Psychoactive Substances

GE1328 BMS CityU 2015

Part 5:

South Pacific and Modern Chemistry

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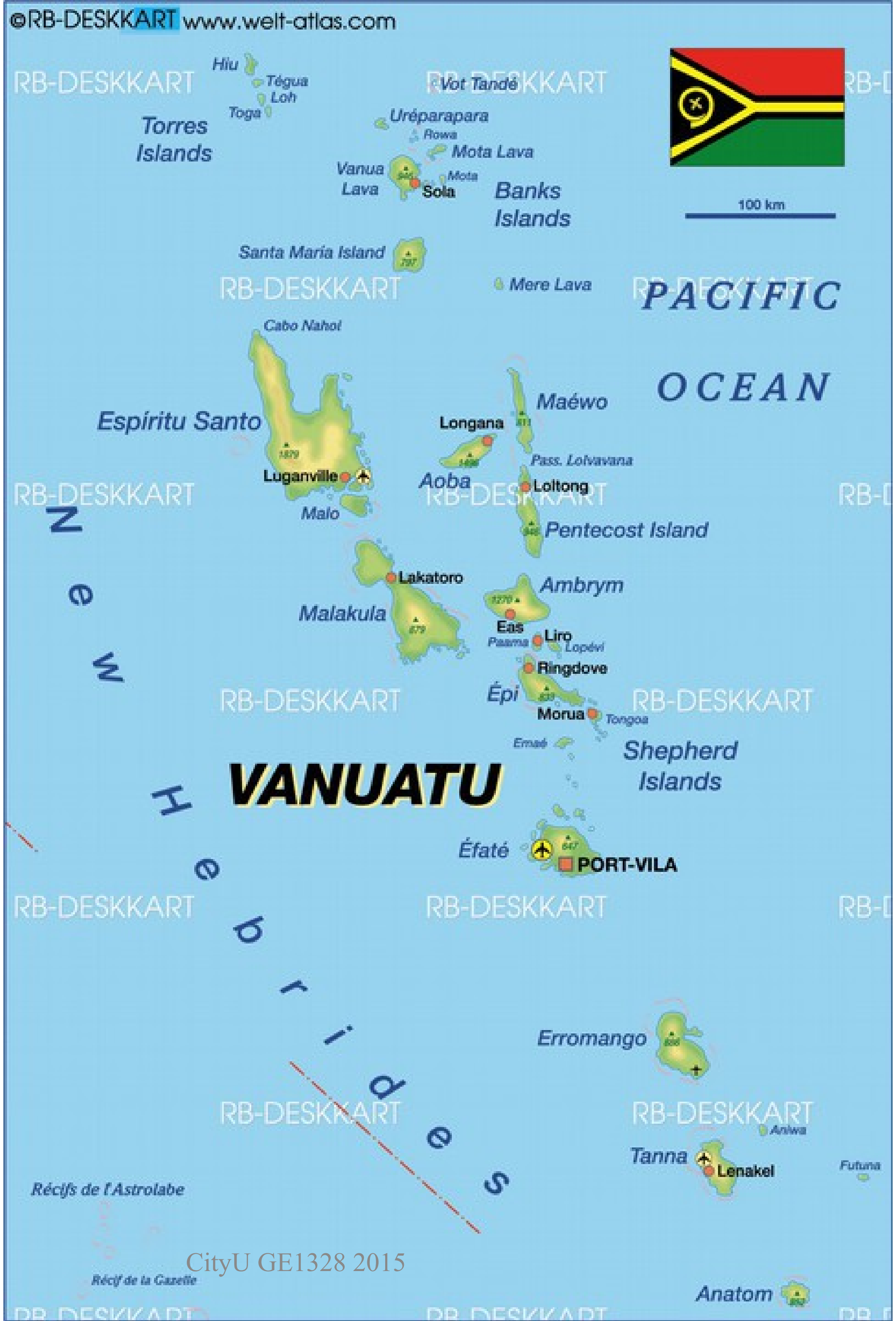
Kava (*Piper methysticum*)

- "Intoxicating pepper". Found and grown in Polynesian culture (South Pacific: Vanuatu+++)
- Roots to make a drink with sedative & anesthetic properties. More active than placebo and most pharmaceuticals.
- Kava is grown in the shade, high humidity, warm temperature. Roots are harvested a 4-5 years of age.
- May cause liver damage. NEVER drink alcohol when drinking kava!


©RB-DESKKART www.welt-atlas.com
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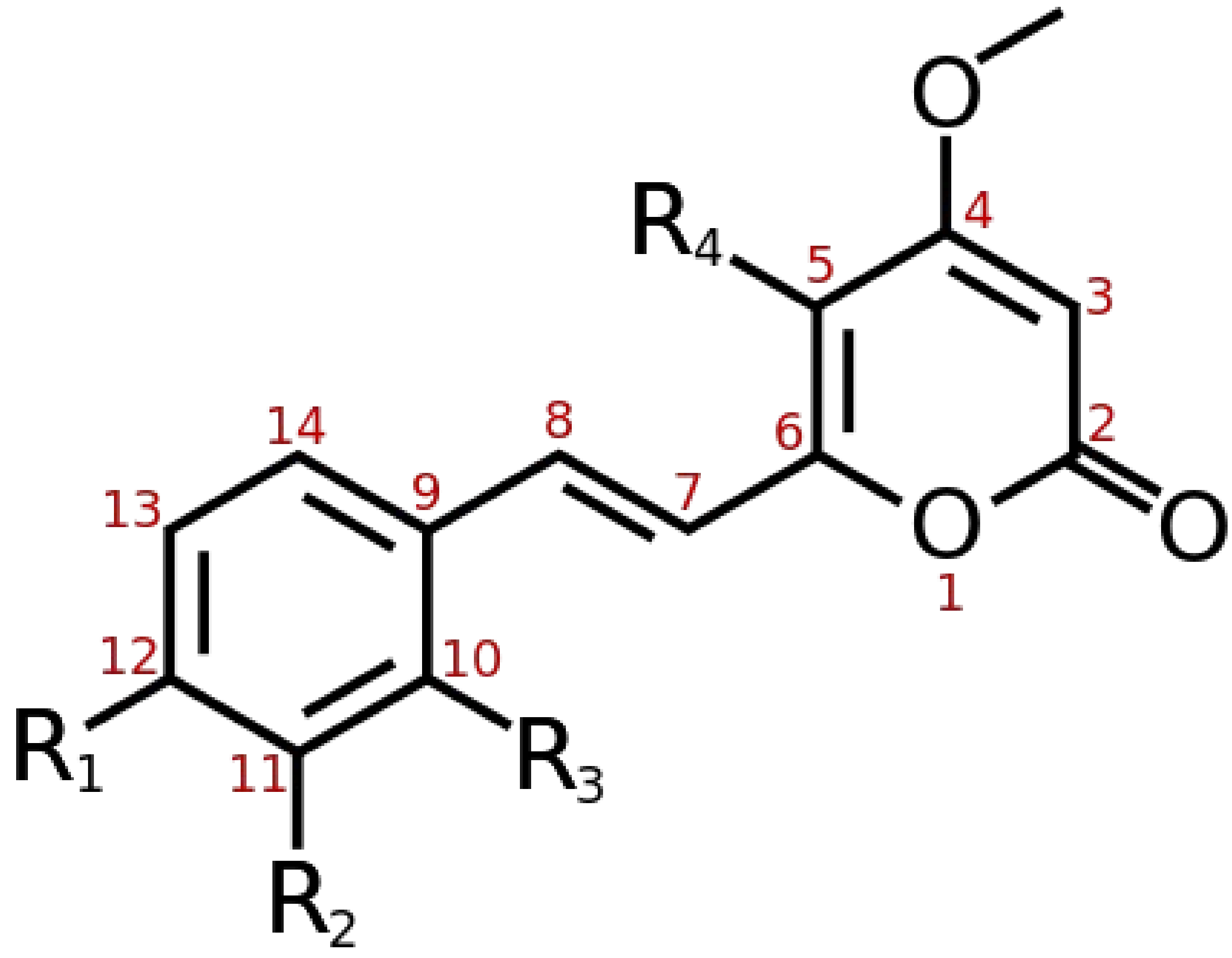
Hiu
Tégua
Loh
Toga
Torres Islands
Vot Tandé
Uréparapara
Rowa
Mota Lava
Vanua Lava
Mota
Sola
Banks Islands
100 km
Santa María Island
Mere Lava
PACIFIC OCEAN
Cabo Nahoi
Espíritu Santo
Maéwo
Longana
Pass. Lolvavana
Luganville
Aoba
Loltong
Malo
Pentecost Island
Lakatoro
Ambrym
Malakula
Eas
Paama
Liro
Lopévi
Ringdove
Épi
Morua
Tongoa
Emaé
Shepherd Islands
VANUATU
New Hebrides
Éfaté
PORT-VILA
Erromango
Aniwa
Tanna
Lenakel
Futuna
Récifs de l'Astrolabe
Récif de la Gazelle
Anatom

