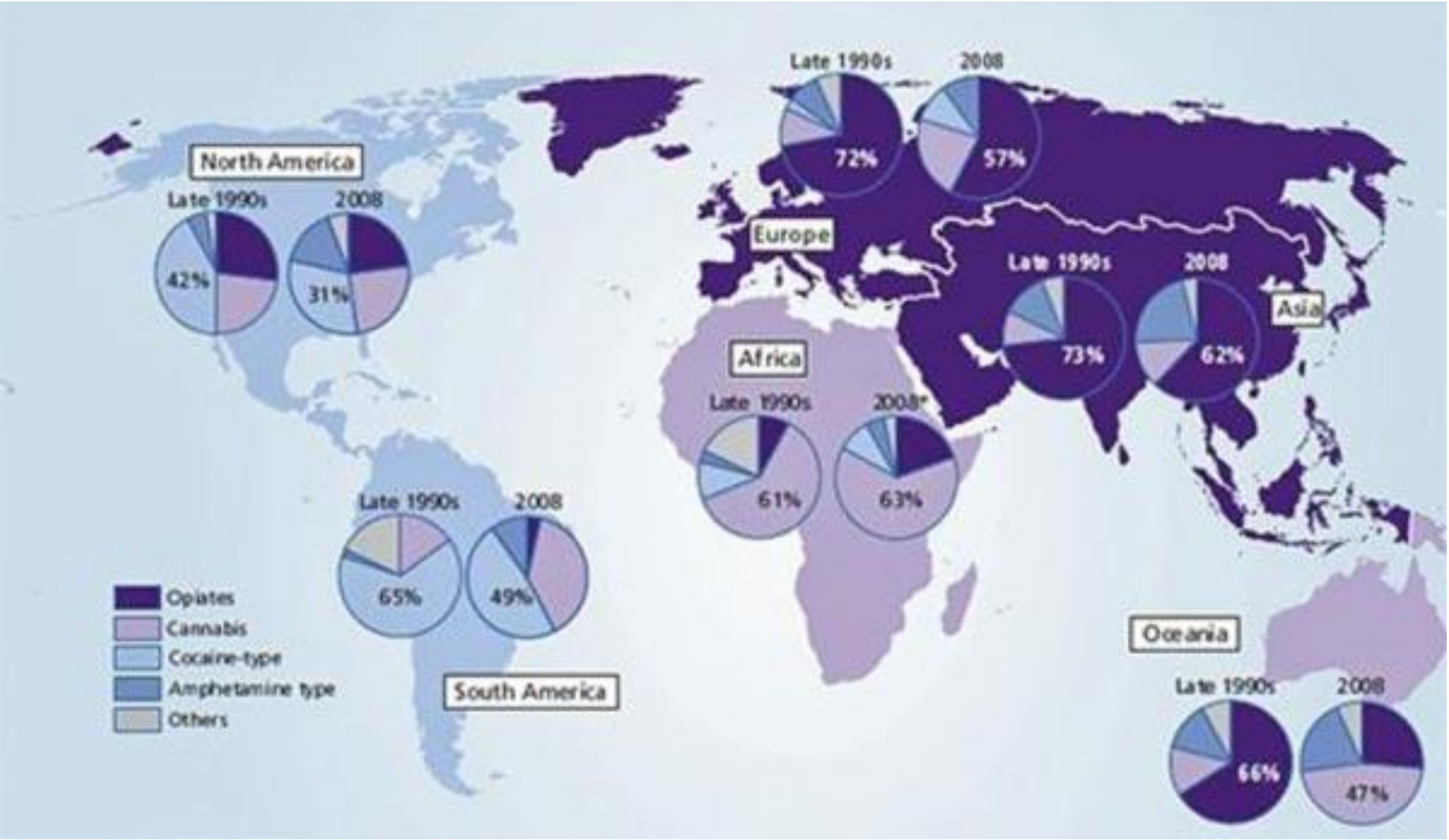
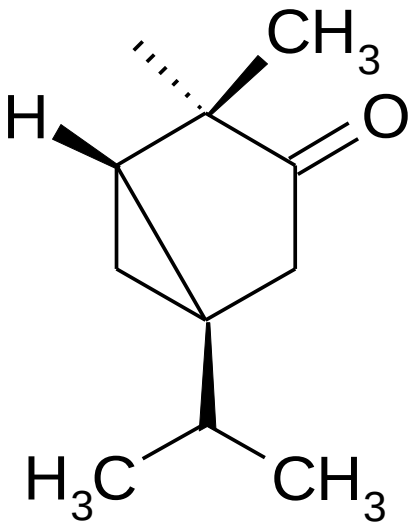
Trends in use of narcotic compounds



- Thujon
  - Natural mixture of isomers α,β (33% α, 67% β)
  - *Artemisia absinthium, Artemisia vulgaris Salvia officinalis, Salvia sclarea*
  - *Tanacetum vulgare*
  - *Thuja occidentalis*
  - Folk medicine:
    - Abortive, emenagogue, digestive, carminative, antiphlogistic, anthelmintic



- Analgesic, analeptic, antidepressive
- Toxicity:
  - CNS effect
    - Tonic-clonic convulsions, cumulative effect
    - Absinthism
      - » hyperexcitability, hallucinations
  - Nephrotoxicity (degenerative changes)
  - Hepatotoxicity
    - Dependent on dosage and sensitivity
- Mechanism of effect:
  - Blocker of $GABA_A$ chloride channel (similar to picrotoxine)
  - α-thujon 2.3 times more effective than β-thujon
  - Low affinity to cannabinoid receptor
  - Metabolism:
    - Reduction of keton to hydroxyl, excretion via urine
    - 7-OH-thujon, dehydrothujon – also active
- Absinthism
- Oscar Wilde:
  - „After the first glass [of absinthe] you see things as you wish they were. After the second, you see things as they are not. Finally, you see things as they really are, and that is the most horrible thing in the world.“

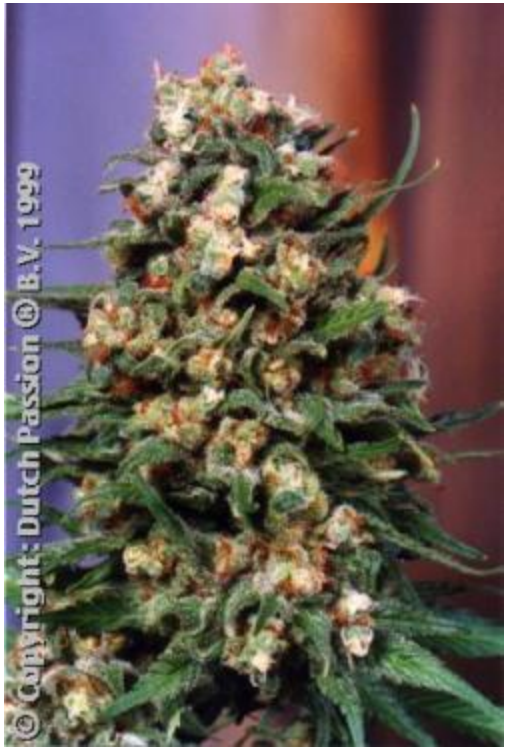
French method
Bohemian method

Blanche
Verte
Absenta
Hausgemacht
Bohemian-style

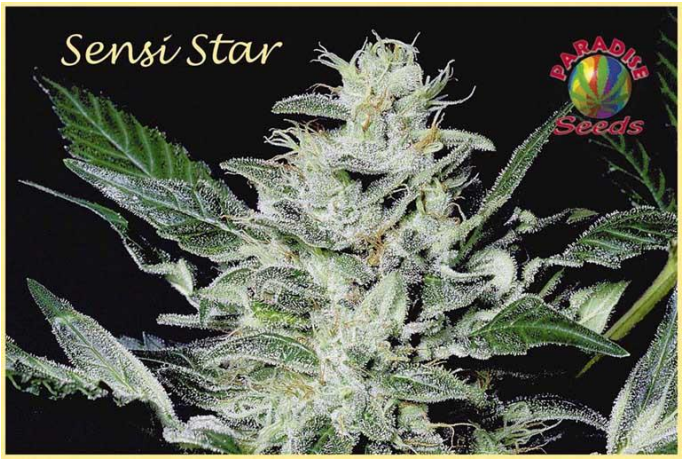
Cannabis spp.

- *Cannabis indica* Lam., *C. sativa* L., *C. ruderalis* Janisch.
- **Shen-nung** (2737-2697 B.C.)
  - malaria, constipation, rheumatism, Gynecologic problems
- **Vine with hemp resin**
  - Surgical anaesthetic
- **European folk medicine**
  - asthma, cough therapy
  - epilepsy, sleep disorders, convulsions
  - pain, rheumatism
  - Externally
  - Skin inflammations and infections
- **Todays application**
  - glaucoma
    - Lowering of intraoccular pressure
  - nausea, vomiting, anorexia
  - cancer (*in vitro* and *in vivo* start of apoptosis – malignant gliom, breast cancer)
  - Parkinson disease, sclerosis multiplex
  - Immunomodulation – Crohn disease
  - Antibiotic and antiviral effect

