PSYCHEDELIC DRUGS (p.l)

1. Terminology

"**hallucinogens**" – induce hallucinations, although sensory distortions are more common

"**psychotomimetics**" – to minic 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.l 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. **<u>Anti-ACh Psychedelics</u>** (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. **<u>Catecholamine-like Psychedelics</u>**
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)

.**<u>Catecholamine-like Psychedelics</u>** (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”, “adam”)

active metabolite is MDA

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

PSYCHEDELIC DRUGS (p.4)

3. Catecholamine-like Psychedelics (cont.)

c. **Synthetic amphetamine-like derivatives** (cont.)

MDMA ("*ecstacy*")

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 appetite	restlessness
insomnia	impaired gait	restless legs

severe toxicities observed:

hypertention	hyperthermia	tachycardia
disorientation	dilated pupils	convulsions
kidney failure	breakdown of skeletal muscle	

note: "*herbal ecstacy*" 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!

PSYCHEDELIC DRUGS (p.5)

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

PSYCHEDELIC DRUGS (p. 6)

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 disapper 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

PSYCHEDELIC DRUGS (p.7)

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 disfunction, 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

PSYCHEDELIC DRUGS (P.8)

5. **<u>Psychedelic Anesthetics, Amnestics & Deliriants</u>** (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,

<u>violent reactions</u> 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/olanxapine, clozapine)