Kava Offering


Piper inebrians.
SI2/18 1

General Structure of Kavalactones

15 have been identified



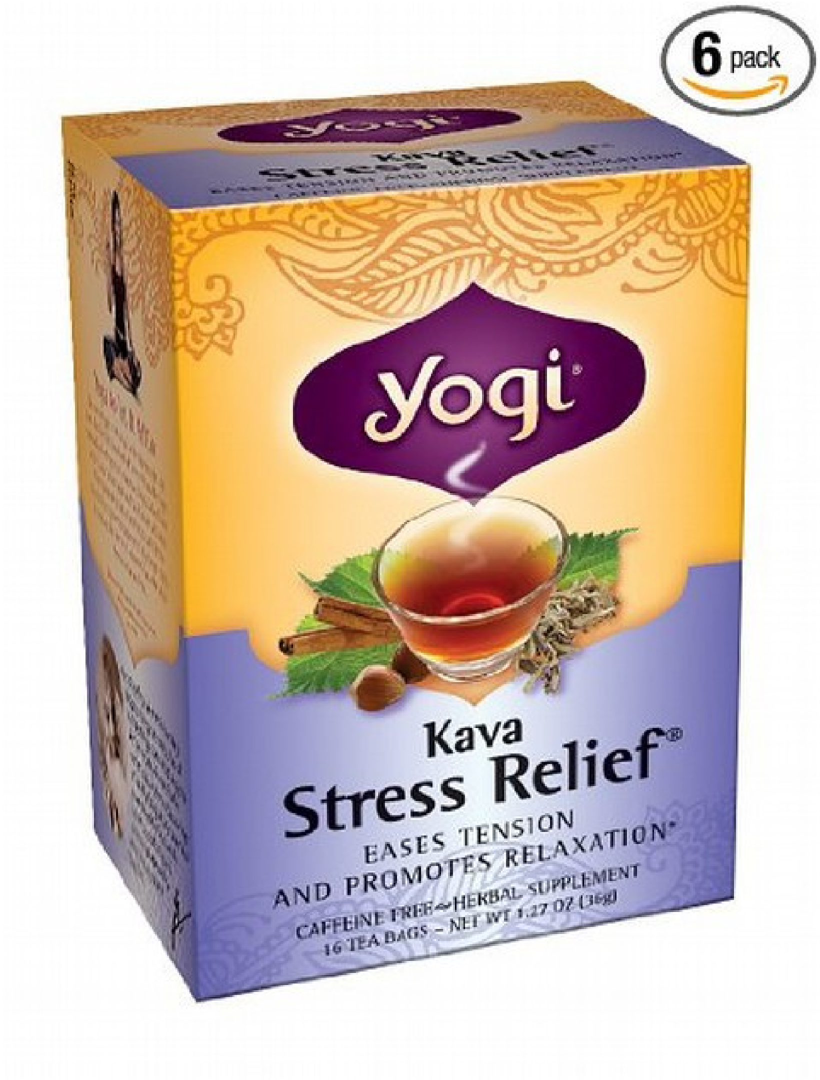
Mechanisms of action

- Potentiate GABA. Long-term use does not affect cognition.
- Desmethoxyyangonin increases dopamine in *nucleus accumbens* (euphoria)
- Kavain Inhibits reuptake of norepinephrine (enhanced attention)
- Yangonin is CB1 antagonist (psychoactive)