AK-47

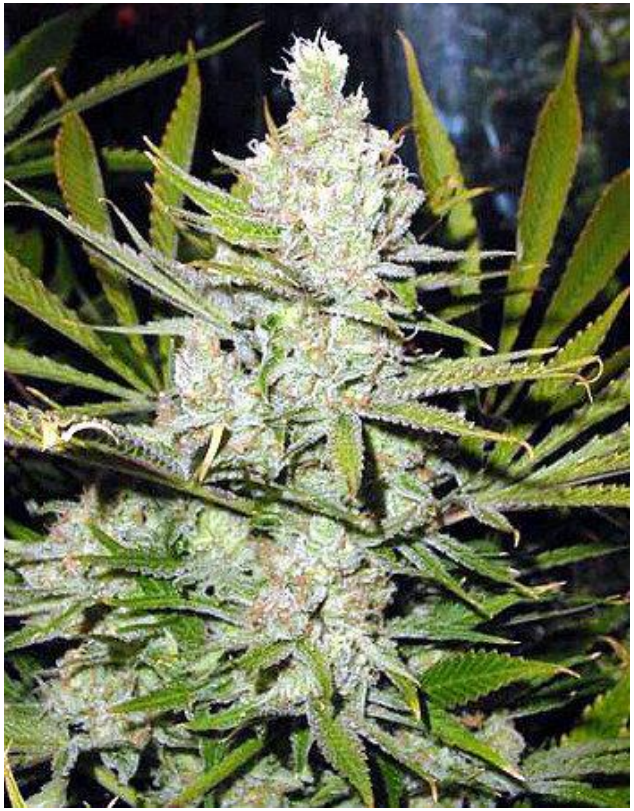


Skunk n.1

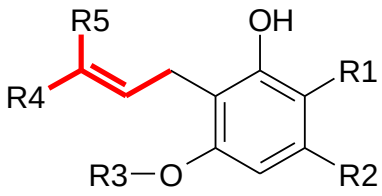


Sensi Star

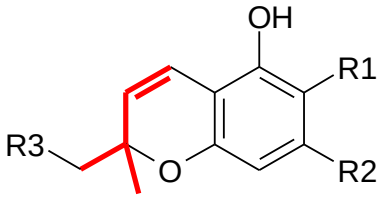
Jack Herer



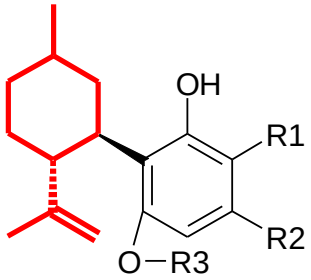
Nothern Lights



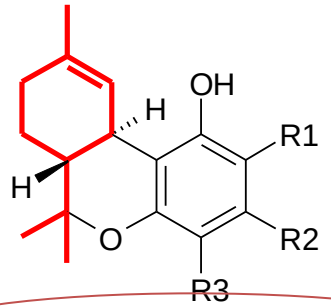
CBG-type cannabinoids



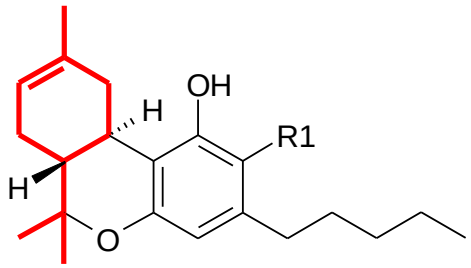
CBC-type cannabinoids



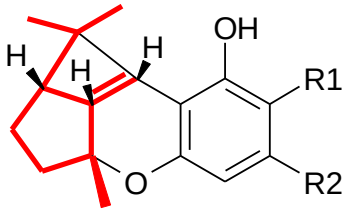
CBD-type cannabinoids



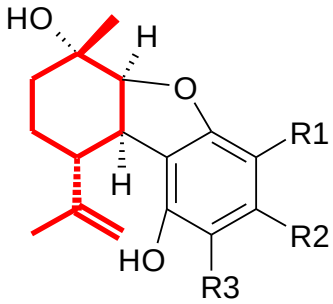
delta9-*trans*-THC-type cannabionoids



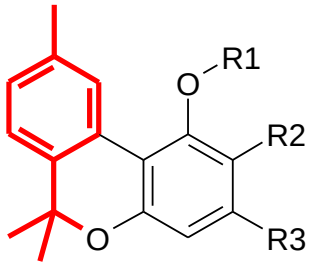
delta8-*trans*-THC-type cannabionoids



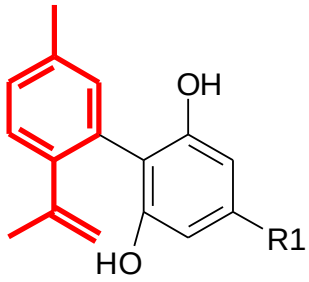
CBL-type cannabinoids



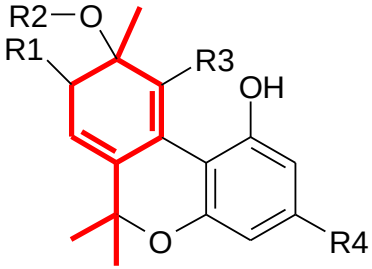
CBE-type cannabinoids



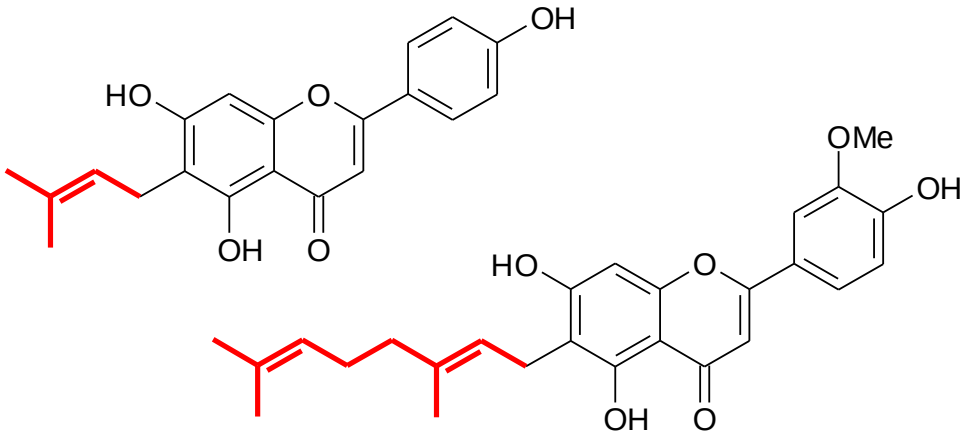
CBN-type cannabinoids



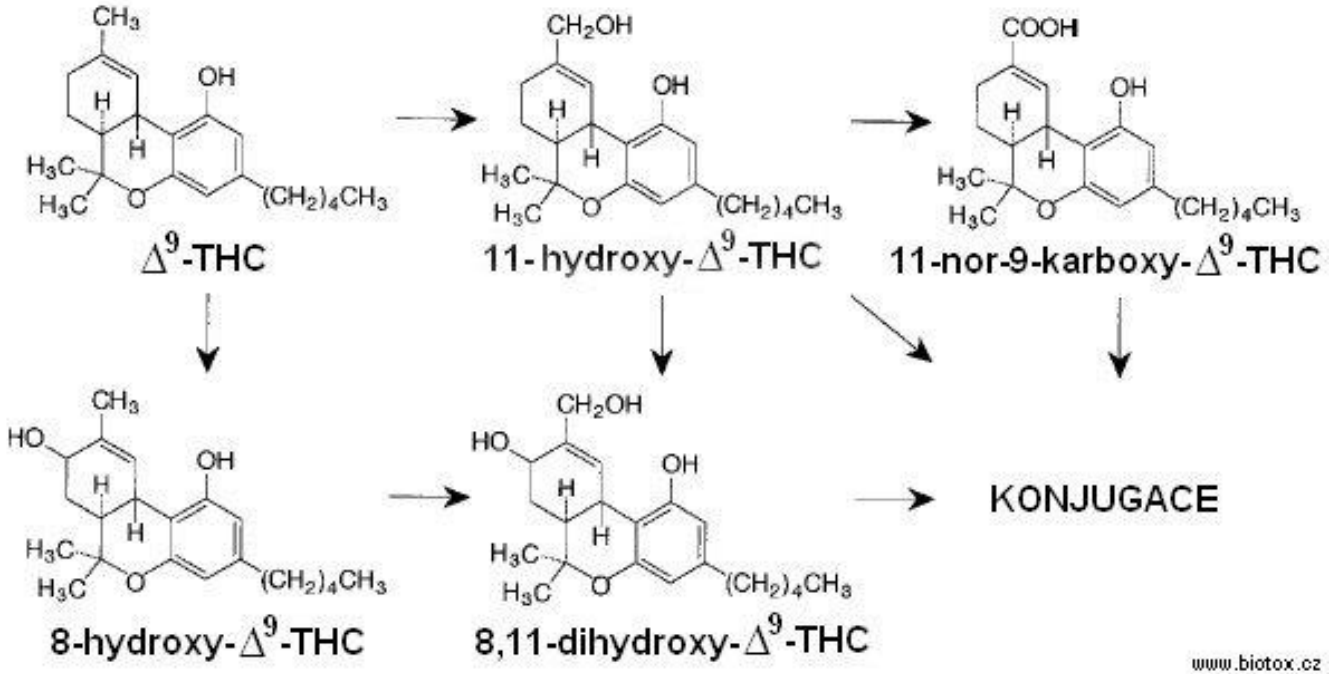
CBND-type cannabinoids



CBT-type cannabinoids

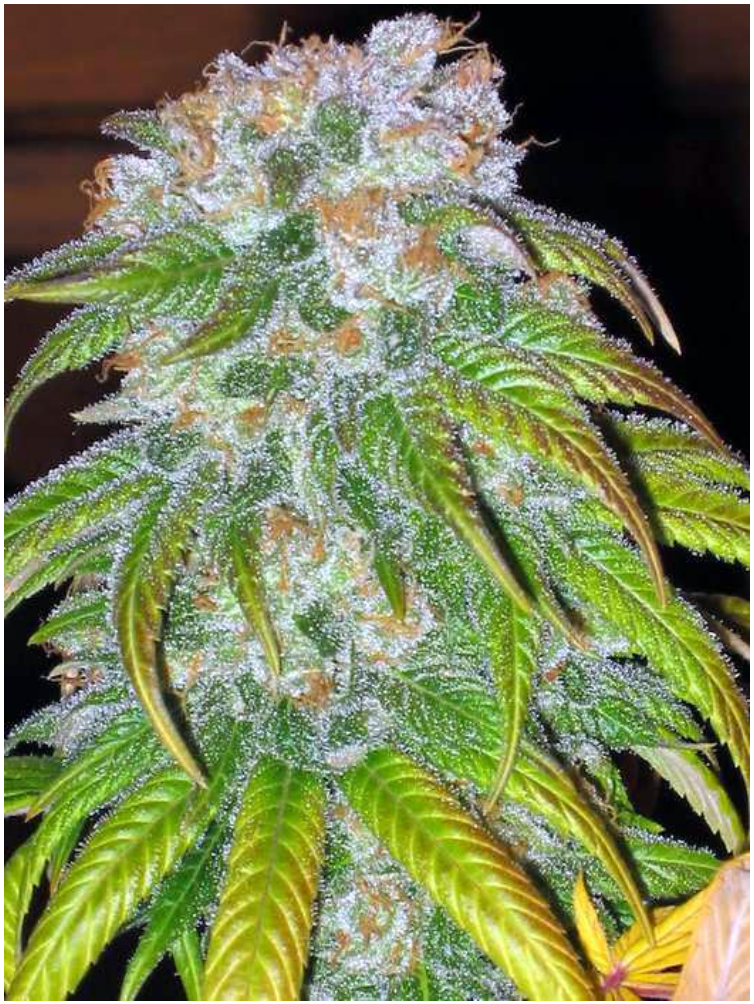


- **Cannabis as drug – THC content**
  - **Marihuana** (female inflorescence) cca 1% THC
  - **Hašhish** (resin obtained by chipping or munching of female inflorescence cca 5 %
  - **Hashish oil** (extract) 20% THC
- **Main contain THC** (levorotary form), CBD (canabidiol) – sedative and antibiotic effect, canabinol (CBN) – high amount of CBN - effect similar to THC, but with feeling of fatigue and drowsiness
- **THC is oxidized by air oxygen** (higher temperature increases effect) to non-active compounds
  - Should be stored in cold and hermetically closed wessels
- **THC soluble in fat and alcohol** (lipophilic), non well in water
- **Biotransformation**
  - Cumulation in organism
  - Half-time 27 days

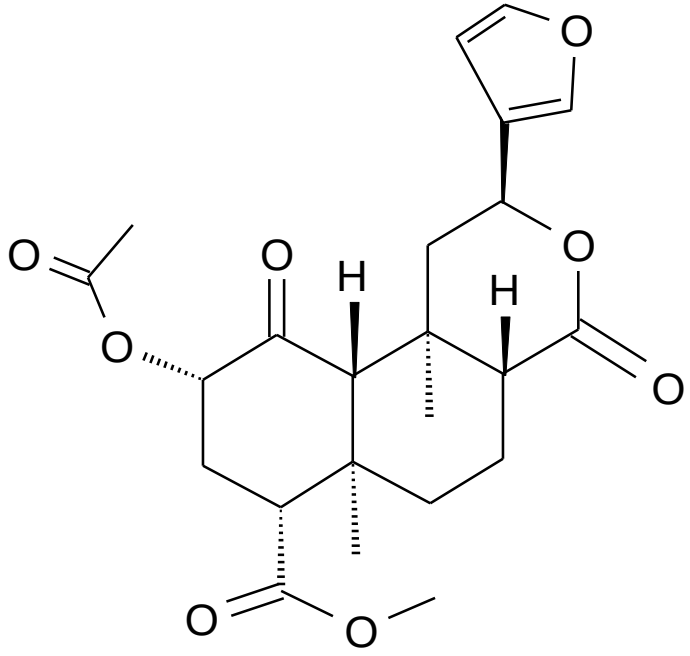


- Cannabis as a drug
  - Way of application
    - Inhalation, smoking
    - Peroraly

- **Cannabis as drug – effects**
  - **Psyche** – effect on CNS
    - Canabinoid receptors
      - THC
      - Endogennous canabinoids
  - **Lungs** – smoking
    - Similar to tabacco
    - Little bit different style of smoking
    - 1 joint – 9 cigarettes
  - **Fertility**
    - Effect on spermias
  - **Effect on foetus**
    - Slower development of children
  - **Risk of higher occurence of schizophrenia**?



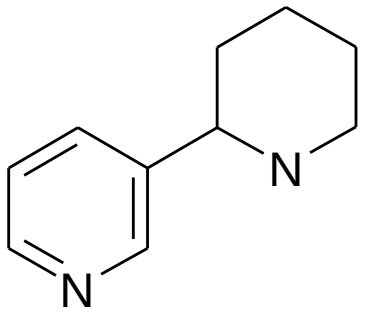
– **Salvinorin A**
  - Diterpen of clerodadiene type
  - *Salvia divinorum* Lamiaceae
  - Hallucinogenic
  - Shamanic plant, *Hierba de la Pastora*

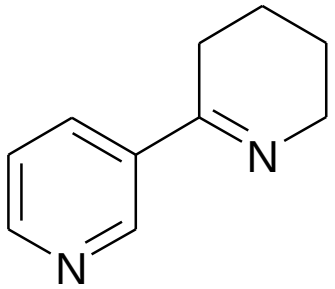


- ***Salvia divinorum***
  - 100 grams of drug
    - Chewing
    - Maceration
  - Smoking of dry leaves and extracts
  - **Effect**
    - Euphoric states
    - Colored visions and hallucinations
    - Rush
- **Salvinorin A**
    - Selective inhibitor kappa-opiod receptors
    - Agonist of D2 receptors
    - Do not affect 5-HT_{2A} receptor

"Salvia Dalinorum" by Luke Brown. www.spectraleyes.com

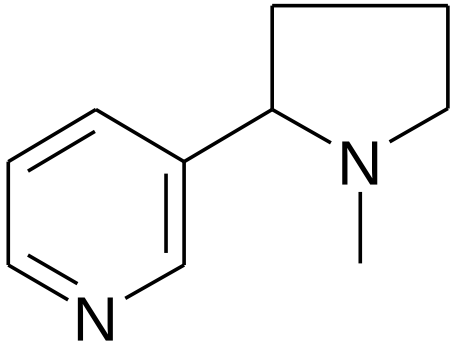
- Anabasine
  - *Nicotiana* spp. Solanaceae
  - *Anabasis* aphylla Chenopodiaceae
  - Similar to nicotine
  - Highly toxic
  - Often intoxications
  - Teratogen
    - Poultry, cattle, pigs
    - So called arthrogryposes
- Anabaseine
  - *Aphaenogaster rudis*



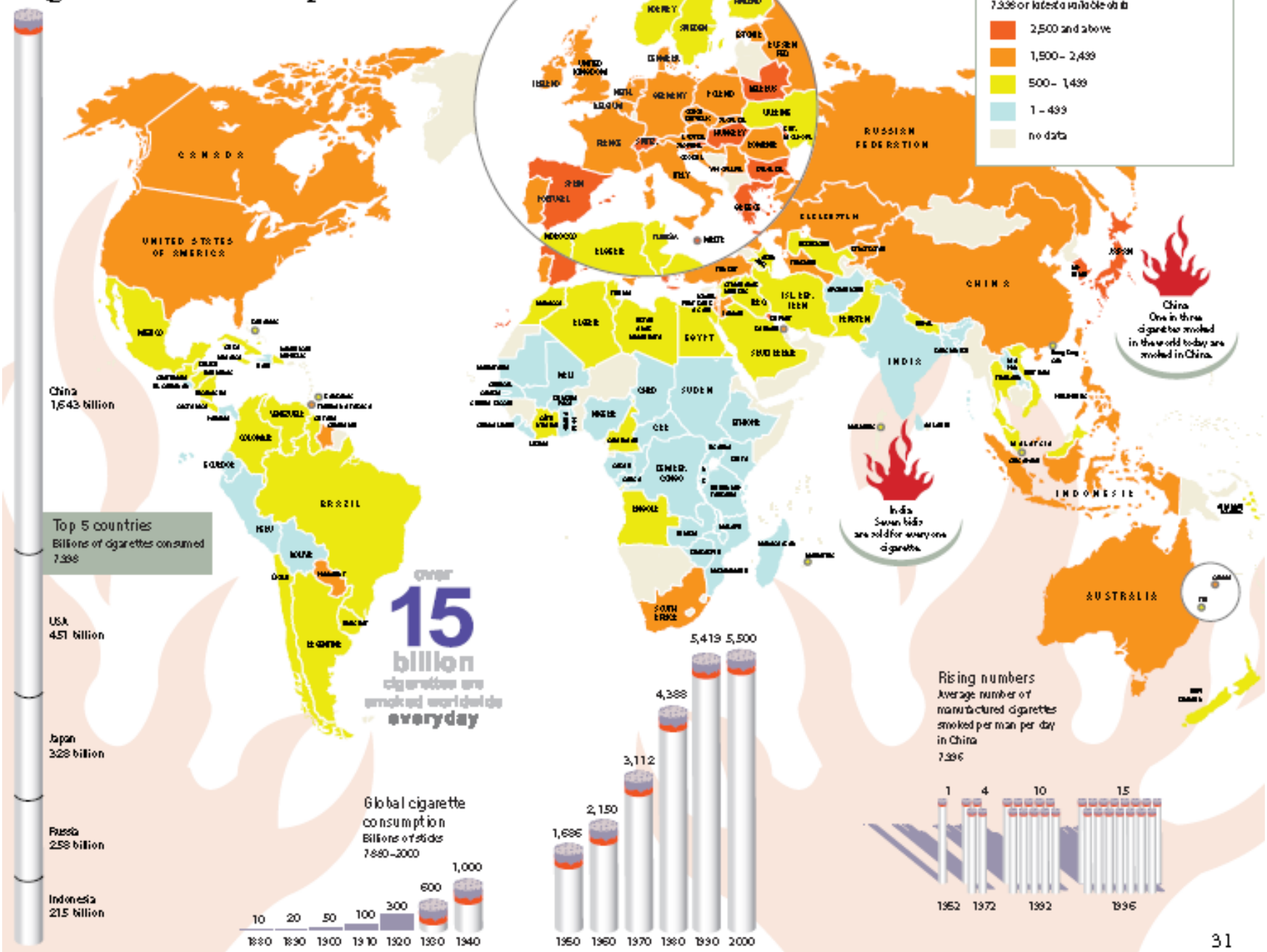


- **Nicotine**
  - *Nicotiana* spp. Solanaceae
  - Highly toxic
  - Common intoxication
  - N-receptors – parasympatomimetic

  Acute intoxication
  - Smoking: headache, pallenes, cold sweat, tremor, vertigo, nauzea and vomiting
  - Perorally: higher doses produce starting nausea with deep breathing, vomiting, furthermore tremor, convulsions, death caused by paralysis of respiratory muscles. Dose of 40-60 mg of nicotine is deadly up to 10 minutes

