGS (p.2)

2. **Anti-ACh Psychedelics** (cont.)

*pharmacological effects:*
  e.g. scopolamine (Donnatal)
  clinically used to tx motion sickness, relax smooth muscles (gastric cramping), mild sedation/anesthetic effect

**PNS effects** --- dry mouth relaxation of smooth muscles
  decreased sweating increased body temperature
  blurred vision dry skin
  pupillary dilation tachycardia, increased BP

**CNS effects** --- *drowsiness*, mild euphoria
  *profound amnesia* fatigue
  decreased attention, focus delirium, mental confusion
  decreased REM sleep no increase in sensory awareness

  as dose increases --- restlessness, excitement, hallucinations, euphoria, disorientation
  at toxic dose levels --- “psychotic delirium”, confusion, stupor, coma, respiratory depression

  so drug is really an intoxicant, amnestic, and deliriant

3. **Catecholamine-like Psychedelics**
   Affect NE, DA especially, also 5HT often
   structurally resemble amphetamines often
   Mescaline, STP (=DOM), MDA, DMA, MDMA ("ecstacy"), TMA, MDE, myristin, elemicin (latter two from nutmeg), PEA

a. **phenethylamine (PEA)**
   found in chocolate
   resembles NE/DA; probably has its effect by being a 5HT2A agonist
PSYCHEDELIC DRUGS (p.3)

Catecholamine-like Psychedelics (cont.)

b. mescaline (from peyote, *Lophophra williamsii*)
   used PO, rapidly & completely absorbed
   effects felt in 1-2 hours, 3½ - 4 hours after dosing see visual distortion
   effects especially
   effects last about 10 hours
   excreted unchanged (not metabolized)

   SPECT analysis shows hyperfrontal activity, esp. in R frontal lobe
   would R hyperfrontal activity --- more – emotions than normal?
   more fear, paranoia?

c. synthetic amphetamine-like derivatives
   structurally similar to mescaline & methamphetamine
   have moderate behavioral stimulant effects (even at low doses)
   have more psychedelic effects as dose increases
   are more potent and more toxic vs. mescaline

   STP = DOM (dimethoxy-methamphetamine)
   MDA (methylene-dioxy-amphetamine)
   DMA (dimethoxy-methylamphetamine)
   MDE (methylene-dioxy-ethylamphetamine) (“eve”)
   TMA (trimethoxy-amphetamine)
   MDMA (methylene-dioxy-methamphetamine) (“ecstacy”, “XTC”,
   active metabolite is MDA “adam”)

   all above are “designer psychedelics” (mescaline-amphetamine-LSD-
   like molecules)
   all have mixed effects on catecholamines (NE, E, DA) & 5HT

   DOM is very potent --- increased risk of OD

   MDE – increases activity in cerebellum & R anterior cingulated
   decreases activity in cerebral cortex
3. Catecholamine-like Psychedelics (cont.)
   c. Synthetic amphetamine-like derivatives (cont.)

**MDMA ("ecstasy")**
- less hallucinogenic, less extreme sense of unreality, less visual distortion
- a potent & selective 5HT neurotoxin (blocks/damages 5HT transporter)
- --- memory impairment (can be severe)
- --- decreased STM, attentional focus
- --- increased impulsivity (less frontal lobe executive function?)

why used recreationally? --- increased sense of well-being, increased emotional sensitivity, little anxiety, no hallucinations, no panic, increased sensory awareness

somatic changes: increased BP (120/70 is normal)
- jaw clenching
decreased appetiterestlessness
- insomniaimpaired gaitrestless legs

**severe toxicities** observed:
- hypertention hyperthermia tachycardia
disorientation dilated pupils convulsions
- kidney failure breakdown of skeletal muscle

note: "herbal ecstasy" is ephedrine + caffeine (severe HBP & cardia arrhythmias)...touted as more "natural" and safer!

d. myristin & elemicin (from Nutmeg and Mace)
- structurally similar to mescaline
- --- unreality, euphoria, visual hallucinations, acute psychotic reactions, sense of impending doom, vomiting/nausea, tremors

…my idea of a good time!
4. 5HT-like Psychedelics

**Mechanism of Actions** (hypothesized):

these substances all structurally resemble 5HT, so it is assumed that they somehow act on the 5HT RSs… but exactly which subtype of RS is not known; and what is the exact effect is not settled (agonist/antagonist/mixed?)

some researchers think that LSD is a partial agonist as the DA2 RS even…

and why doesn’t a 5HT agonist (e.g. an SSRI) --- hallucinations? even in “serotonin syndrome” we do not see hallucinations…

**Sites of Actions**

these drugs act on pontine dorsal Raphe system (the major brain area that uses 5HT), which “filters” incoming stimuli (novel vs. familiar)

thus, familiar sensory stimuli are misperceived as “novel”

loss of sensory “constancies” (size, shape, color, etc.)