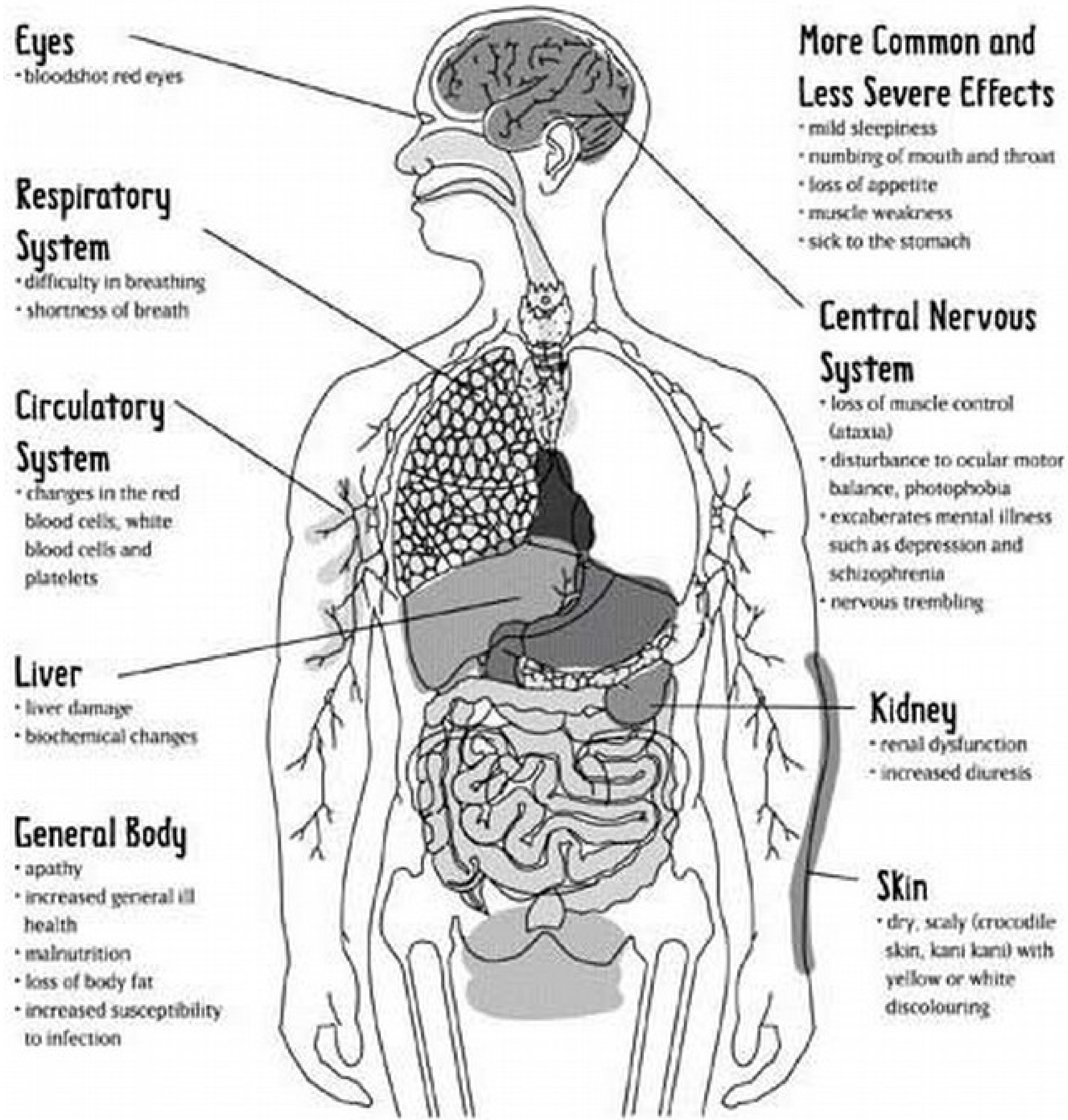
Preparation of Kava and Effects

- Chewing [from someone else…]
- Pounding, then emulsion with water
- Red, sensitive eyes
- Somnolence & sleep. ½ life ~9 hours
- Relieves anxiety. More effective than tricyclics and benzodiazepines

Available from Amazon.com

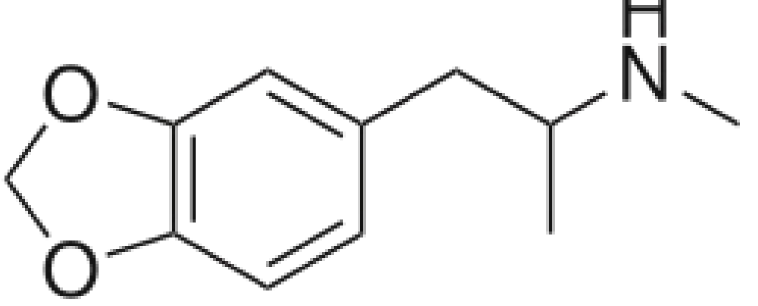


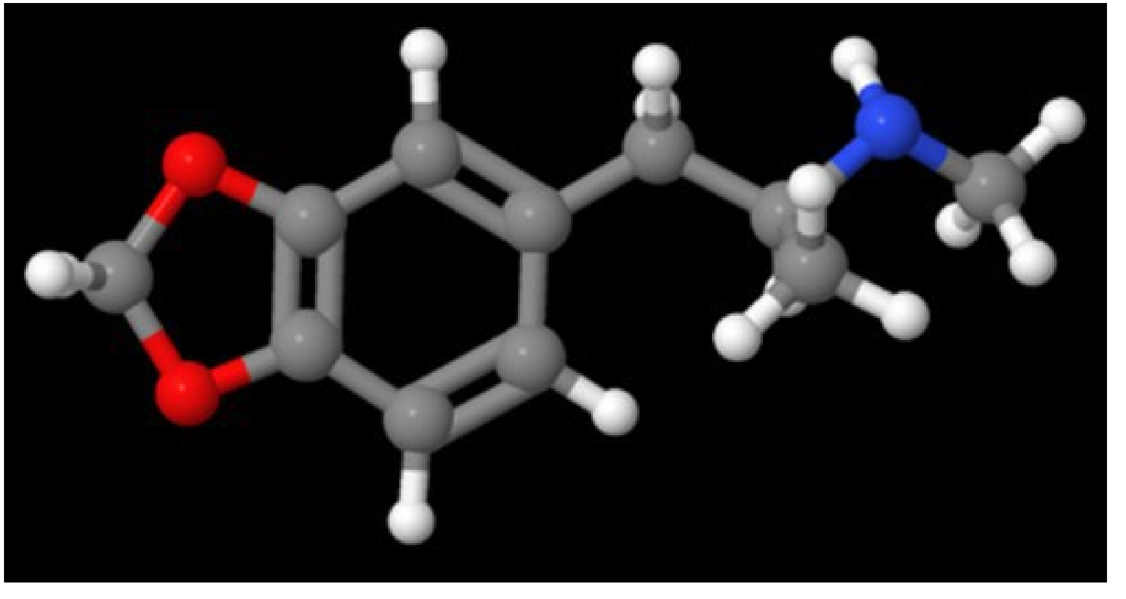
Two Famous Kava Drinkers


Eyes
• bloodshot red eyes
Respiratory System
• difficulty in breathing
• shortness of breath
Circulatory System
• changes in the red blood cells, white blood cells and platelets
Liver
• liver damage
• biochemical changes
General Body
• apathy
• increased general ill health
• malnutrition
• loss of body fat
• increased susceptibility to infection
More Common and Less Severe Effects
• mild sleepiness
• numbing of mouth and throat
• loss of appetite
• muscle weakness
• sick to the stomach
Central Nervous System
• loss of muscle control (ataxia)
• disturbance to ocular motor balance, photophobia
• excaberates mental illness such as depression and schizophrenia
• nervous trembling
Kidney
• renal dysfunction
• increased diuresis
Skin
• dry, scaly (crocodile skin, kani kani) with yellow or white discolouring