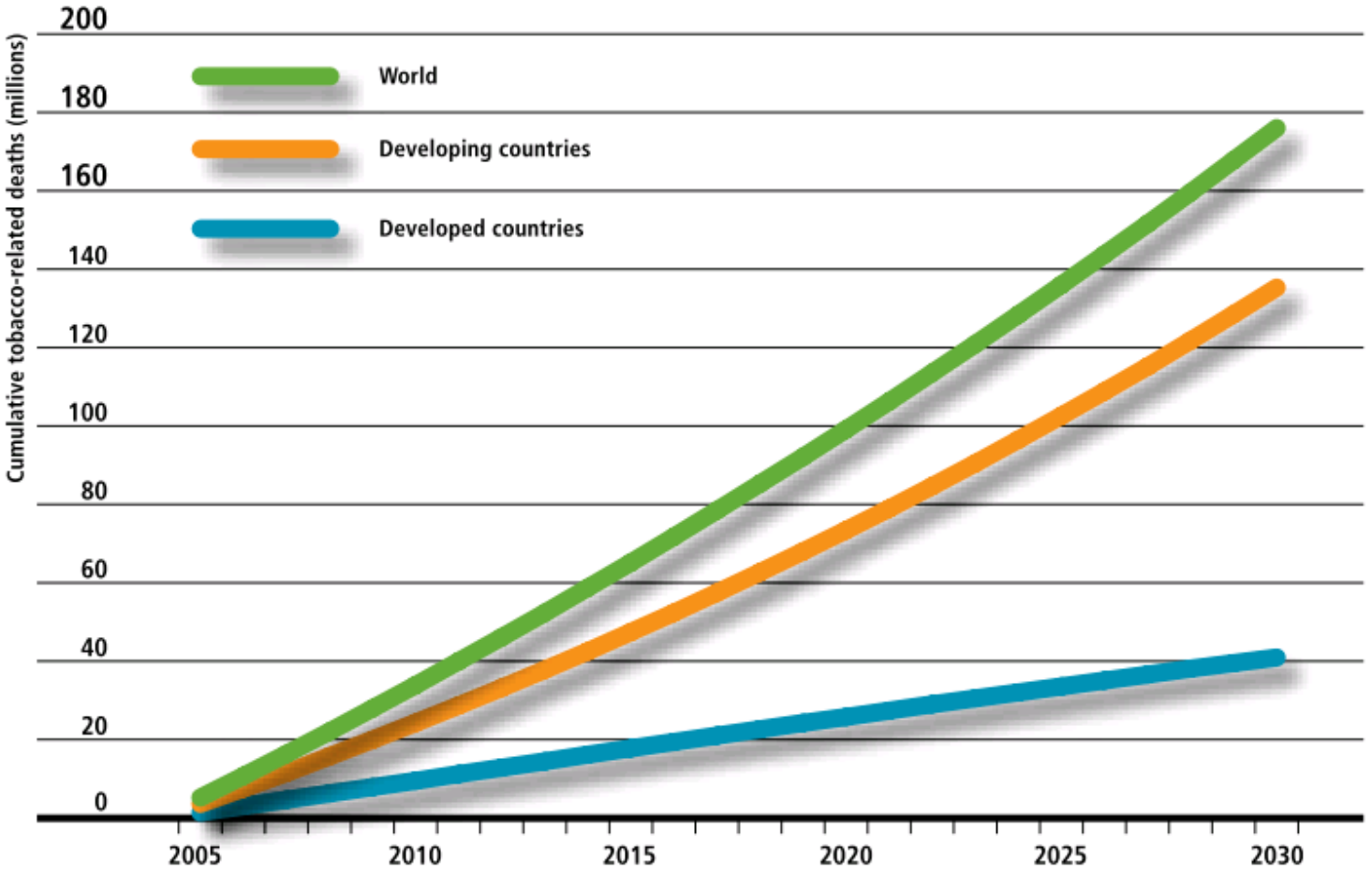


Cigarette Consumption



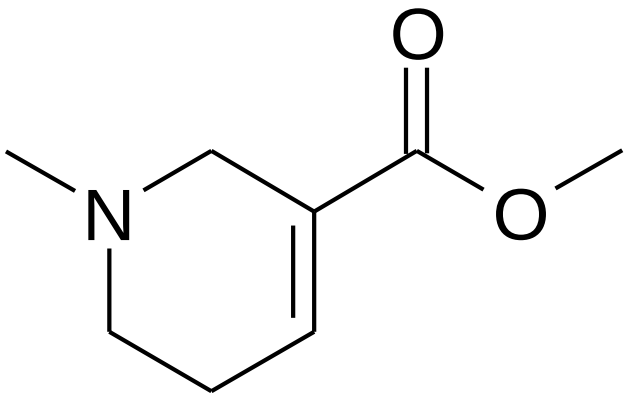
TOBACCO WILL KILL OVER 175 MILLION PEOPLE WORLDWIDE BETWEEN NOW AND THE YEAR 2030

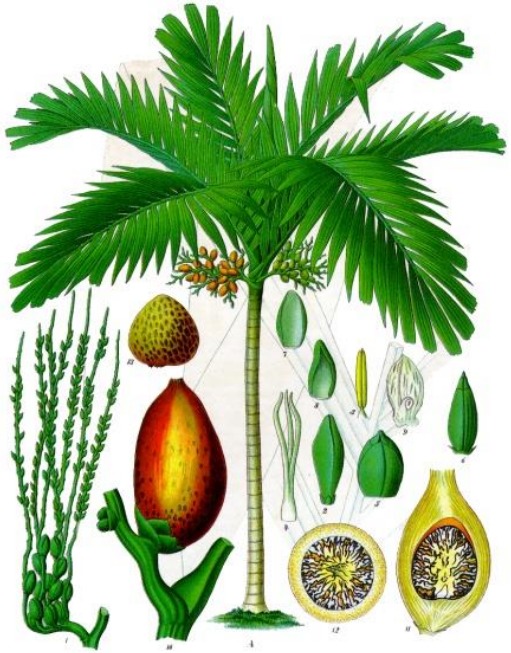
Cumulative tobacco-related deaths, 2005–2030



Source: Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Medicine*, 2006, 3(11):e442.

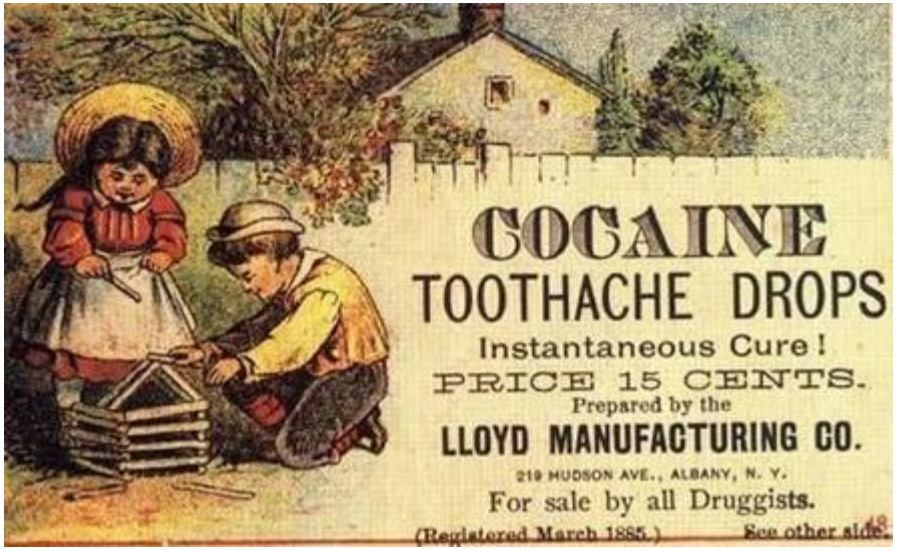
- Arecoline
  - *Areca catechu* betel Arecaceae
  - Muscarine effect
  - Higher doses can affect also nicotinic receptors
  - Salivation, perspiration, miosis

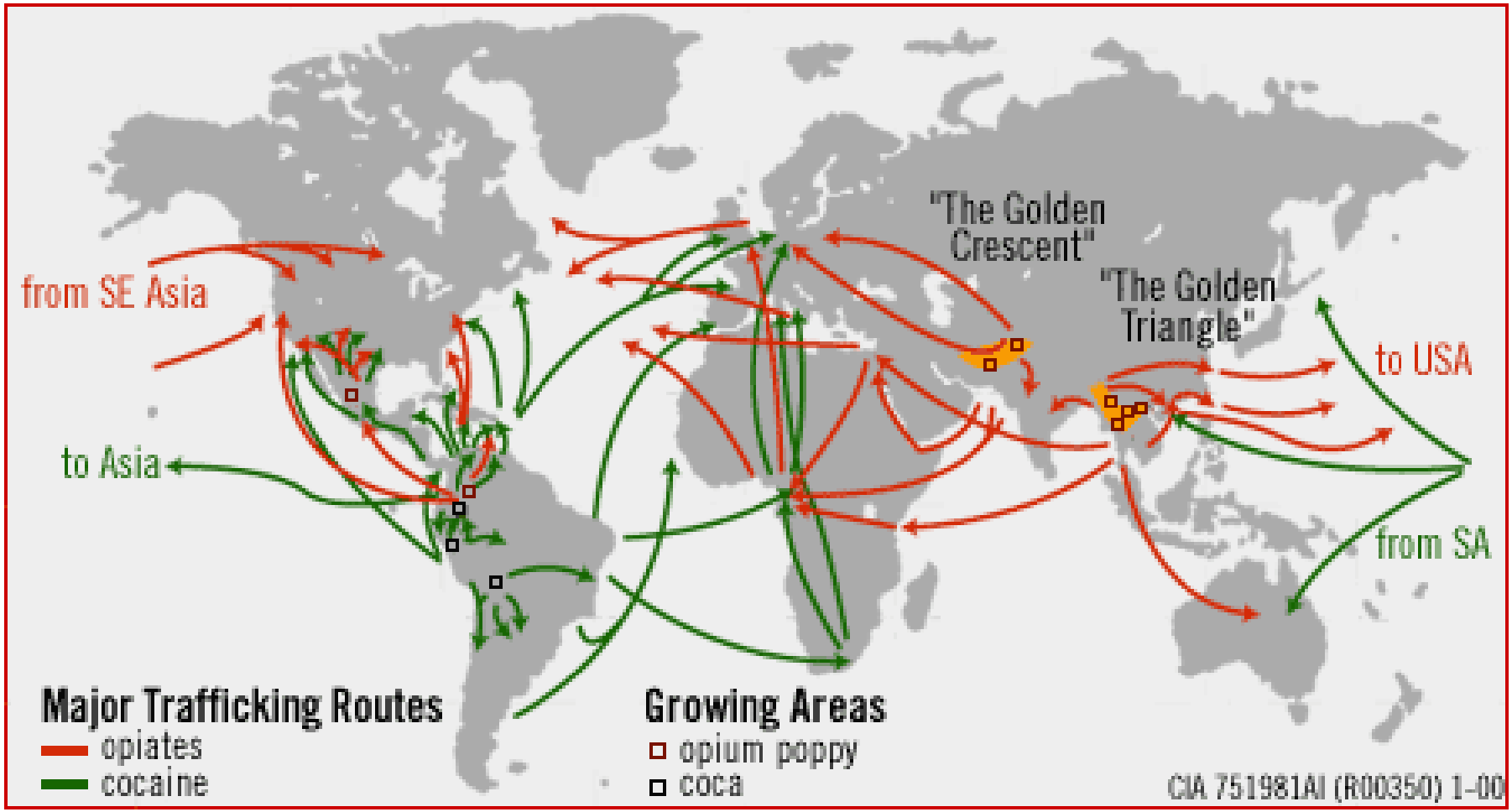


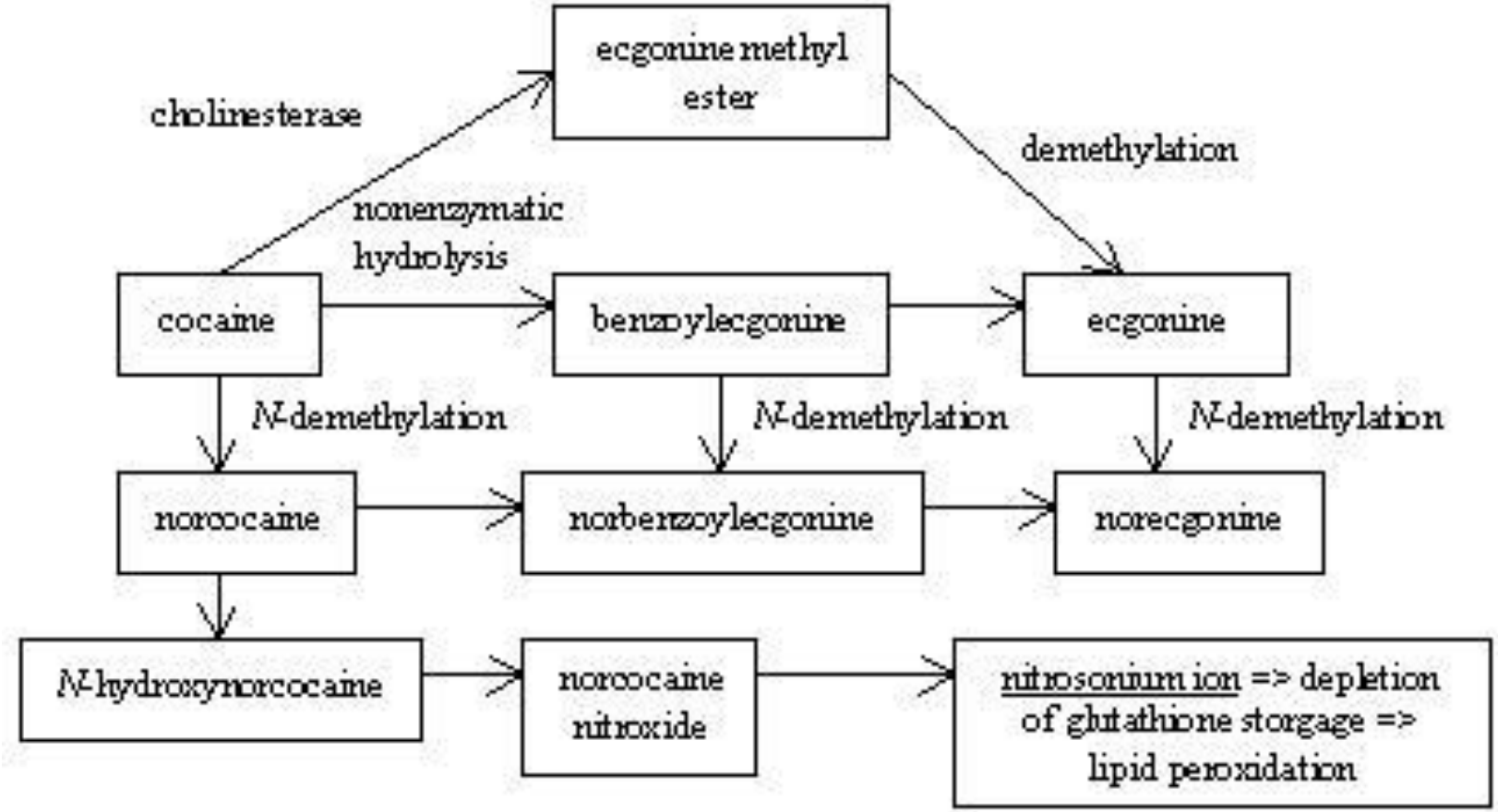


Areca catechu L.
Image processed by Thomas Schoepke
www.plant-pictures.de

- **Cocaine**
- *Erythroxylon cocca*, Erythroxylaceae
  - History
    - Indians for tribe of Chibcha
    - Inkas
    - Spanish
    - Coca-cola till 1904
    - 1860 Albert Niemann – pure cocaine
    - Sigmund Freund, Carl Coller