e.g. LSD (lysergic acid diethylamide)

a very potent drug

--- increased sense of self-awareness, altered internal reality, relatively few general changes in body physiology

taken PO, absorbed readily

peak blood levels w/i 3 hours, duration 6-8 hours

metabolized by liver enzymes
difficult to detect in urine do to smallness of amonts

a very sensitive assay can detect w/i 30 hours of use

crosses BBB & placenta

physiological effects: stimulates the SNS (increased body temperature, dilated pupils, slight increase in HR & BP, increased glucose in blood some dizziness, drowsiness, nausea
4. 5HT-like Psychedelics (cont.)
   e.g. LSD (cont.)
   low level of toxicity, TI = 280
   most deaths associated w/ LSD are accidental, suicide or homicide

   psychological effects:
   changes in perception, thinking, emotion, arousal, self-image
   esp. visual changes
   time slows, sensations intensify, synesthesias can occur
   increased ability to visualize
   decreased logical thought
   labile mood, increased tension & anxiety

   tolerance develops rapidly, and will disappear rapidly (w/i 3-4 days)
   cross-tolerance occurs w/ other psychedelics

   no physical dependence/addiction, no cravings; little/no w/d effects seen

   adverse reactions (which may be due to pre-existing problems)
   chronic and intermittent psychotic-like states
   persistent & recurrent depressive states
   increase in pre-existing psychiatric illness
   disrupted personality or chronic brain syndrome (“burnout”)
   flashbacks which are long-lasting (can occur in months or years after use)
   perceptual distortions

   e.g. DMT (dimethyl tryptamine)
   very potent, very short-acting (30 minute effect)
   e.g. Bufotenine (5-hydroxy-DMT)
   very potent, 2 hour ½ life, metabolized by MAO
   e.g. Psilocybin (which is inactive) & Psilocin (its active metabolite)
   (4-phosphoryl-DMT; 4-hydroxy-DMT)
   found in mushrooms
   less potent than LSD or DMT; peak levels 2 hours, duration 6-10 hours
5. Psychedelic Anesthetics, Amnestics & Deliriants

are structurally unrelated to the other psychedelic drugs
do not involve 5HT, nor ACh, nor DA
have unique psychedelic properties

e.g. PCP (phencyclidine) (“angel dust”)
developed as an anesthetic, but abandoned because --- a psychotic state with both + and – Sxs of schizophrenia
elim. ½ life is 11-51 hours (mean average 18 hours)
urine drug screen will detect up to 7 days after use
used PO, nasally, IV, or smoked

e.g. ketamine (Ketalar)
also an anesthetic agent, very safe w/ few cardiovascular effects
but also will --- a psychotic state
abuse of drug began in 1960’s, initially with PCP and then with “special K”

Mechanism of Action (of both PCP and ketamine)
prevents influx of Ca++ ions into glutamate-releasing neuron
thus, is a glutamate antagonist
binds as a noncompetitive antagonist on the NMDA glutamate RS
note: which supports the role of the NMDA RS in psychosis)
explains why one sees toxic, reversible psychosis with acute use
explains why one sees persistent schizophrenic Sxs (hallucinations, flattened affect, delusions, thought disorders, cognitive dysfunction, social withdrawal)
with chronic use

note: Would PCP/ketamine be useful in blocking glutamate cascade post-CVA?

note: No wonder PCP/ketamine has such potent amnestic effects
block NMDA RS/glutamate --- no LTP --- no memory
5. Psychedelic Anesthetics, Amnestics & Deliriants (cont.)

PCP (cont.) psychological effects:
   PCP dissociates S from self & from environment
   S is in an unresponsive state w/ intense analgesia & amnesia
   eyes open, appears awake but unresponsive

   with low doses --- mild agitation, euphoria, excitement, disinhibition, may be
   rigid, unable to speak or move, or may speak
   unresponsive to pain
   psychotic Sxs – withdrawn, unable to concentrate, bizarre thoughts/responses
   catatonic posturing

   with high doses --- coma, stupor, HBP, may have depressed respiration,
   violent reactions to stimuli, seizure activity, paranoid, panic, rage, confused,
   delusions may last for weeks-months afterward

   may show dependence & abuse, addiction
   PCP is the only psychedelic drug that animals will self-administer
   PCP --- stimulates the DA system
   Ketamine --- stimulates the opiate RSs (antagonistic at Mu & Kappa RSs)

Treatment of PCP/Ketamine User:
   minimize sensory inputs
   oral administration of activated charcoal
   precautionary physical restraint
   sedation (BZD or antipsychotic: Haldol, Zyprexa/olanzapine, clozapine)