MDMA Ecstasy

3,4-methylenedioxy-methamphetamine



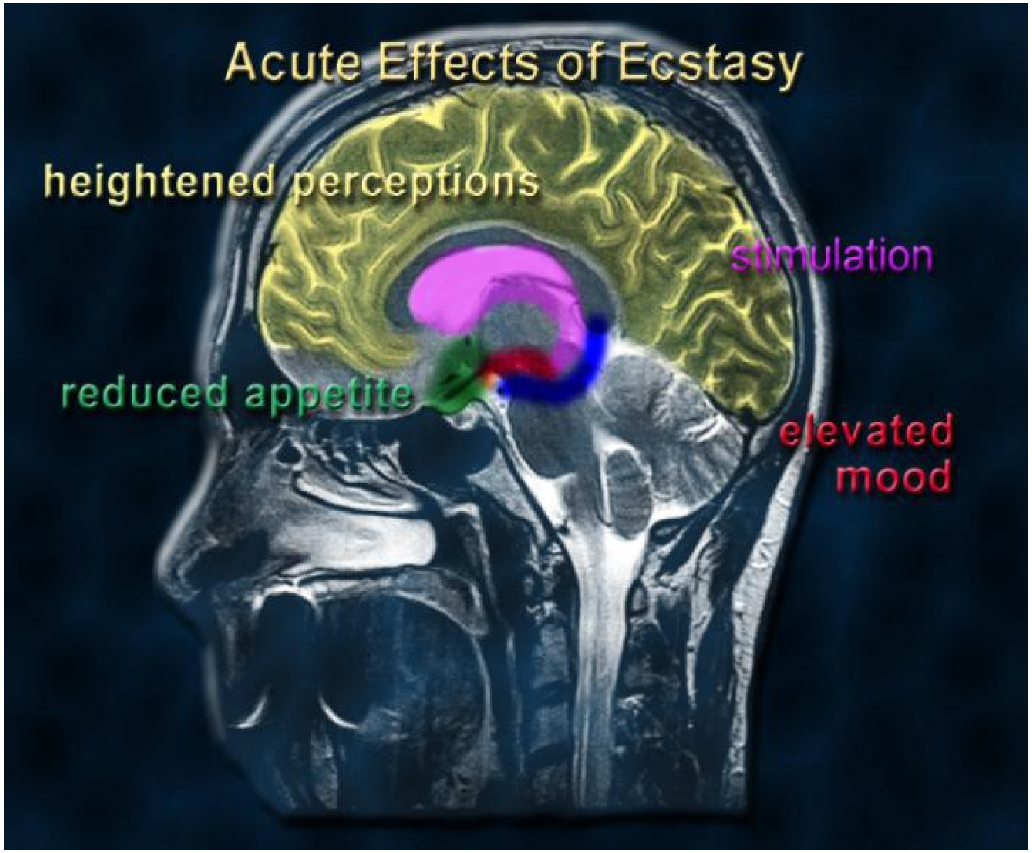


History

- Synthesized, patented by Merck (1912, 1914)
- Studied as appetite suppressant but never marketed (50s and 60s)
- Researched by Army intelligence as potential truth serum (50s)
- Limited recreational use (60s)
- Psychotherapeutic use (mid-late 70s): called "penicillin for the soul"
- Use leaks out to expanding recreational use- acquires name of Ecstasy (early 80s)
- DEA places MDMA in Schedule I (1985-88)
- Use spreads to Europe, becomes part of raves, spreads back to U.S. (late 80s)

Short Term Effects

- More trusting
- Increased empathy
- Mildly intoxicating



Ecstasy experience

"The drug removes all your neuroses. It takes away the fear of response. There is an overwhelming sense of peace, you are at peace with the world. You feel open, clear, tender. I can't imagine that anyone is angry under its influence, or selfish or mean or defensive. You have lots of insight into yourself, real insight, which you hold on to after the experience is gone"

EFFECTS OF MDMA USE

PHYSIOLOGICAL

- Sensatory awareness
- Loss of appetite
- Nausea
- Muscle ache
- Tachycardia
- Hypothermia
- Cardiological complications
- Liver damage

PSYCHOLOGICAL

- Euphoria
- Anxiety, depression, and panic attacks
- Depersonalization
- Paranoia
- Psychotic experiences
- Cognitive deficiencies, e.g., memory loss and decreased planning ability

Settings of Use

The settings at which MDMA is being used
Are diversifying according to all presenters
And these include:

- **Raves and concerts**
- **Clubs and bars**
- **House parties**
- **At home with friends or other private settings**

The setting of use (e.g. crowd and high temperature at rave) needs to be explored when studying the negative outcomes of use . . .

MDMA Ecstasy XTC X E

- The tablets/capsules have many forms, weights, colors, and names with little reliable identification of the active ingredients

- XTC/MDMA may be. . .
  - MDMA (3,4 – methylendioxy-N-methamphetamine)
  - MDA (3,4 – methylendioxy-N-amphetamine)
  - MDE (3,4 – methylendioxy-N-ethylamphetamine)
  - MBDB, amphetamine, heroin, caffeine

MDMA Administration

- Intranasal
  - Bumpers
  - Inhale “bumps” from the back of the hand
  - Other paraphernalia such as spoons, pen caps
- Oral
  - Pills and capsules
- Anal Insertion
  - “Booty bumping”

“Ecstasy” may not be MDMA

Methyl
Salicylate,
Caffeine

90%
DXM

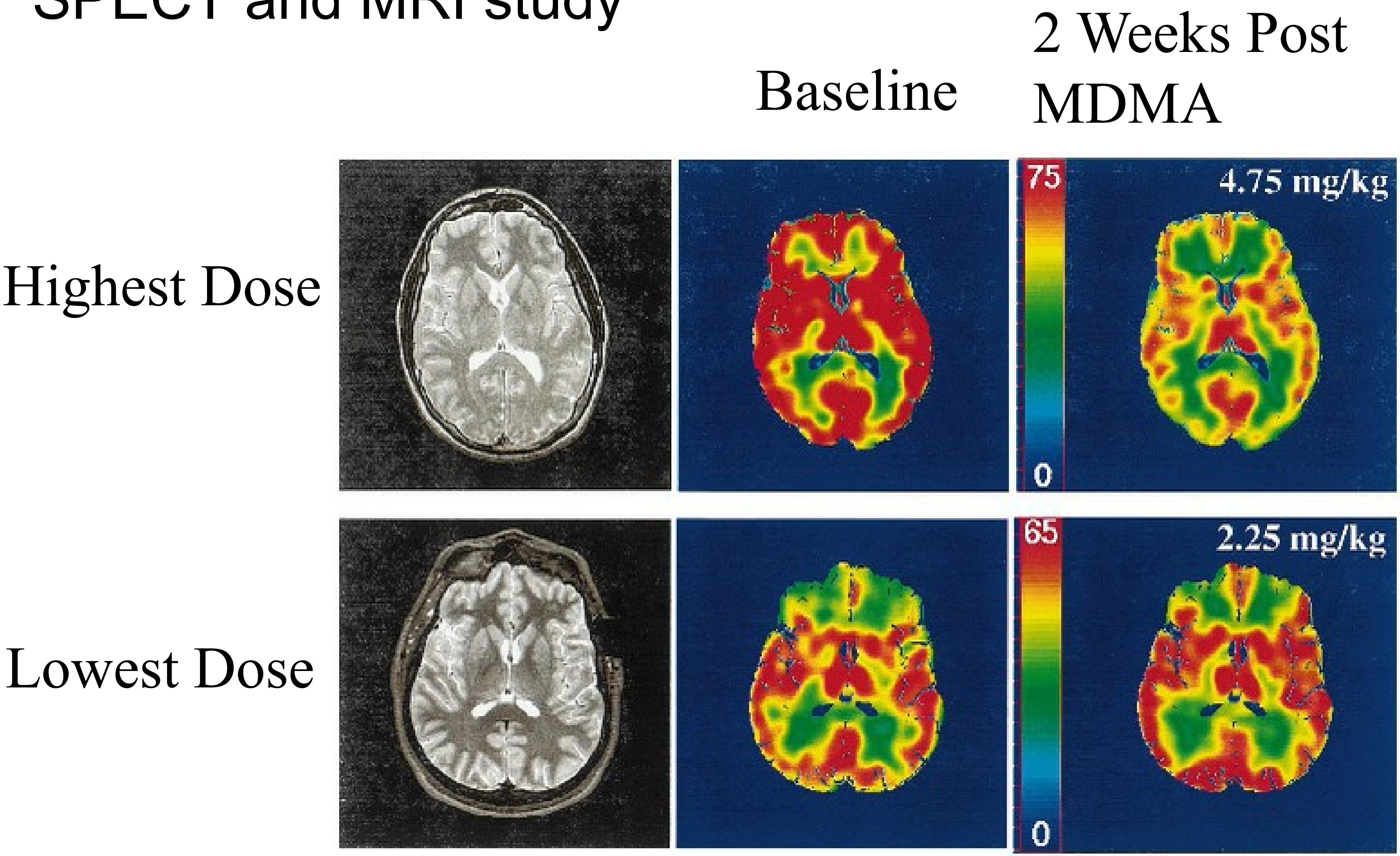
MDMA

MDA

- These are some of the “Ecstasy” pills tested by the dancesafe organization (www.dancesafe.org)