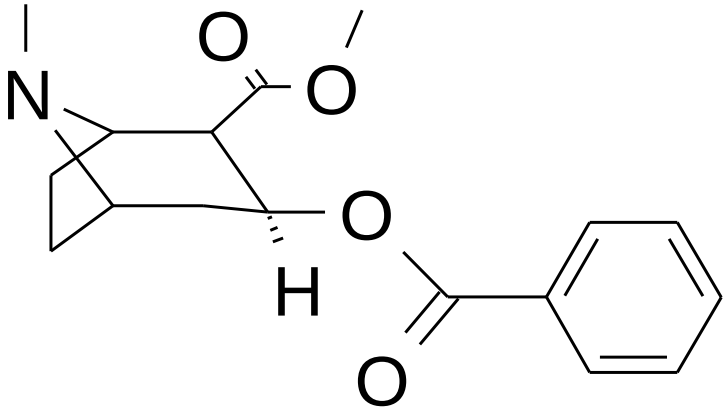

"The Golden Crescent"
"The Golden Triangle"
from SE Asia
to Asia
to USA
from SA
Major Trafficking Routes
opiates
cocaine
Growing Areas
opium poppy
coca
CIA 751981AI (R00350) 1-00



–Metabolism

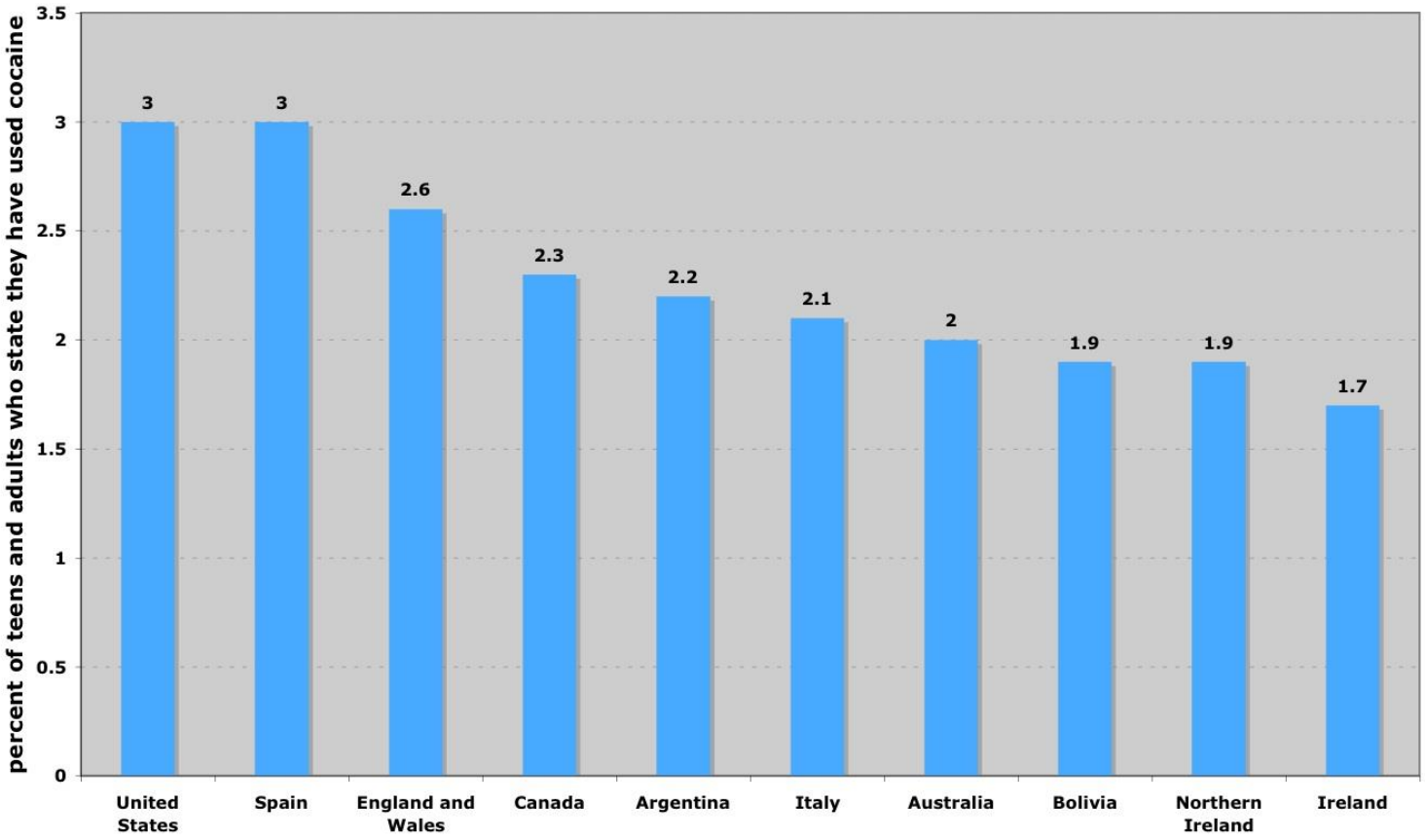
– Formation of ethylderivate during ethanol intoxication

- **Mechanismus účinku**
  - Indirect sympatomimetic (inhibitor reuptake of noradrenaline)
  - Block of ion channels of neurons (disorder of signal transmission)
  - Adrenergic stimulation
- **Peripheral effects**
  - Vazoconstriction, hypertermia, mydriasis
  - Low doses - ↓ of heart rate
  - High doses - ↑ of heart rate, cardiac arrest
- **Central stimulation**
  - Euphoria, exhaustion of neurotransmiteres (NA), short depressive effect
  - Rise of psychic dependence
    - Does not trigger physical dpendence
  - Intelectual stimulation, hyperactivity, hyperlucidity
  - Self-delusion, paranoid psychosis



- Cocaine
  - Complication during usage
    - Cardiovascular arrest
  - Way of administration
    - As chlorid or base
    - Chlorid
      - Snuffling, i.v.
    - Base
      - Smiking (crack), inhalation
    - Mixture with heroine
      - snowball
    - Mixture with alcohol
      - Cardiotoxic
      - Highly euphorizing

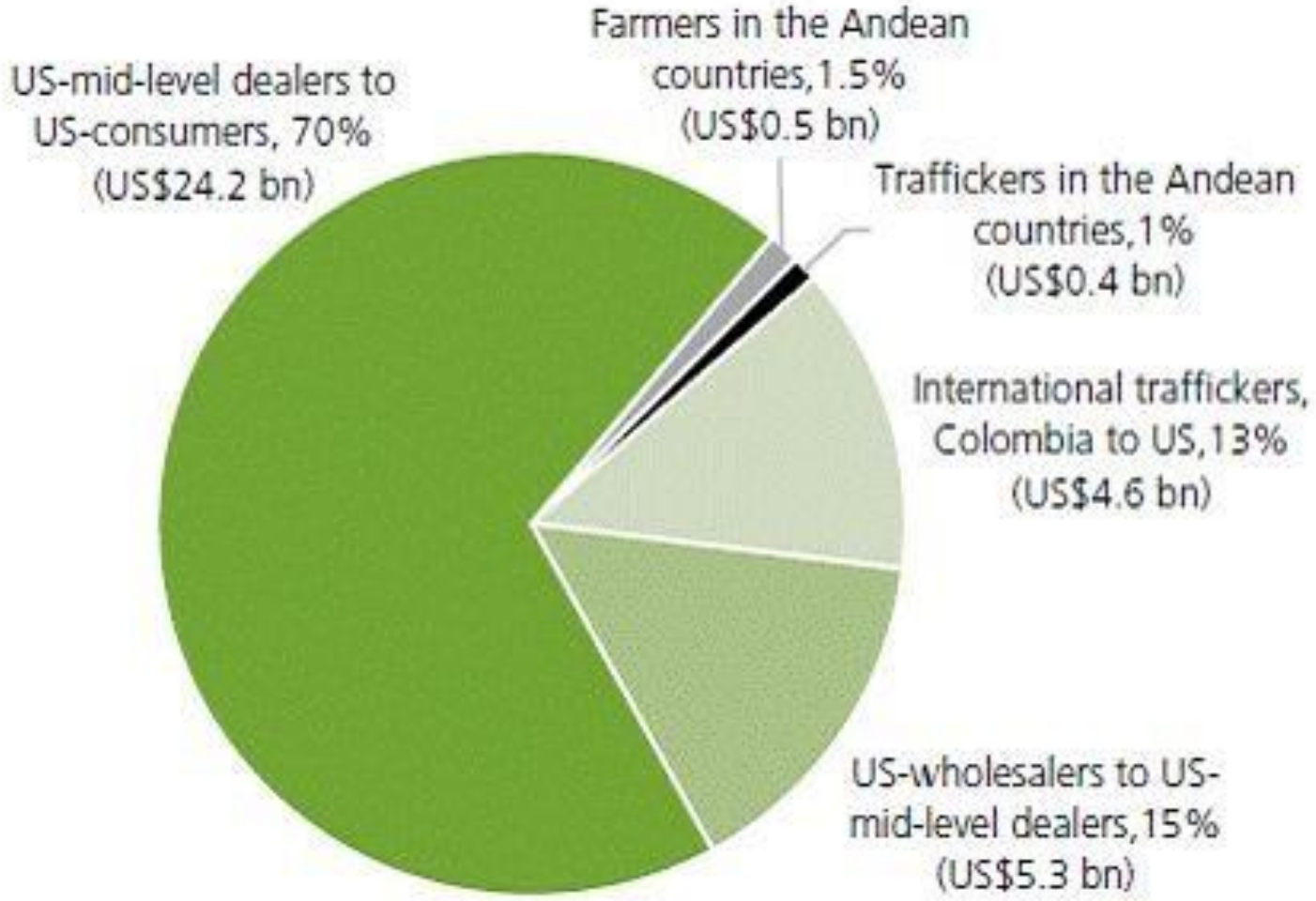
Top Ten Cocaine Using Countries



Data from the United Nations Office on Drugs and Crime
http://www.unodc.org/unodc/en/illicit-drugs/index.html

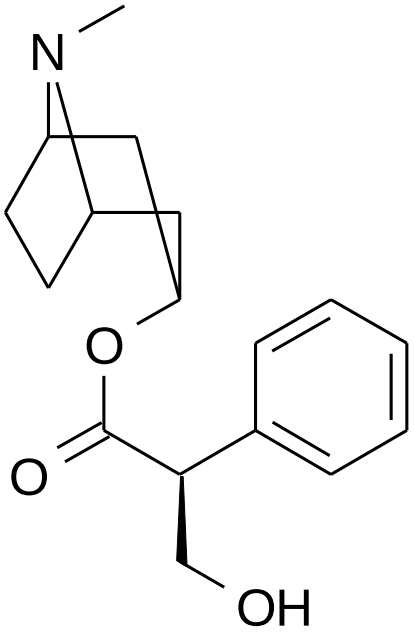
FIG. 87:

DISTRIBUTION OF GROSS PROFITS (IN %) OF THE US$ 35 BILLION US COCAINE MARKET, 2008

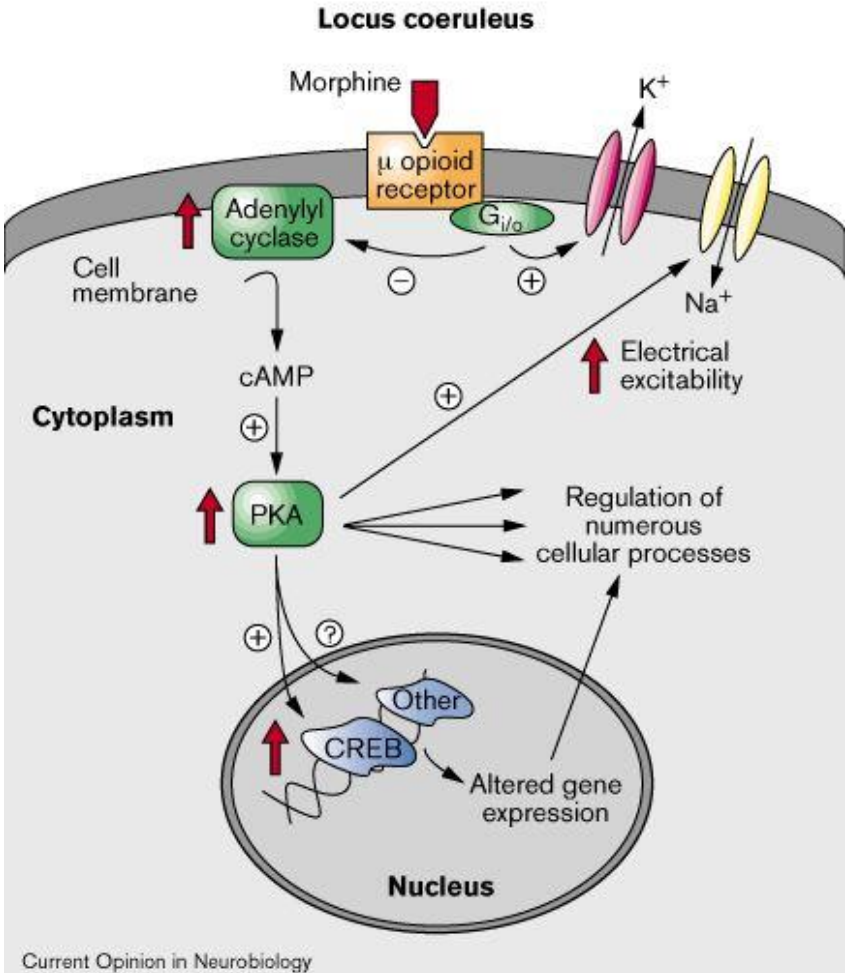


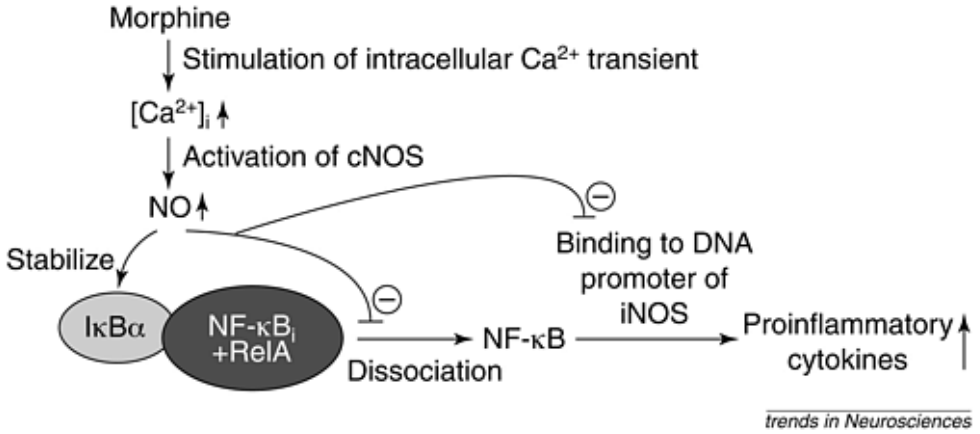
Source: Original calculations

- Tropane alkaloids
  - Azabicyclo[3,2,1]octan
  - Apoatropin, atropin, hyoscyamin, scopolamin
  - Solanaceae
  - Parasympatolytics
    - Competitive antagonists of acetylcholinergic receptors
    - Muscarine type
  - Intoxication
    - Red pigmentation of face, dry mucose, thirst
    - Tachycardia, mydriasis
    - Hypertermia, central excitation, hallucination
    - Coma, respiratory failure

