Phencyclidine

Dissociative anaesthetic
- Parke Davis in 1950 (Serylan®)
- withdrawn from human use in 1965
- related to ketamine (“K” Ketalar, Ketaset®)

Illicit use
- 1967 in San Francisco (PeaCe Pill)
- Widespread in late 1970’s, early 1980’s
- (1980 - 22% of kids in grades 11-12 in N.Y.)
- Cheap, mostly distributed by the Crips nowadays

Street names
- PCP, angel dust, crystal, horse tranquilizer
  “sherm” “embalming fluid” on cigarettes or marijuana
- sold under many names and preparations
- very often sold as Δ9-THC
- take orally, intranasal or i.v.; or smoke
### Effects

**Low dose (1-5 mg)**
- Alcohol-like effect (giddy drunken-like state, disinhibition)

**Moderate dose (5-10 mg)**
- Distortion of space & time, psychotic reactions (panic, agitation, depression, catatonia, paranoia)
- "Anaesthetic" and analgesic effects
- Blank stare, amnesia, mutism

### Toxic psychosis

**High dose (> 10 mg)**
- Model of acute schizophrenia, including true hallucinations
  - Can last up to 1-7 days with high doses
- Sometimes violent, abusive behavior

**Overdose**
- Respiratory depression/seizures

### Self-administration

**Reinforcing effects**
- Readily self-administered in animals
  - To point of intoxication
  - Modest tolerance
  - Addiction and withdrawal
### Mechanisms of action

Two distinct binding sites
- Sigma site
  - generalizes with benzomorphans
- PCP site ("PCP receptor")

PCP site
- part of the NMDA glutamate receptor

### Glutamate (glutamic acid)

Ubiquitous excitatory transmitter
- Depolarizes virtually all cells
  - Primary transmitter for fast excitatory signalling

### Glutamate receptors

<table>
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<th>Ionotropic subtypes</th>
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<tr>
<td>Non-NDMA Types</td>
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<tr>
<td>AMPA</td>
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<td>Kainate</td>
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<td>NMDA</td>
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<tr>
<td>Selectively binds N-Methyl-D-aspartate</td>
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<th>Metabotropic subtypes</th>
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</table>
**Glutamate receptors**

**PCP/NMDA interactions**

Noncompetitive antagonist at NMDA receptor
- site inside channel - blocks it
- not antagonize AMPA/kainate effects

**Other actions**

Effects on many transmitter systems
- Action at sigma site
- Enhances DA release
Neuropathology

- Multiple vacuoles form in cytoplasm of some neurons and mitochondria disappear 2-4 hrs after treatment
  - Increasingly obvious 4-12 hrs after drug
  - Disappear within 24 hrs
  - Only certain parts of cortex
- Related to acute toxic psychosis?

Eight day old rats treated once with PCP or MK-801 and brains examined 24 hours later.

Sustained activation of NMDA receptors at critical stages in development activates programmed cell death.

See with PCP, ketamine (special K) and ethanol.
Control Drug

Degenerating neurons

Excitotoxicity

- Glutamate excitotoxicity
- MK-801

Hallucinogens

Common features
Hallucinogen
- the ability to evoke hallucinations, pseudohallucinations; illusions
Psychotomimetic
- ability to mimic endogenous psychosis
Phantasicum, Psychedelic
- "mind-expanding" change in perception of reality
Major classes

The LSD ‘Family’
- indole type hallucinogens
- structural similarity to 5-HT (serotonin)
- LSD (lysergic acid diethylamide)

Major classes

The Phenylethylamines
- structural similarity to CA’s
- mixed hallucinogenic and stimulant effects
- mescaline

LSD type hallucinogens

LSD (lysergic acid diethylamide)
- acid, blotters, windowpane, etc.
LSD type hallucinogens

LSD (lysergic acid diethylamide, LSD-25)
  - Hofman (1938)
  - led to Imitrex & Zomig

LSD type hallucinogens

LSD (lysergic acid diethylamide)
  - ergot

LSD

- Absorption and metabolism
- Tolerance
LSD type hallucinogens

Psilocybin and Psilocin
- magic mushroom
- Psilocybe genus

DMT (Dimethyltryptamine)
- naturally-occurring LSD-like substance in plants; e.g. Piptadina peregrina (bean plant)

Morning Glory Seeds
- lysergic acid amide (LSA)

Bufotenin (5-hydroxy-DMT)

Harmine and Harmaline

The phenylethylamines

- structural similarity to CA’s
- mixed hallucinogenic and stimulant effects
- mescaline
Mescaline

- In peyote cactus (Lophophora Williamsii)
- Mescal button

Methoxyamphetamines

- Synthetic derivatives of mescaline
- Many are so-called “designer drugs”

DOM (dimethoxymethylamphetamine)
- Called STP often

TMA (trimethoxyamphetamine)
- Similar to mescaline, but more potent

MDA and MDMA
- Methylenedioxyamphetamine and methylenedioxymethamphetamine
**Major effects (LSD)**

Sensory-Perceptual
- pseudohallucinations
- illusions
- synesthesias, etc.

Psychic Experiences

Somatic Effects

**Adverse effects**

- Bad ‘trips’
- Flashbacks

**Mechanisms of action**

- Common action for hallucinogenic effects sensory-perceptual effects and psychedelic effects
- Only short-term tolerance to LSD, no withdrawal, dependence or addiction
- LSD not lethal at very high doses
- Cross tolerance for hallucinogenic effect
- Focus on 5-HT systems (structural similarity)
Serotonin (5-hydroxytryptamine)

- Receptors 5-HT1, 2, 3, 4, 5, 6 (14 subtypes known)
- Synthesis & storage
- Inactivation & degradation

Raphe

Mechanisms of action

- Initial prevailing view from peripheral tissues
  - Block action of 5-HT (antagonist?)
- Second view: agonist at inhibitory autoreceptors
  - Increases 5HT content and 5HIAA down turnover down?
  - Inhibits firing of 5HT neurons
  - Discredited by presynaptic lesion studies

Current Postsynaptic hypothesis

- Binding to 5-HT receptors (over 14 subtypes)
  - LSD is fairly promiscuous (5-HT1, 2/5/6/7 types)
  - Mescaline not to 5-HT1/5/7
  - All have affinity for 5-HT2 family
  - 5-HT2A shows greatest expression in neocortex

- Hypothesis: LSD and other hallucinogens are 5-HT2A postsynaptic receptor agonists