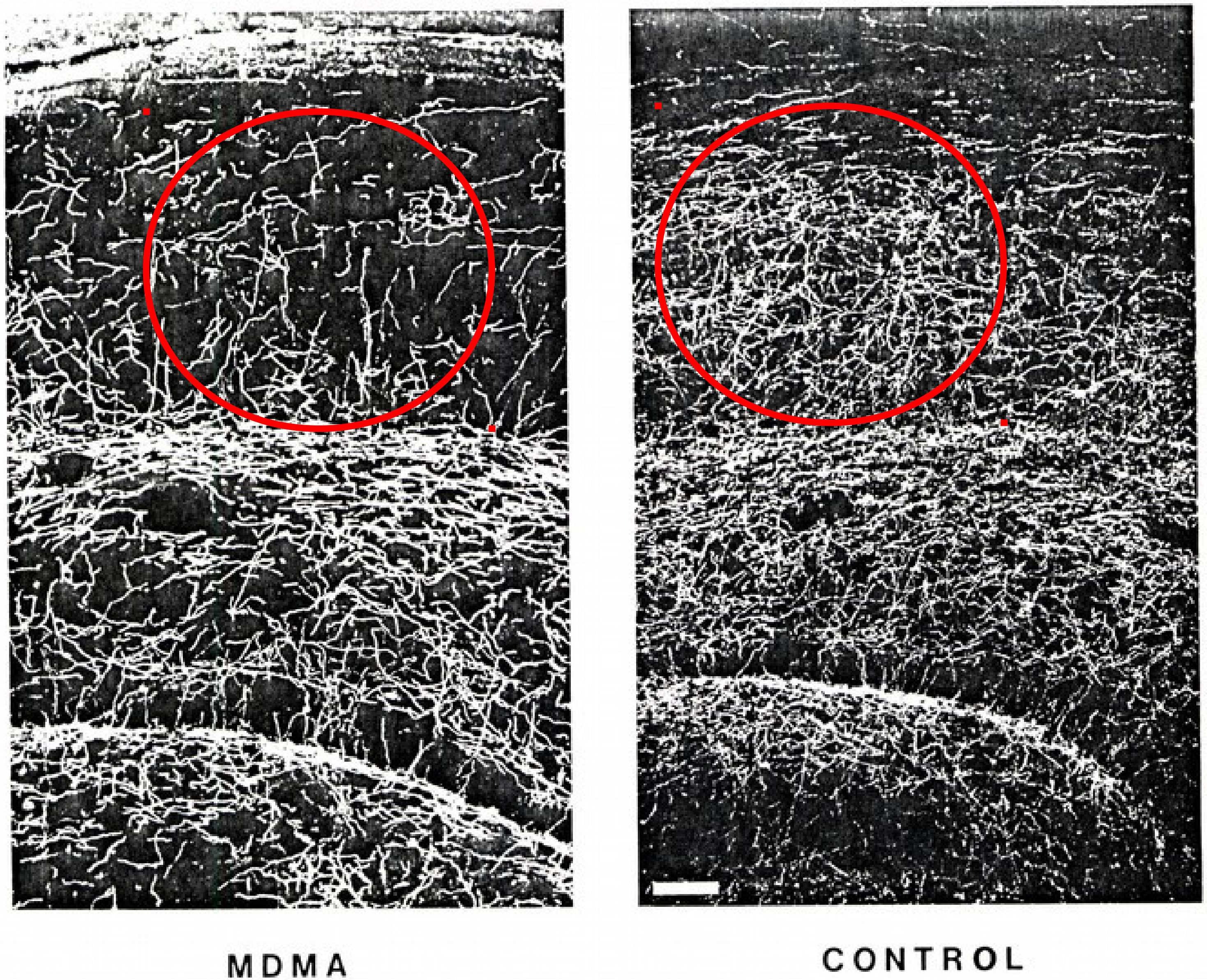
Effect of MDMA on cerebral blood flow: A co-registered

SPECT and MRI study



L. Chang Psychiat Res (2000) 98: 15)

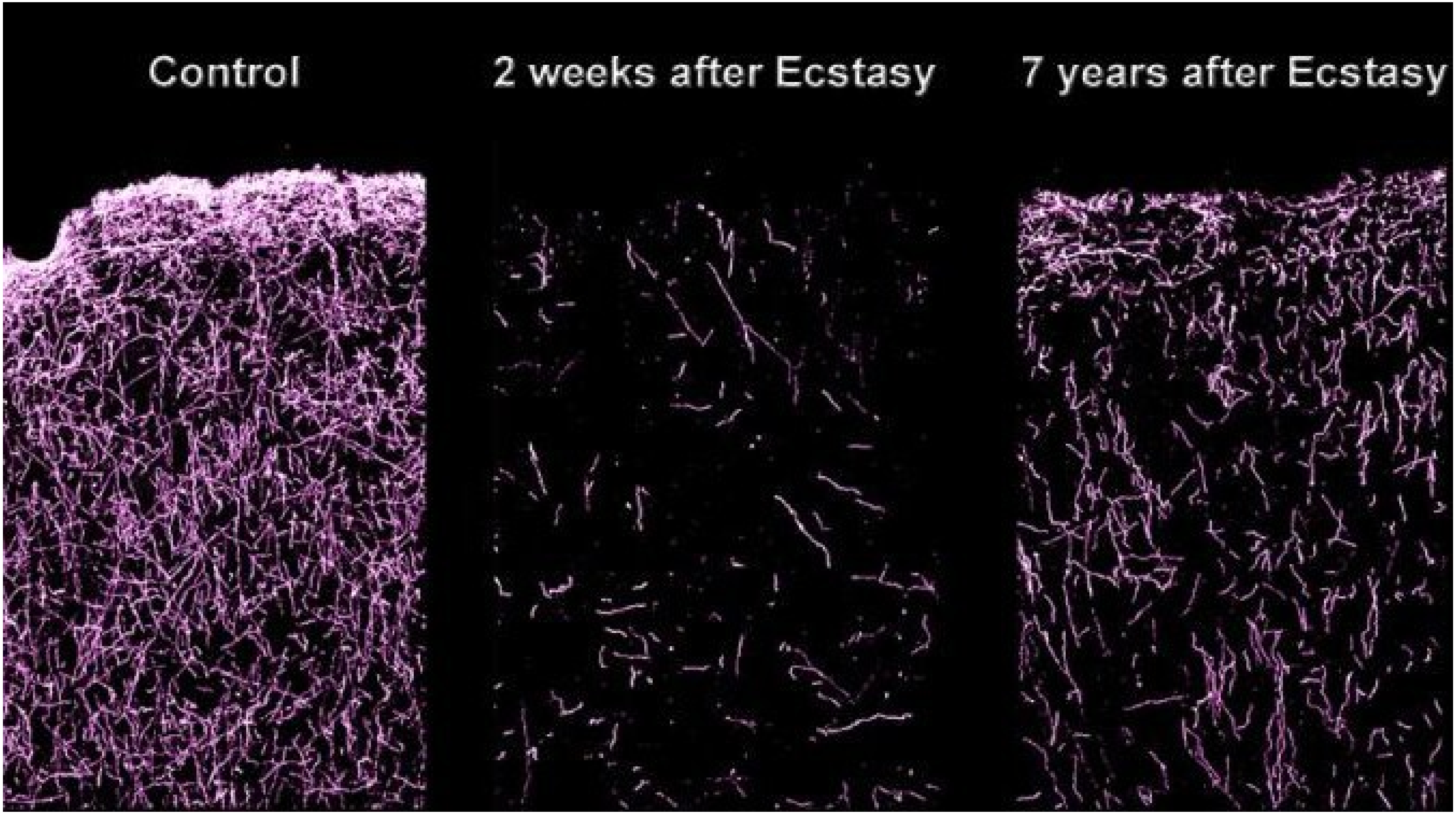
Rat Hippocampus (2 wks after 20 mg/kg; 2X daily, 4 days)