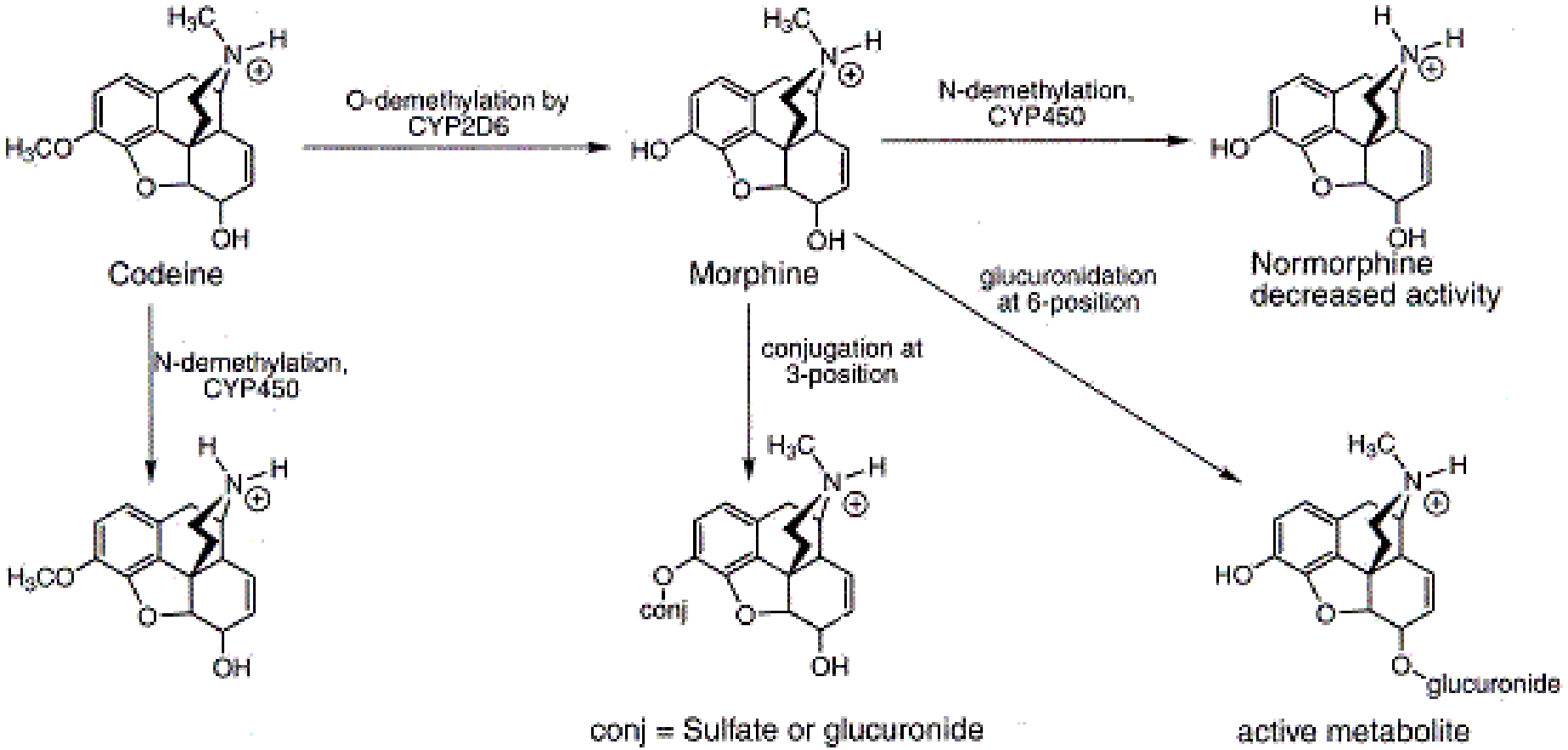


- **Morphine, codeine, heroine**
  - –Morphinan alkaloids
  - –Effective levorotary form
  - –Morphinan type of alkaloids
    - Typical for *Papaver* spp. Papaveraceae
    - Morphine
      - –*P. somniferum, P. setigerum* Papaveraceae
  - –Stereospecific, reversibile linkage to opioid receptors
    - At diiferent levels of CNS
  - –Agonist at presynaptic receptors of myelinized fibers of small diameter
    - Nociception, inhibition of substance P release
    - Uprise of physical dependance
      - –Inhibition of enkephaline production and simultaneous occupation of receptors
      - –Insufficiency of natural ligands and morphinans
        - » Withdrawal syndrome
  - –Effect on respiration
    - Depression of respiratory centre
      - –Decrease of sensitivity to hypoxia and pCO_2
      - –Dependent on dose
      - –Tempo of onset dependent on way of administration
  - –Miosis of central origin
  - –Depression of centre for cough
  - –Complex effect on centre for vomiting
    - Nausea and vomiting
  - –Influence on hypophysis
    - ↓secretion of FSH, LH, ACTH
  - –Influence on hypothalamus
    - ↑secretion of ADH
  - –Influence on fibers of smooth muscles
    - Constipation and urinary retention





- Metabolism of morphine



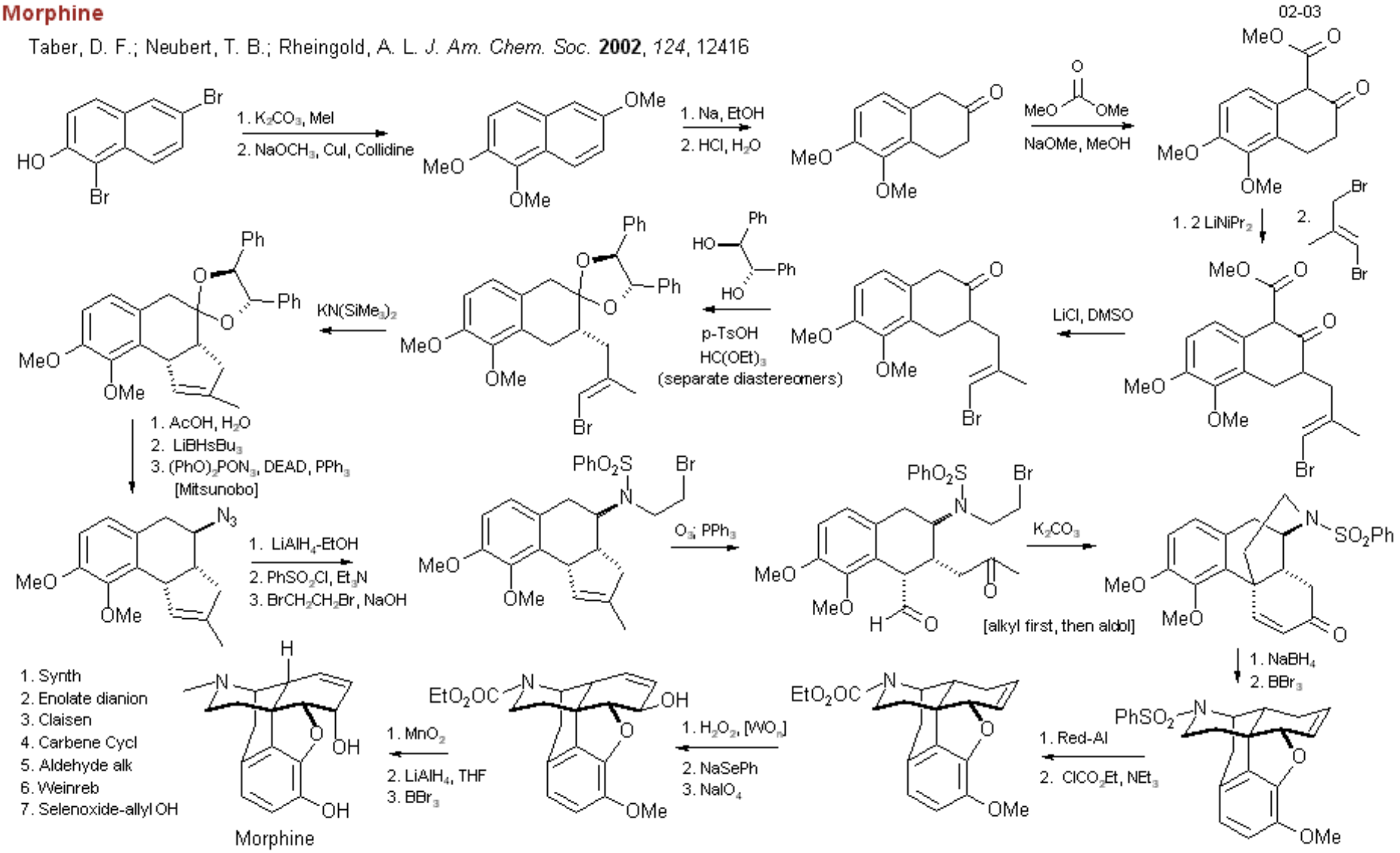
- Symptoms of withdrawal
  - Chronic users
    - Nasal bleeding, perspiration, lachrymation, anxiety
    - Mydriasis, myalgia and pain of joints
    - Insomnia, tachycardia, arrhythmias, polypnoe, dispnoe
    - Nausea, diarrhea
- Acute intoxication
  - Usually overdose from different reasons
  - High dosage
    - Immediate depression of CNS
  - Lower dosage
    - Initial short stimulation
    - Successive malaise, fatigue, somnolence
    - Heart rate decreases and tends to fade
    - Respiration slow and shallow
    - Loss of consciousness
    - Relaxation of muscles, extinction of reflexes
    - Cold, pale, wet skin
  - If the dose high enough
    - Coma, relaxation of muscles
    - Circulatory failure, cyanosis
    - Death caused by CNS depression
      - Respiratory arrest

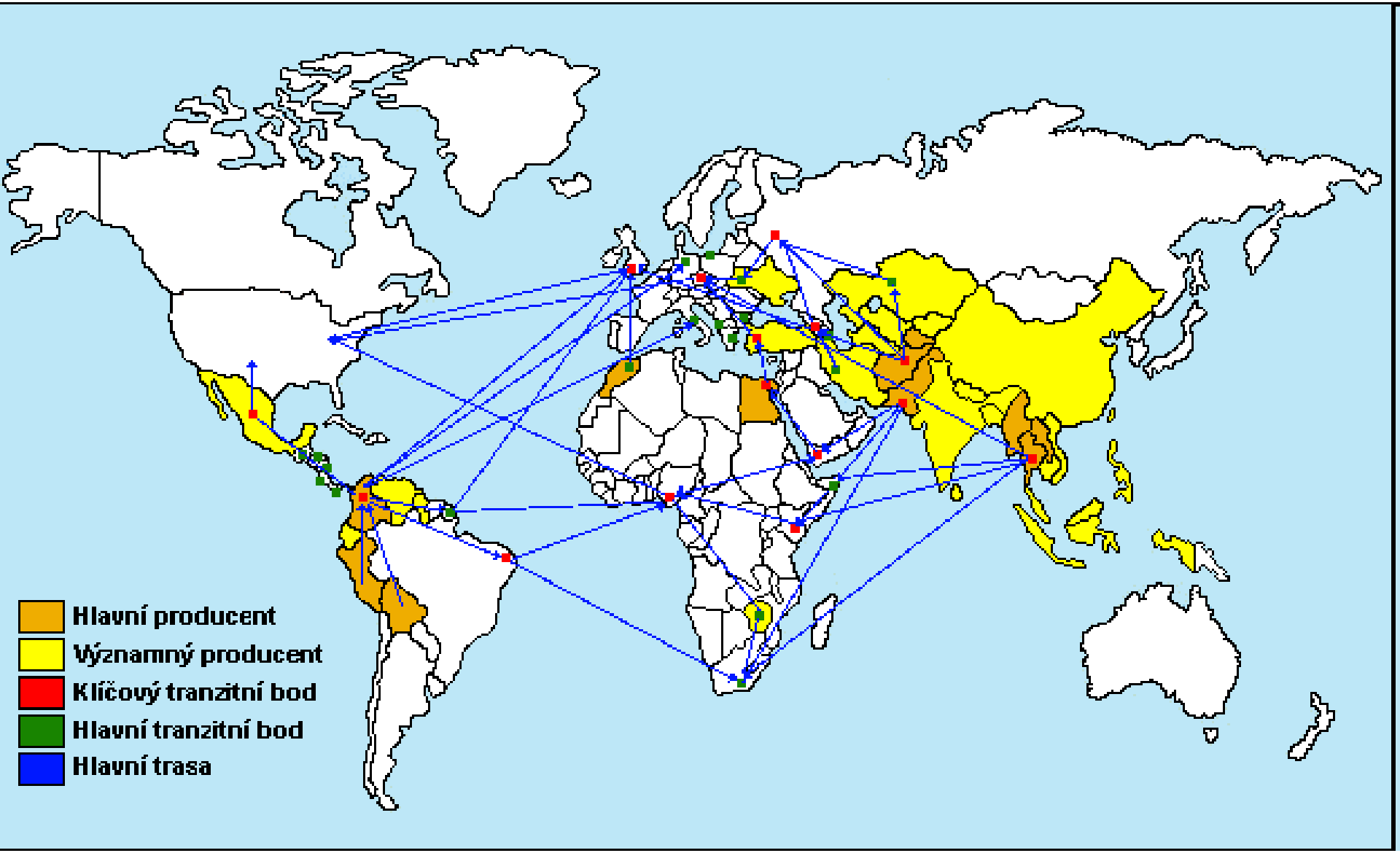
- Chronic intoxication
  - Morphinism
    - Short time of uprise
      - Strong analgetic
      - Experiments with drug
    - Tolerance to dosage
    - Combination of health problems
      - Social excomunication
        - » Psychical and physical dilapidation
      - Criminality
      - Prognosis adverse
        - » Accompanying diseases
        - » Suicidal tendences

Morphine

Taber, D. F.; Neubert, T. B.; Rheingold, A. L. *J. Am. Chem. Soc.* **2002**, *124*, 12416