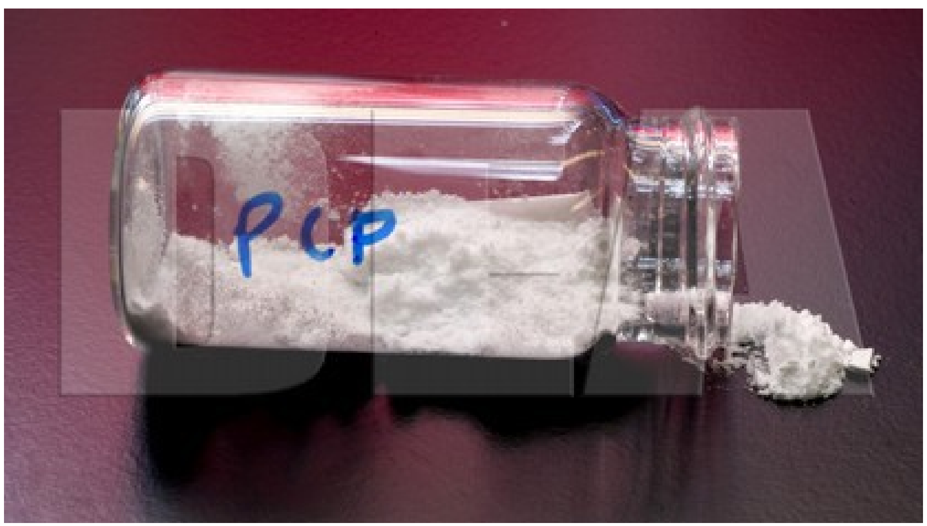
(O'Hearn et al. J. Neurosci. 8 [1989] 2788)

- **Result: long-term loss of 5HT fibers**

Brain Changes in Monkeys



PCP and Ketamines



Background and History: PCP

- PCP or phencyclidine
  - Chemical name 1-(1-phenylcyclohexyl) piperidine
  - 1950s – first tested as a potential anesthetic agent by Parke, Davis and Company
  - caused and unusual form of anesthesia
  - showed no response to painful stimuli
  - exhibited trancelike or catatonic like state with vacant facial expressions, staring eyes, and maintenance of muscle tone
  - did not produce respiratory depression as other barbiturate
  - some patients began to develop problematic reactions
  - agitation rather than quieting during induced states
  - mild – blurred vision, dizziness, disorientation
  - severe- hallucinations, severe agitation, violence
  - 1965 – clinical use of PCP terminated
  - 1967 – PCP found its way to the streets
  - mid 1970s – PCP use and abuse became more widespread throughout the country
  - street names – PeaCe Pill, angel dust, hog

Background and History: Ketamine

- Ketamine
  - Safer alternative to PCP
  - Parke, Davis was adamant about finding a less toxic compound in its behavioral effects
  - CI-581 was developed in 1962
  - Less potent and shorter action
  - Used particularly for surgery in children
  - Sedative and immobilizing agent for veterinarians
  - Legal as a prescription under the trade names Ketalar, Ketaset, and Vetalar
  - Despite low potency, ketamine can still cause adverse emergency reactions similar to PCP

Ketamine: Pharmacokinetics

- Marketed as an injectable liquid
  - Occurs most often
  - I.V. or I.M.
- Evaporated and sold as a powder
  - Occurs on streets
  - Intranasal
    - Snort small line or pile called bumps
    - Produces small high
  - p.o.
- Tolerance

PCP: Effects

- Sub-anesthetic dose
  - Psychological effects
    - Detachment from body, sensations of floating
    - Numbness, dreamlike state
    - Apathy, loneliness, negativism or euphoria
  - Physiological effects
    - Drowsiness, difficulty maintaining concentration

Ketamine: Effects

- Sub-anesthetic dose
  - Similar effects to PCP
    - Floating, dreamlike state, detached from body
- Anesthetic dose
  - 1mg/kg
  - Lose all mental contact with environment
  - Eyes remain opened and retain muscle tone
- Dissociative anesthesia
- “K-Hole”
  - Spiritually uplifting or terrifying

Noncompetitive Antagonists of NMDA Receptors

- Principal molecular target for both is NMDA receptor
- NMDA is an important ionotropic receptor for glutamate
- Both are noncompetitive antagonists
- They block the receptor at a different site than the site at which NMDA or glutamate binds
- NMDA plays a role in glutamate signaling
- Cerebral cortex and hippocampus contain many NMDA receptors
- Behavioral and subjective effects are thought to be mediated by NMDA receptor antagonism
- Dextromethorphan is common in OTC cough and cold medications and is another noncompetitive NMDA antagonist with abuse potential