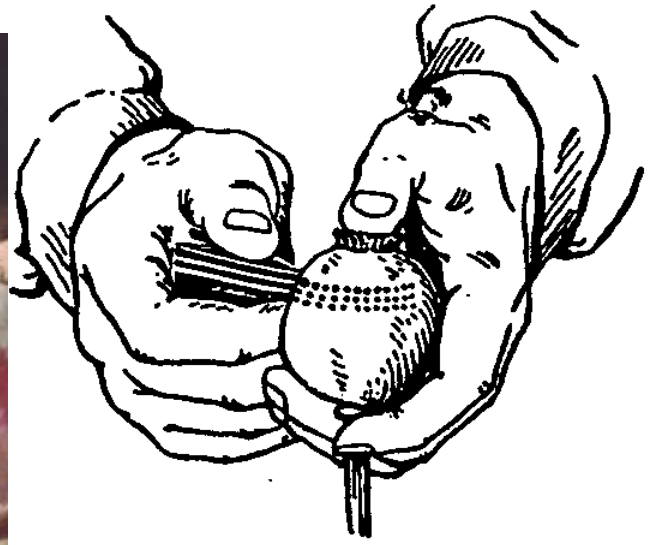
02-03

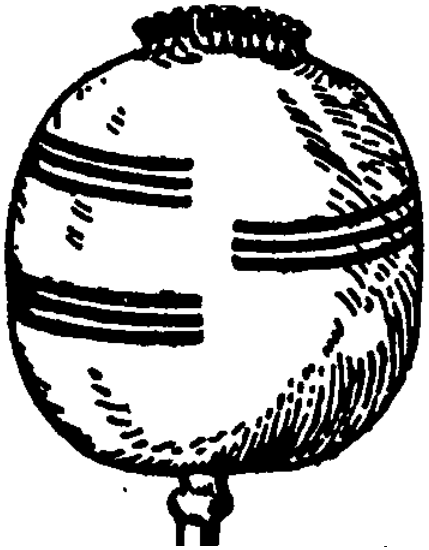


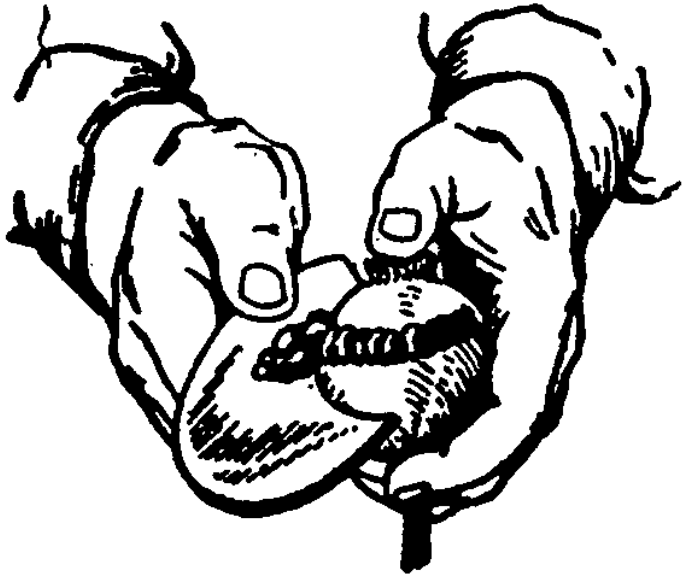


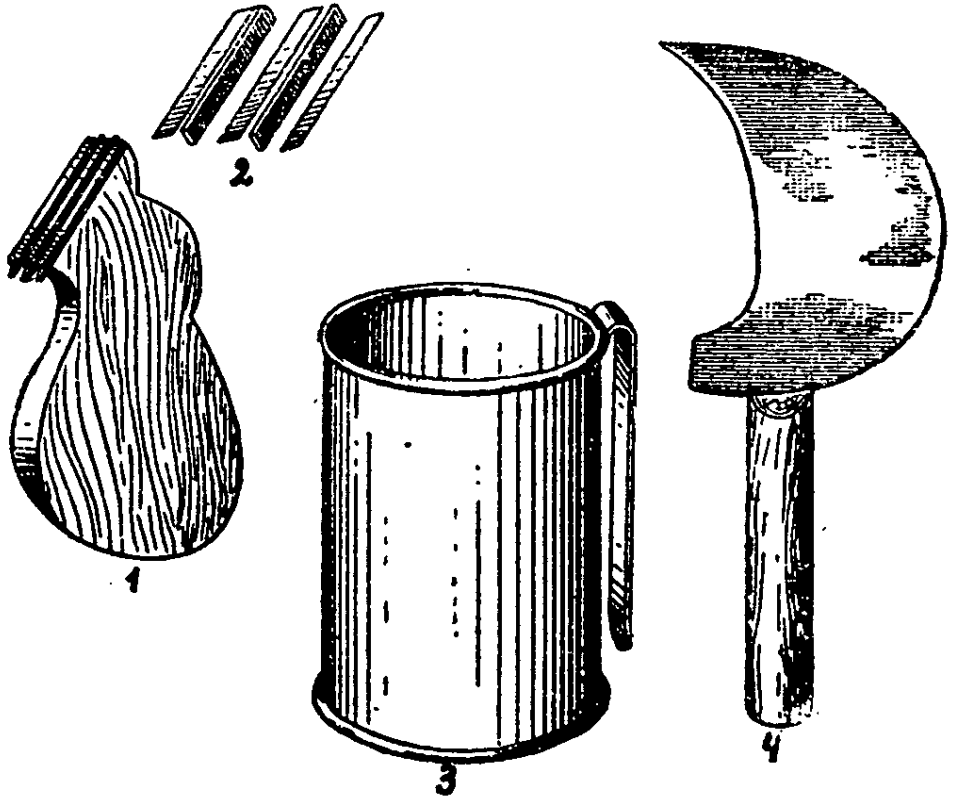
http://www.mujweb.cz/www/jpdepot/danger/Drugs.htm


www.rawa.or





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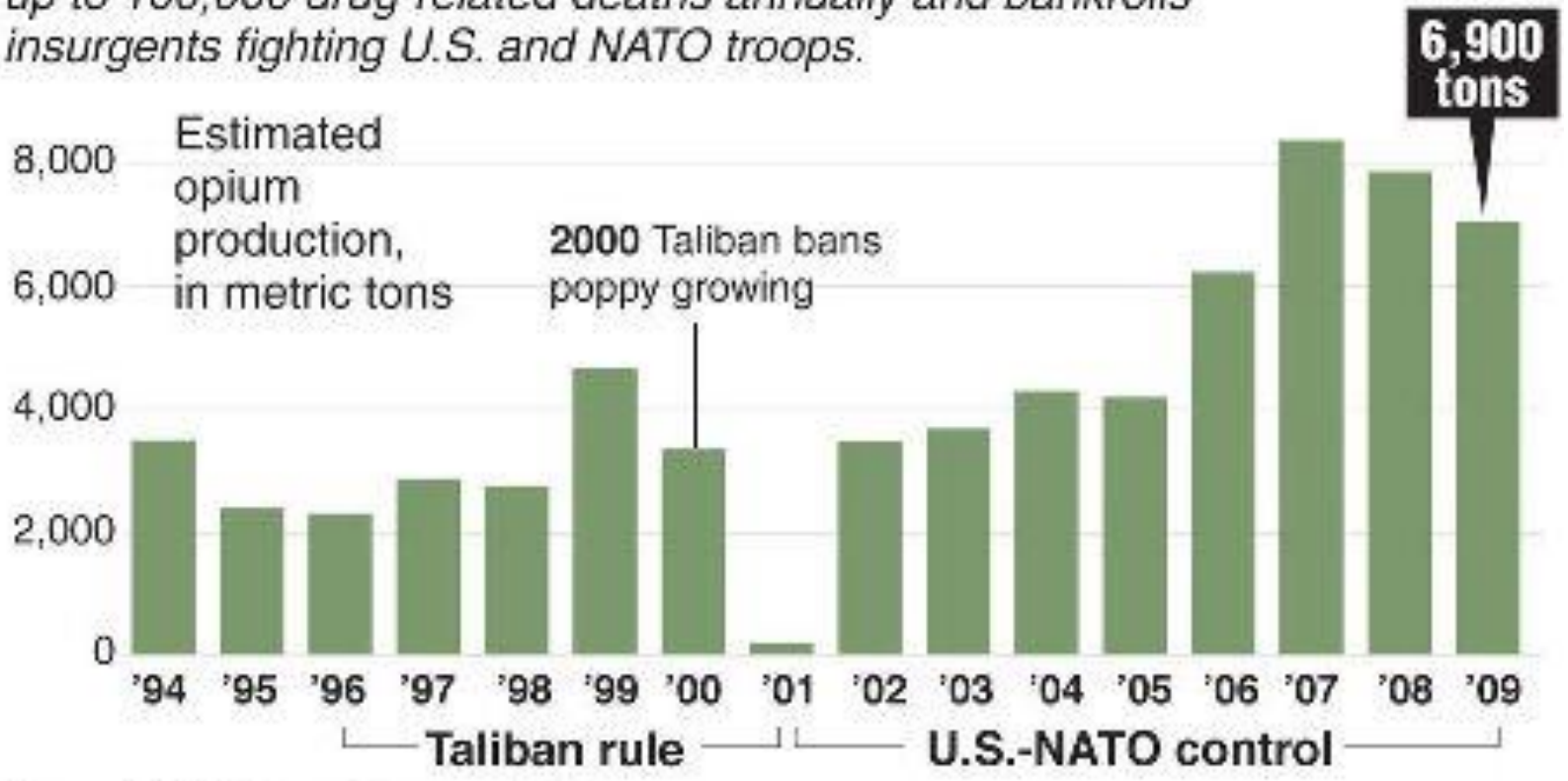
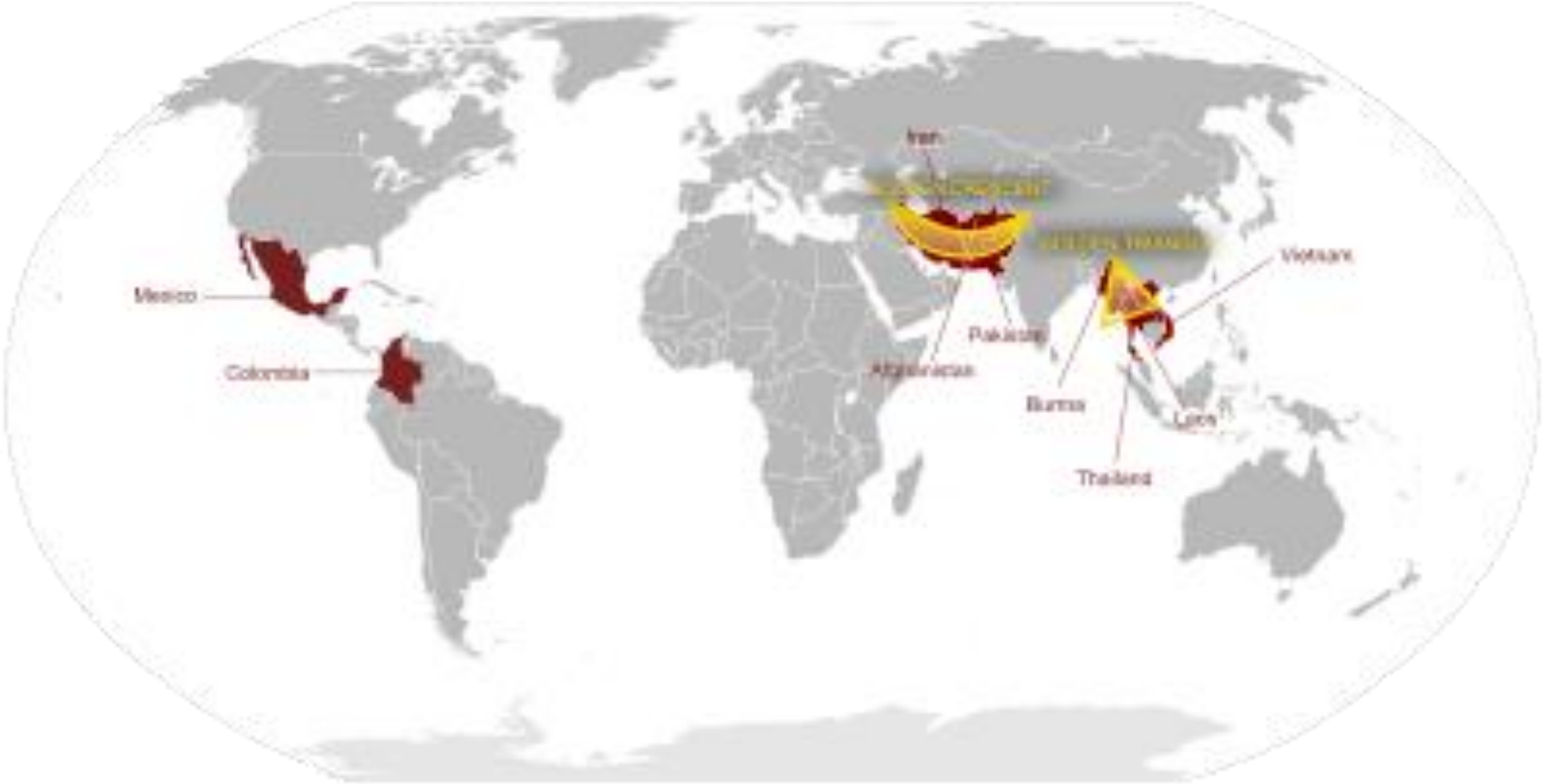
Afghanistan's deadly crop