Drugs of Abuse

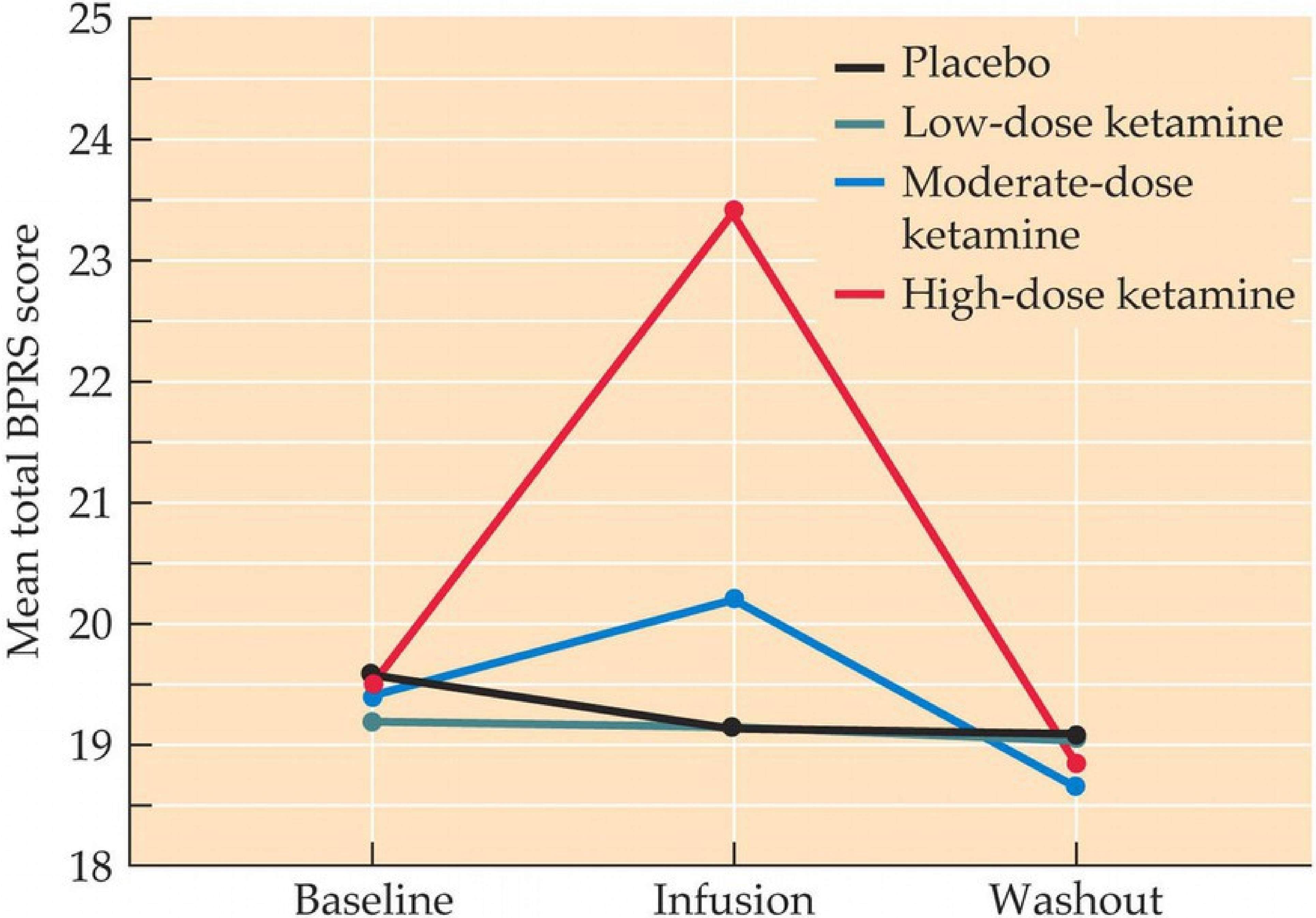
- **Abuse**
  - Prevalence of PCP use is much lower than that of other majorly abused drugs
  - There are currently no comparable statistics for ketamine

- **Who uses it?**
  - People at raves
  - Medical or veterinary practitioners
  - Marcia Moore and Dr. John Lilly

- **Tolerance and Dependence**
  - Karl Jansen's Ketamine Research (2001)
    - Research demonstrated dose escalation and compulsive use
    - Many ketamine dependent subjects studied were described as highly intelligent
    - Overcoming ketamine was described as "harder than heroin"

PCP, Ketamine, and schizophrenia

- Why these drugs may be helpful:
  - Perceptual, cognitive, and affective responses mirror those of schizophrenia
  - Administration of either drug to schizophrenic increases their symptoms
- Research
  - Healthy participants were given doses of ketamine (IV)
    - Positive symptoms
      - Hallucinatory responses, conceptual disorganization, and bizarre thought content
    - Negative symptoms
      - Blunted affect, emotional withdrawal, and motor retardation
  - Psychotic-like reactions diminished afterwards



PSYCHOPHARMACOLOGY, **Figure 14.13**

Future Research

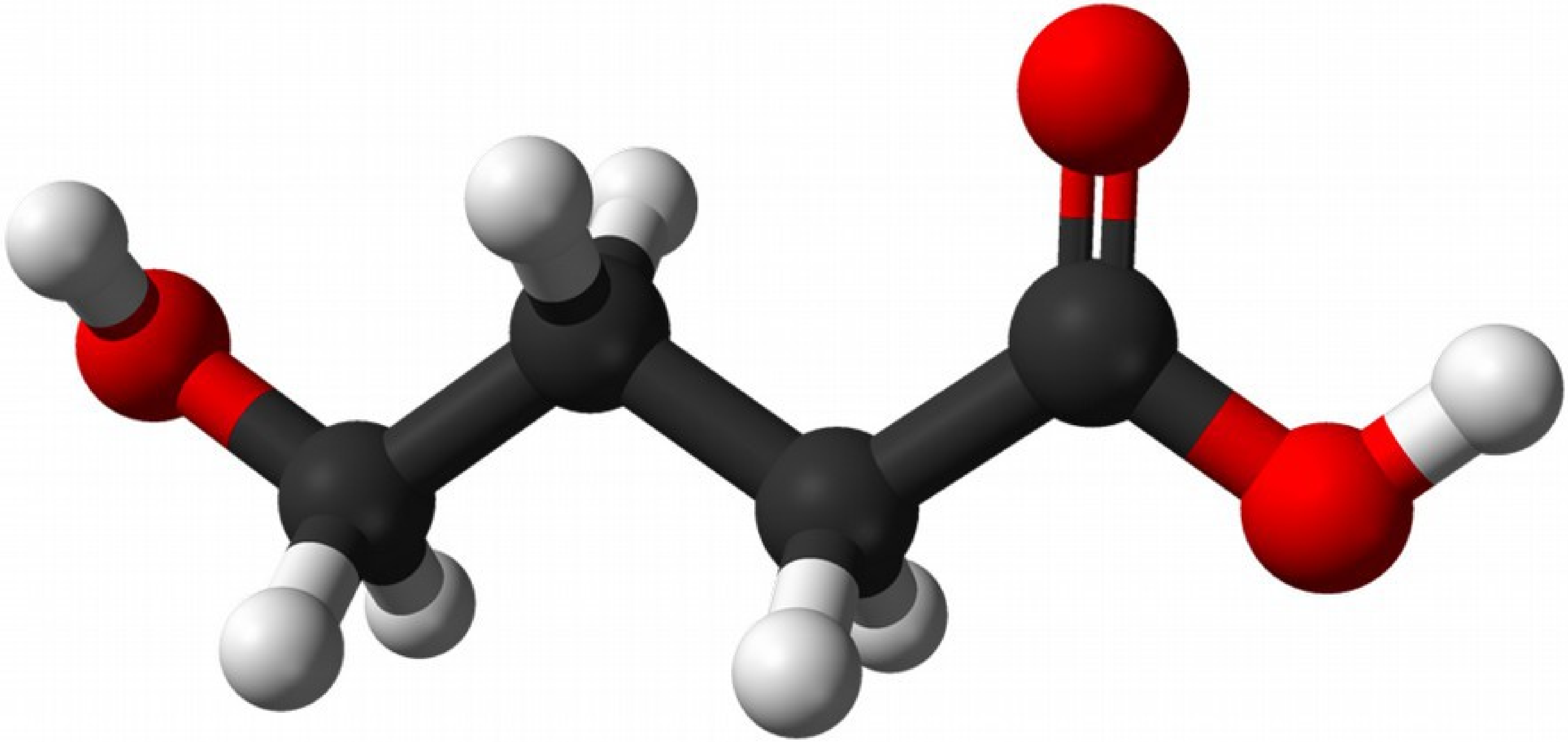
- Animal Models
  - Long term PCP administration may provide a model for the severe cognitive deficits in schizophrenic patients
  - Researchers found 2 weeks of twice daily PCP administrations to monkeys caused deficits in object retrieval detour learning tasks one week after the last drug dose
    - Detour task involves the prefrontal cortex
  - Repeated PCP treatment has lead to a reduction in DA utilization in the prefrontal cortex