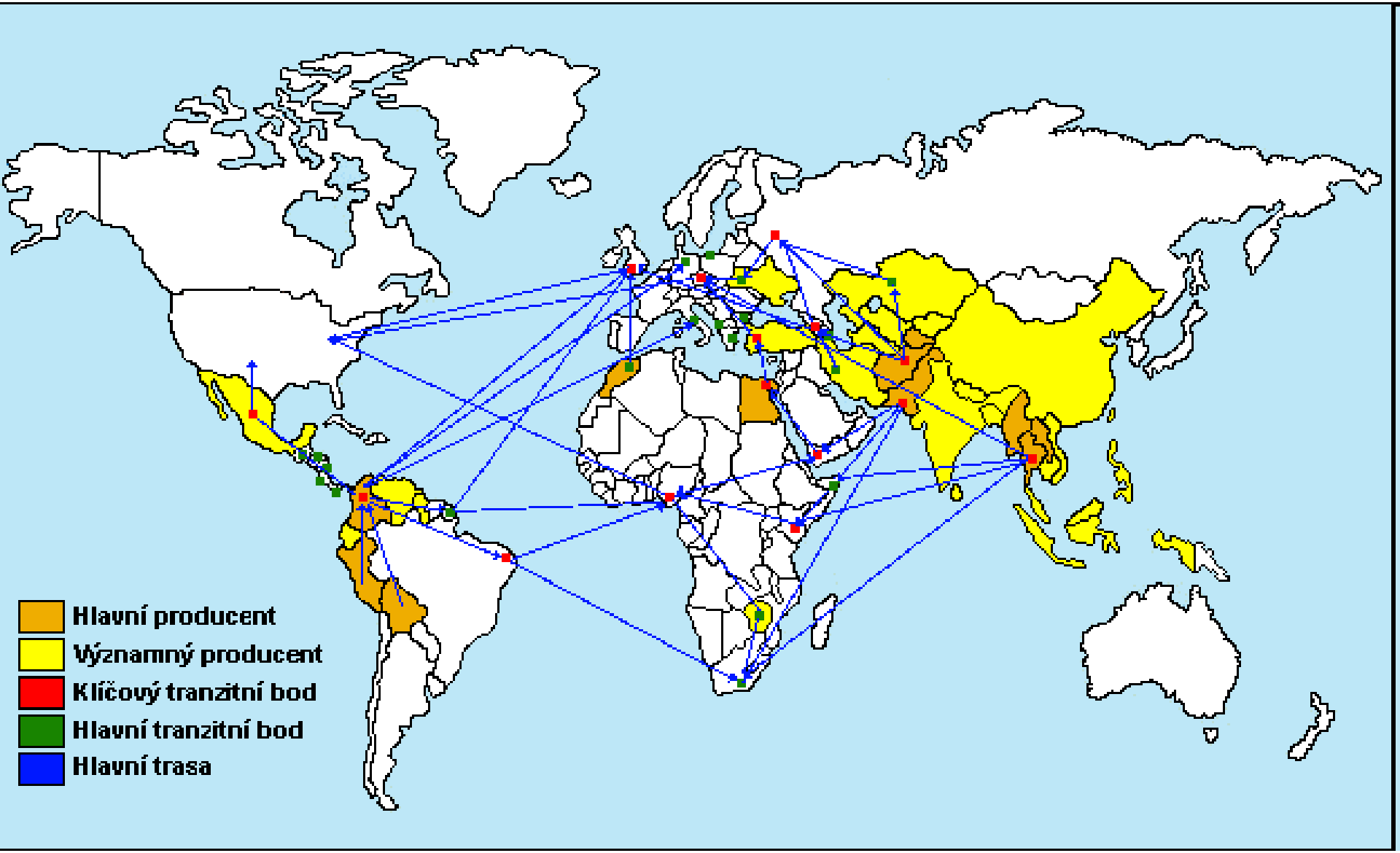
Afghanistan produces 90 percent of the world's opium. The drug causes up to 100,000 drug-related deaths annually and bankrolls insurgents fighting U.S. and NATO troops.*



Source: U.N. Office on Drugs and Crime
Graphic: Judy Treible

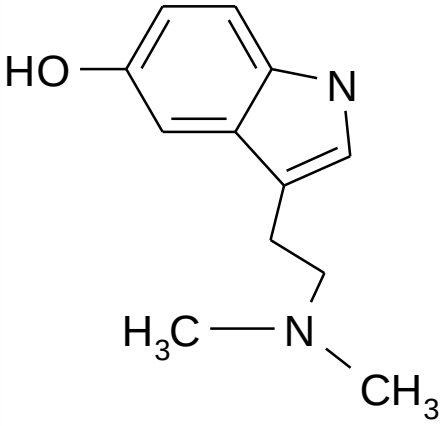
*Heroin is made from opium

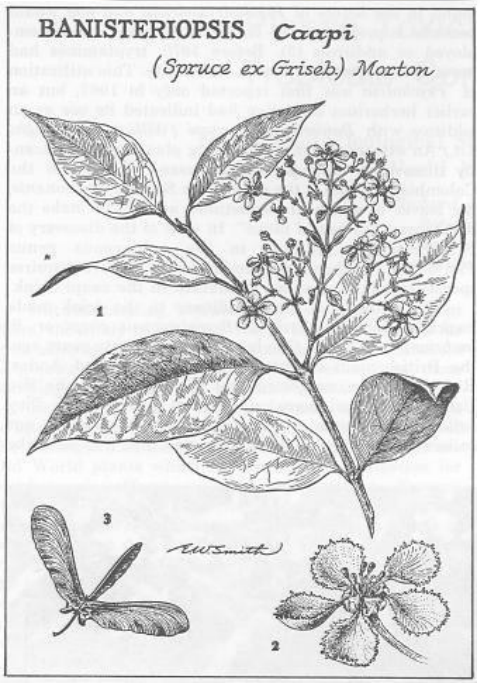

Iran
Mexico
Colombia
Pakistan
Afghanistan
Burma
Laos
Thailand
Vietnam

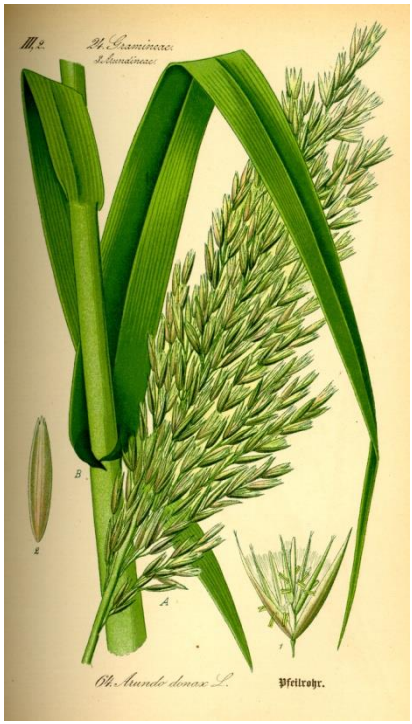


http://www.mujweb.cz/www/jpdepot/danger/Drugs.htm

- Tryptamines
  - Bufotenine
    - In water poorly soluble compounds
    - *Piptadenia peregrina* Mimosaceae
      - Cojoba Tree
    - *Arundo donax* Poaceae
    - Several fungi and frogs
    - Intoxication
      - Halucinogennic efect, influence on psychic
        - » Similar to LSD and mescaline
      - Frame of mind: anxiety, percetion disorders
      - Mydriasis, hypertension
      - High dosage
        - » Respiratory paralysis
        - » Motoric paralysis
  - *N*,*N*-dimethyltryptamine (DMT)
    - *Prestonia amazonica* Apocynaceae
    - *Piptadenia peregrina* Mimosaceae
    - Shortly effective halucinogennic compound
      - 0,7-1mg/kg
    - Model psychosis
      - Vegetative symptomatology
      - Emocional and perception disorders
      - Illusions and visions
      - Space-time distortions



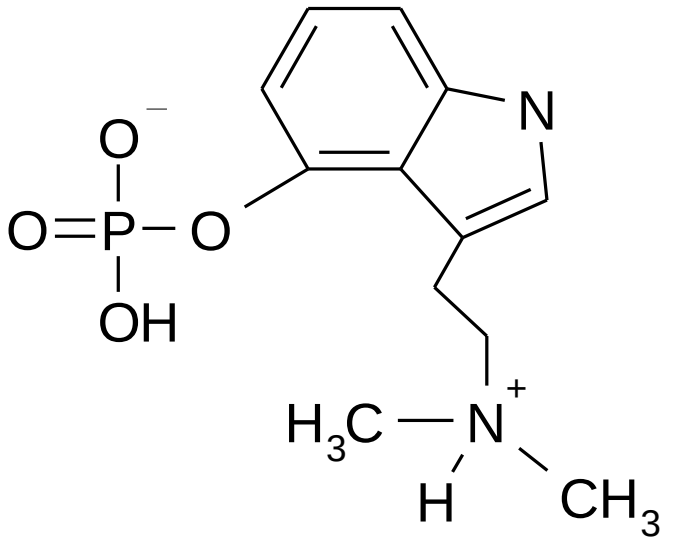




Tukanoan Indian with stems of three "kinds" of caapi preparatory to making hallucinogenic drinks from the bark. Rio Vaupes, Colombia. (Photograph by G. Reichel-Dolmatoff)

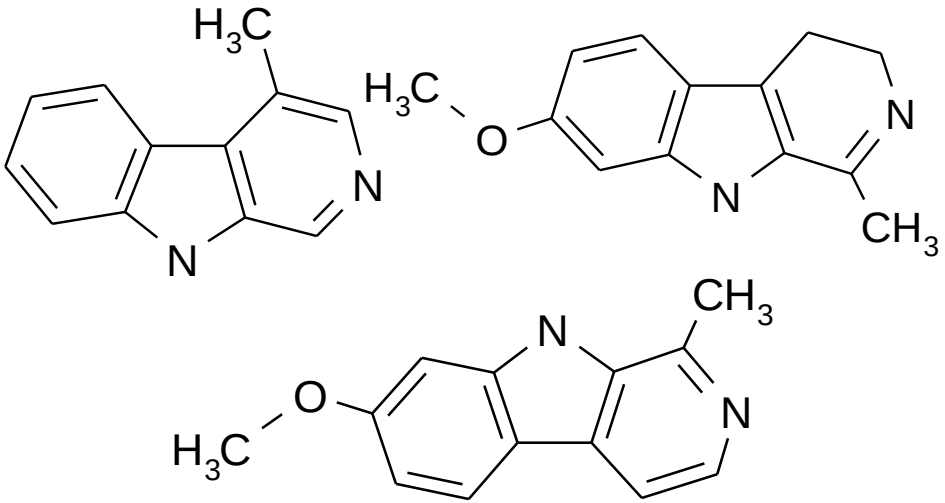

VIROLA
theiodora
(Spr. ex Bth.)
Warburg
2
1
3
E.W. Smith

- **Psilocyne, psilocybine**
  - ***Psylocibe, Conocybe, Stropharia***



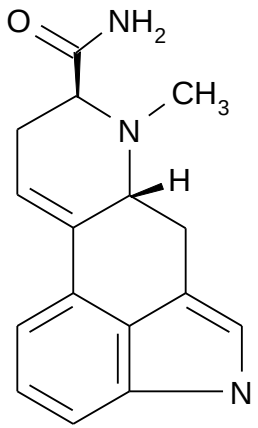
  - ***Psilocybe***
    - 0,2 % to 0,6 % of psilocybine
    - 10 mg p.o. dose
    - Chewing – better absorption from oral cavity
    - 8 hours for excretion cca 80 %, 5-6 hours of effect
- Starting symptoms
  - Headache, anxiety and weariness, unwitting yawning (often without drowsiness), extraordinary convulsions, balance disorders, tremor and sweating.
- Psychic symptoms
  - Deformation of reality perception, warm colored visions, caleidoscopic effect
  - Changes of mood, euphoria, happyness, extraordinary depression and irritation
  - Psychoses connected with depersonalisation, disorders of time perception, direction and distance, false imaginations
- Acute toxicity
  - Relatively low (deadly dossage of psylocybine for human is approx. 17 gramů)
  - Risk of hasty decisions
  - Latent psychic dideases (for example schizophrenia)

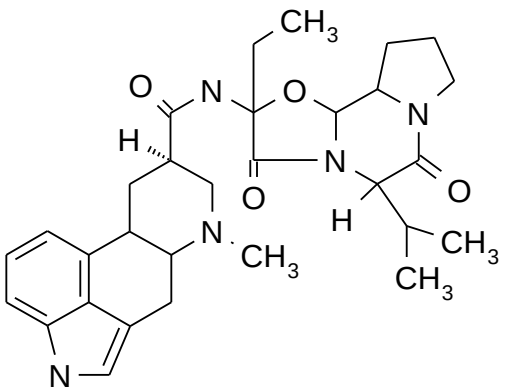
- β-carboline indol alkaloids
  - Harmane, harmaline, harmine
  - *Peganum harmala, Zygophylum fabago, Tribulus terrestris* Zygophyllaceae
  - *Passiflora incarnata* Passifloraceae
  - Inhibitory MAO
    - Elevated levels of neuromediators
      - » Serotonine, noradrenaline
    - Especially in brain
      - » Central effect
    - Early symptoms of intoxication
      - » Nausea, vomiting, pale skin
      - » Signs of aggression
    - Further progression
      - » Half-sleep with dreaming
      - » Hallucinations

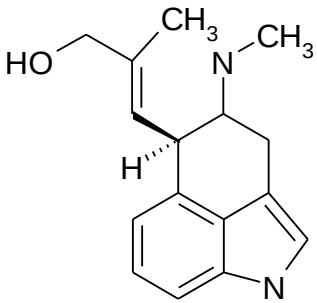


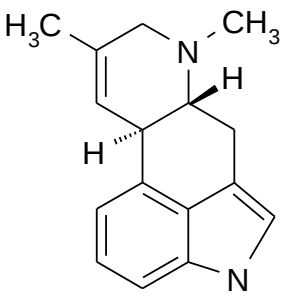
Peganum harmala

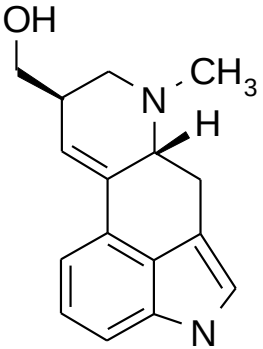
- Ergolines
  - Hlavně čeleď Convolvulaceae
    - *Rivea corymbosa*, *Ipomoea* spp.
  - Ergine (lysergamide)
    - Toxic dose 1 µg/kg p.o.
    - Mexican ceremonial drugs
      - Ololiuqui, coaxihuitl and further
  - Ergosine
    - Similarly to ergine
    - Inhibition of prolactine secretion
  - Chanoclavin
  - Agroclavine
  - Lysergol