- The future treatment of schizophrenia
  - Animal models using chronic PCP administration may help us to understand and treat some of the underlying mechanisms involved in schizophrenia

Summary

- PCP and Ketamine classified as dissociative anesthetics
- Acute effects – sensory distortions and altered body image, cognitive disorganization, and various affective changes
- High doses of ketamine = state called “k-hole”
- K-hole – user feels separated form their body
- Both are reinforcing to animals
- May be mediated by both dopaminergic and non-dopaminergic mechanisms
- Direct molecular target is glutamate NMDA receptor
- User dose escalation and compulsive use indicates development of high tolerance and dependence
- May help to understand the neurochemical processed underlying schizophrenia

GHB
(Gamma Hydroxybutyric acid)



GHB Street Names

- "Liquid Ecstasy"
- "Liquid x"
- "Georgia home boy"
- "Fantasy"
- "G"

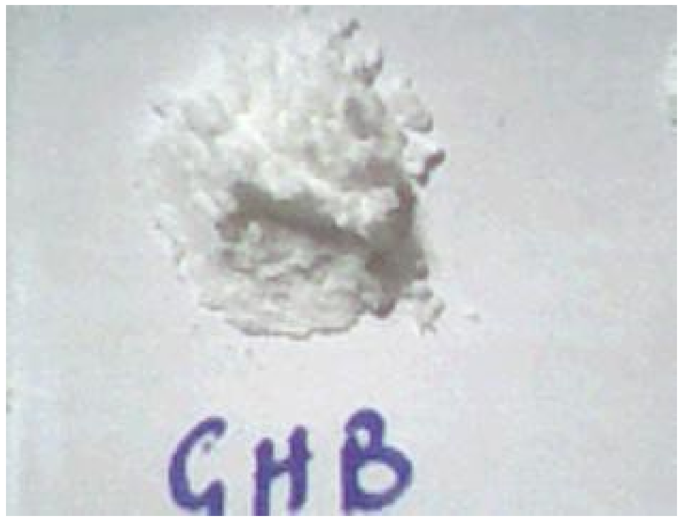
GHB

It makes the user feel relaxed, happy, and sociable.

Club and rave scene use

GHB is often taken because users find that it enhances their experiences of being in a club, party, or rave; small doses of GHB can act as a stimulant and aphrodisiac. GHB is sometimes referred to as *liquid ecstasy*, *lollipops*, *liquid X* or *liquid E* due to its tendency to produce euphoria and sociability and its use in the dance party scene.

Appearance of GHB



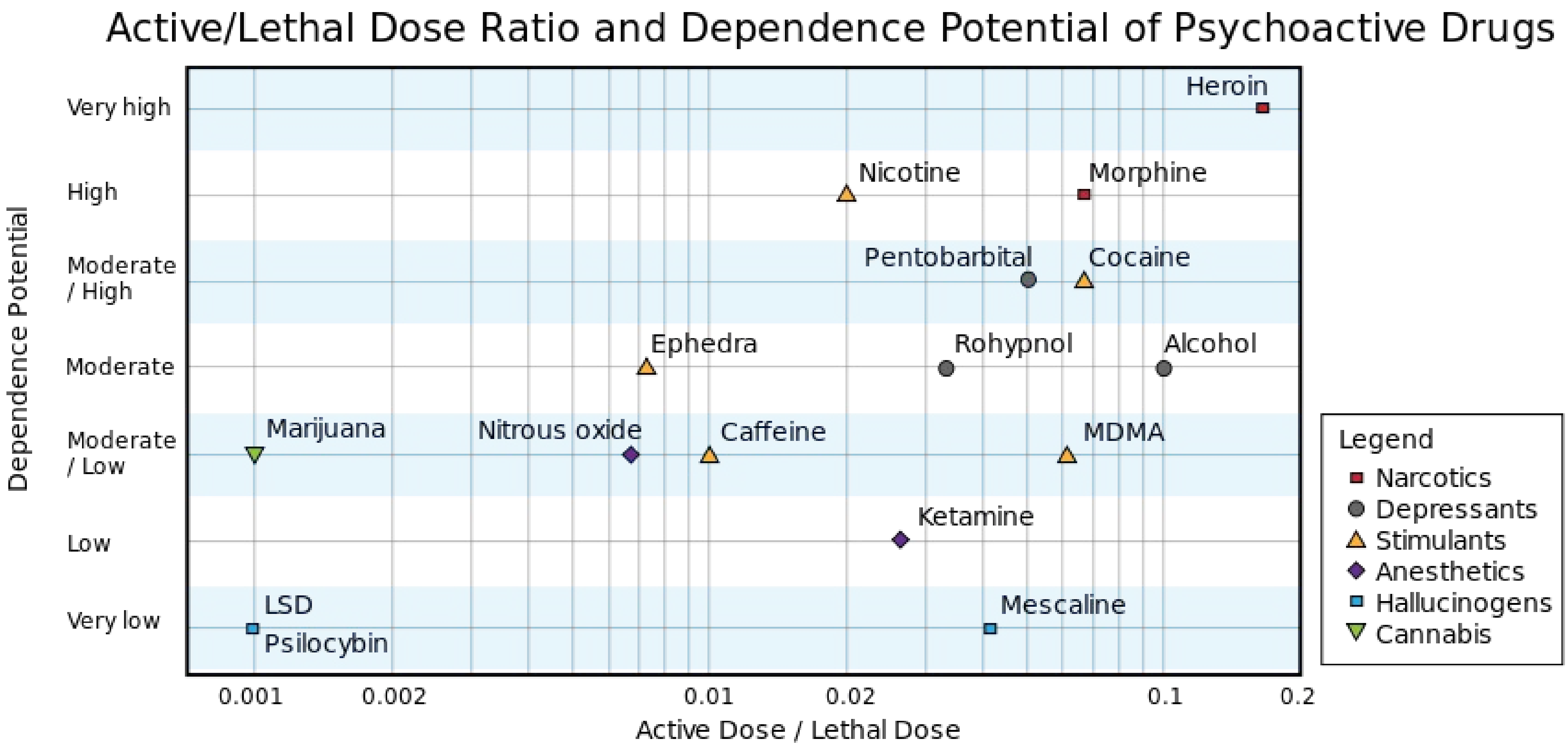
http://www.streetdrugs.org/html%20files/GHB.html

http://www.lcpcopp.ca/events/mfl08/depressants.php

- An odorless, colorless, liquid form.
- It can also be in powder or pill form.
- Usually ingested in a liquid mixture; most commonly mixed with alcohol.

Long-Term Effects

- Unconsciousness
- Seizures
- Severe respiratory depression
- Coma
- Death
- Insomnia
- Liver Failure



Active/Lethal Dose Ratio and Dependence Potential of Psychoactive Drugs
Dependence Potential
Very high
High
Moderate / High
Moderate
Moderate / Low
Low
Very low
Heroin
Nicotine
Morphine
Pentobarbital
Cocaine
Ephedra
Rohypnol
Alcohol
Marijuana
Nitrous oxide
Caffeine
MDMA
Ketamine
LSD
Psilocybin
Mescaline
0.001
0.002
0.01
0.02
0.1
0.2
Active Dose / Lethal Dose
Legend
Narcotics
Depressants
Stimulants
Anesthetics
Hallucinogens
Cannabis

Human beings have a basic need to find ways to cope with their environment and existence.