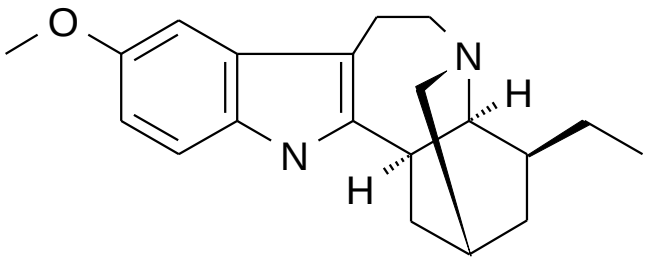


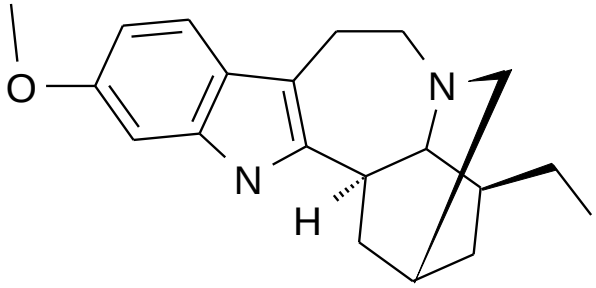


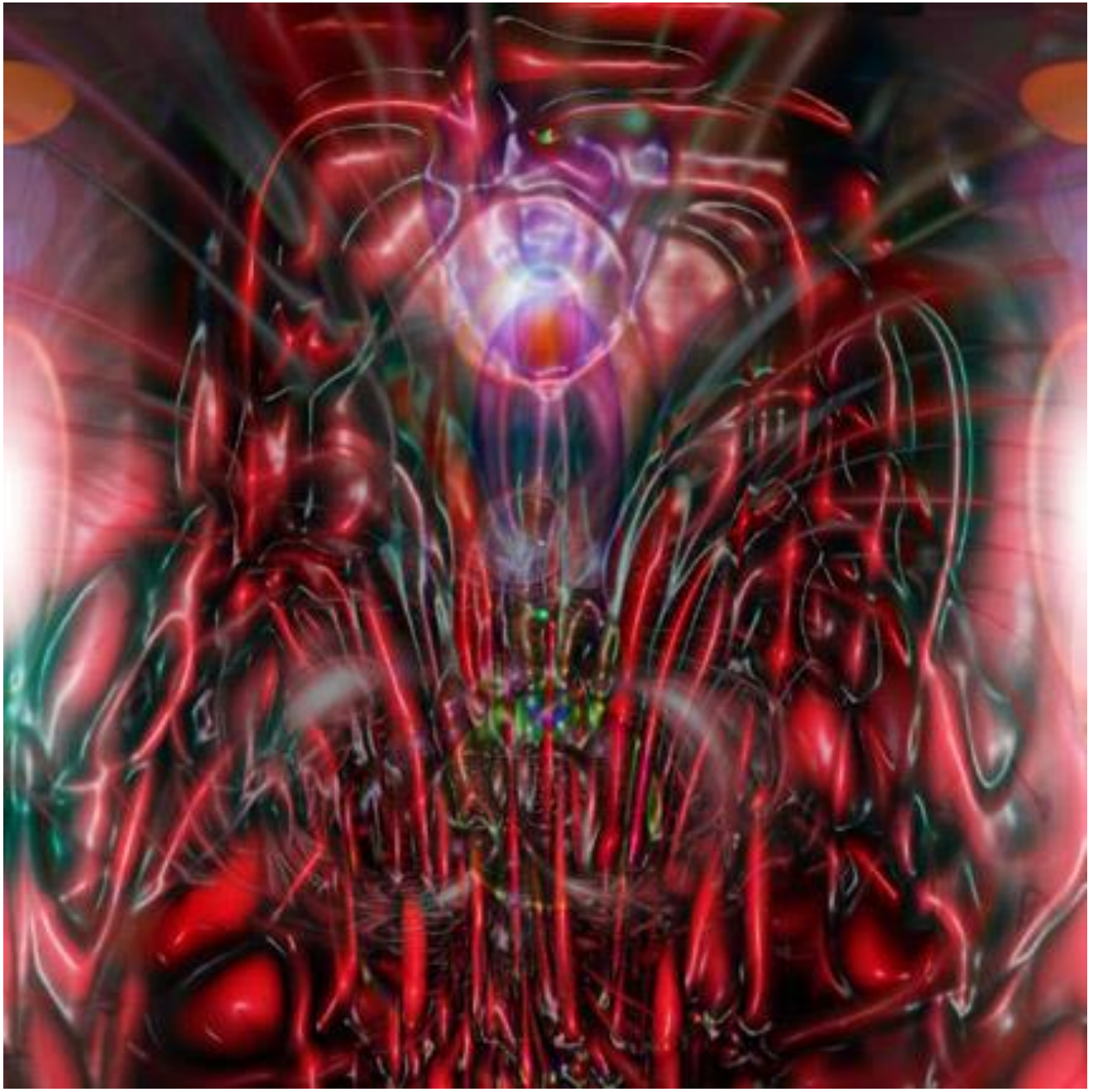




- Ibogaine, tabernathine
  - Tabernanthae iboga, Voacanga spp. Apocynaceae
  - Activity in CNS
    - Inhibitor of neronal nicotine receptors
    - Lower dosage
      - » Central stimulation
      - » Tremor, bristlin hair
      - » Salivation, mydriasis
      - » Anxiety, aggression
    - High doses
      - » Hallucination - serotonine effect
      - » Deep depression and anxiety
  - Cardiovascular system
    - Negative ionotropic and chronotropic effect

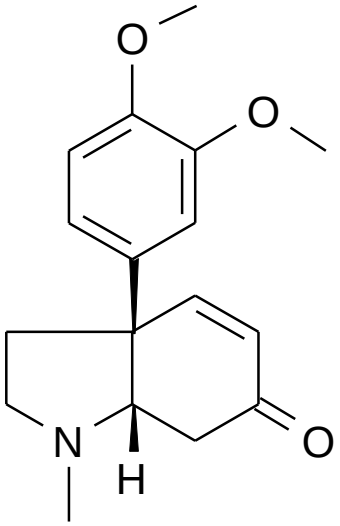






- Other indol alkaloids
  - **Mezembrenone, mezembrine, mezembrinol**
    - phenyloxyindols
    - *Sceletium* alkaloids Aizoaceae
    - Narcotic, coca-like effect
    - Addictive drug
      - channa

Kosmatec



- **Amines**
  - **Ephedrine**
    - Aromatic amine
    - *Ephedra* spp. Ephedraceae
    - Sympathomimetic activity
      - Increase of blood pressure and peripheral vasoconstriction
      - Penetration to CNS
    - Acute intoxication
      - Sweating, headache, anxiety
      - Muscular weakness and tremor
      - Mydriasis
      - Palpitation
      - Insomnia
  - **Galegine**
    - *Galega officinalis* Fabaceae
    - Derivative of guanidine
    - Damage of mitochondrial function
    - Convulsions, breath difficulties, pulmonary edema

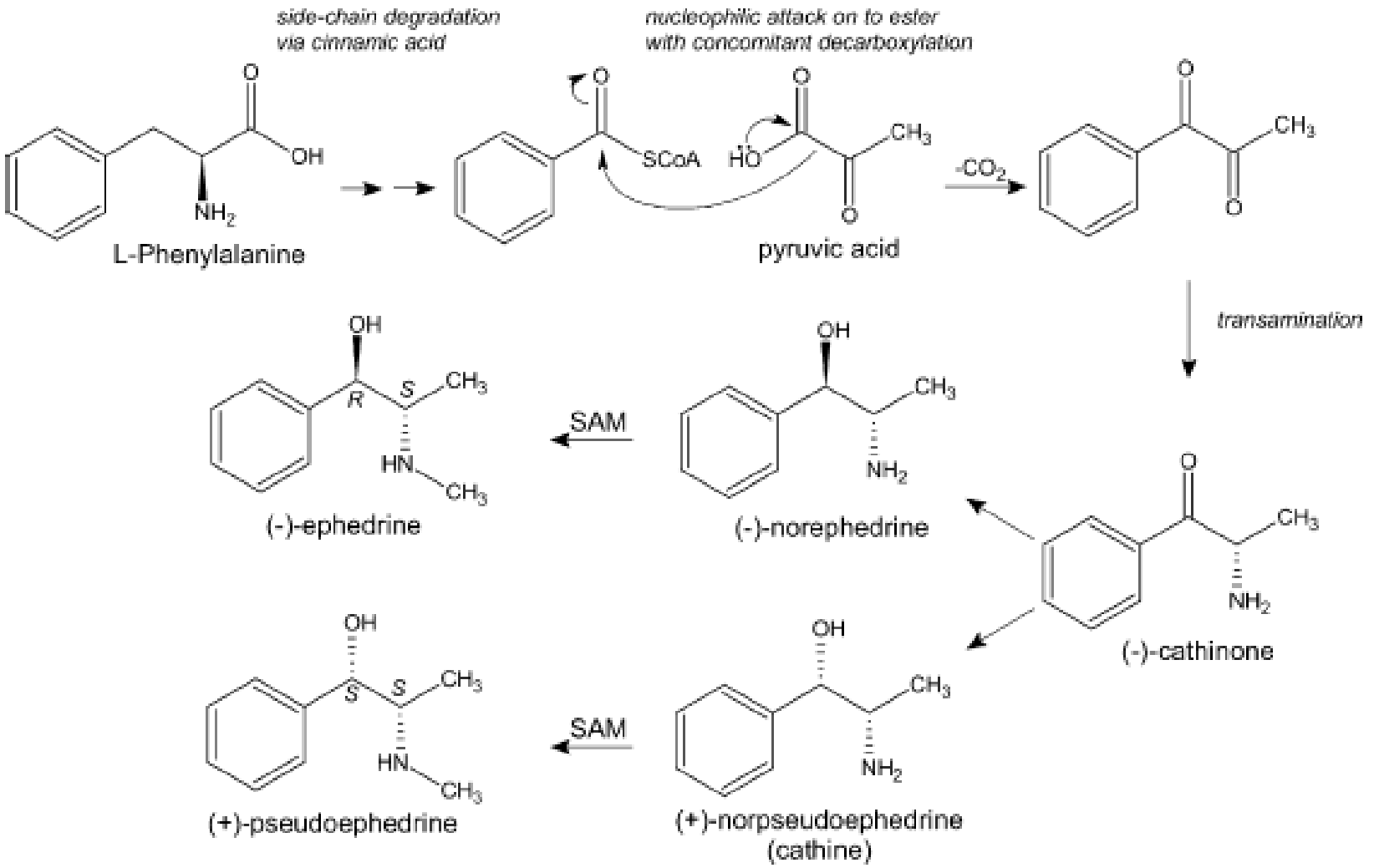
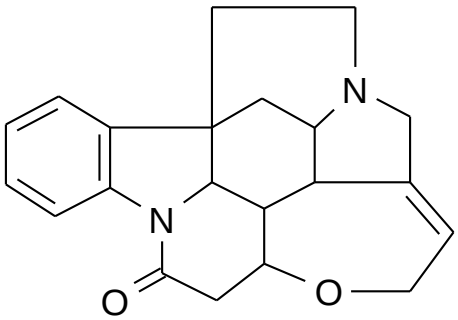


Fig. 1. Synthesis of ephedrine and related alkaloids.

- **Khatamines**
  - Arylalkylamines
  - *Catha edulis*, *Maytenus crucorii* Celestraceae
  - *Ephedra* spp. Ephedraceae
  - **Khatine and khatinone** the most important
  - **Khatinone**
    - Similar properties to amphetamine
    - During drying converts to norpseudoephedrine and norephedrine
  - Drug is used via chewing
    - North-East Africa
    - Fast decomposition prevents large transportation and business
    - Suppression of sleep, stimulation, against fatigue
  - Intoxication
    - Anorexia, hyperthermia, stimulation of respiratory centre
    - Mydriasis, arrhythmia, hypertension
    - Psychic symptoms
      - » Anxiety, panic attack, aggresivity

–Brucine, strychnine

- *Strychnos* spp. Loganiaceae
- Toxicity
  - –Stimulation of vasomotoric and respiratory centre
    - » Block of inhibition aminoacid glycine
  - –Spinal convulsant
- Metabolism
  - –Good gut absorption
  - –Partially excreted unchanged via urine
  - –Metabolism in liver
- Intoxication
  - –High sensitivity on sensoric stimuli
  - –Convulsions
    - » Generalized with agonizing pains
    - » Respiratory and metabolic acidosis
  - –Rapid onset of effect without warning
    - » Anxiety, twitches of members and face, frightening image
  - –Death caused by paralysis, total exhaustion, spastic paralysis of respiratory muscles, anoxia



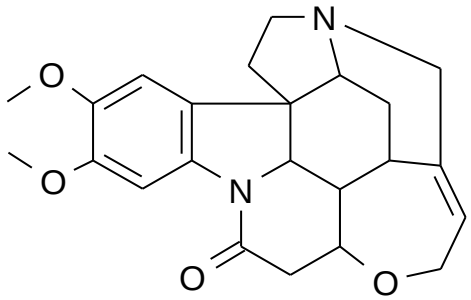
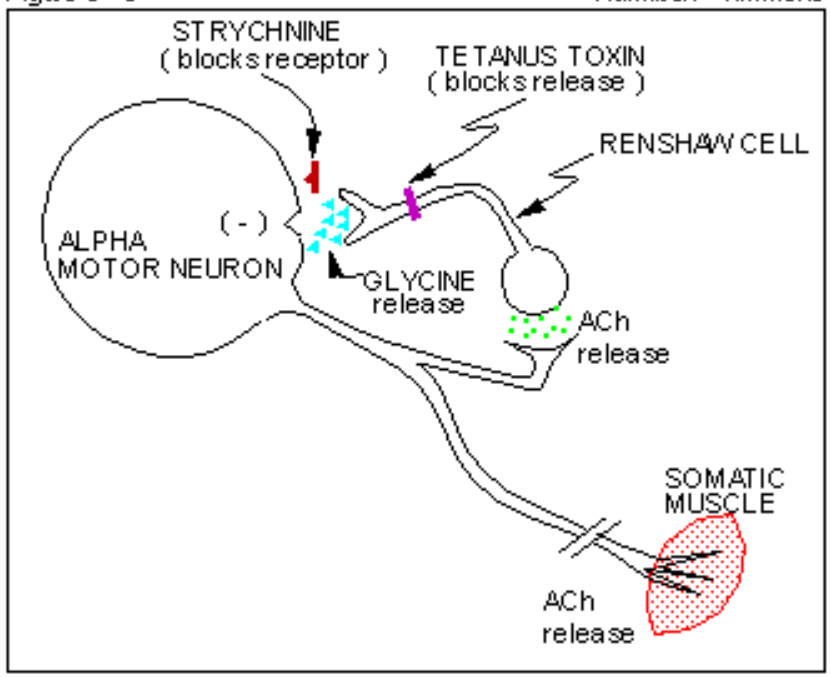
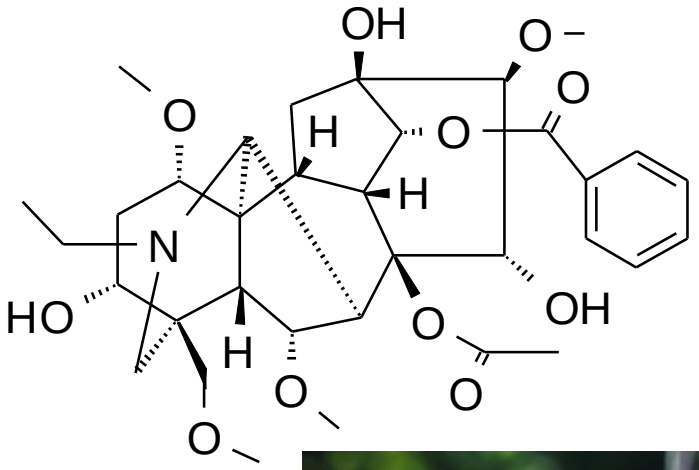


Figure 8 - 9 Hamilton - Timmons

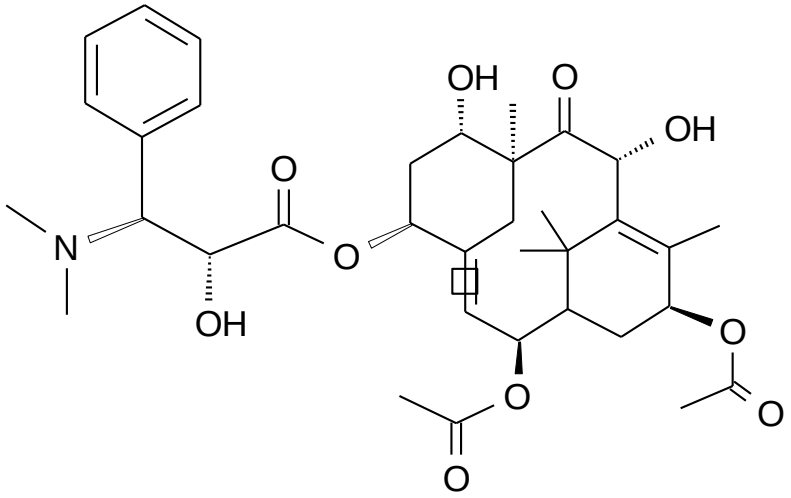



Strychnos nux vomica

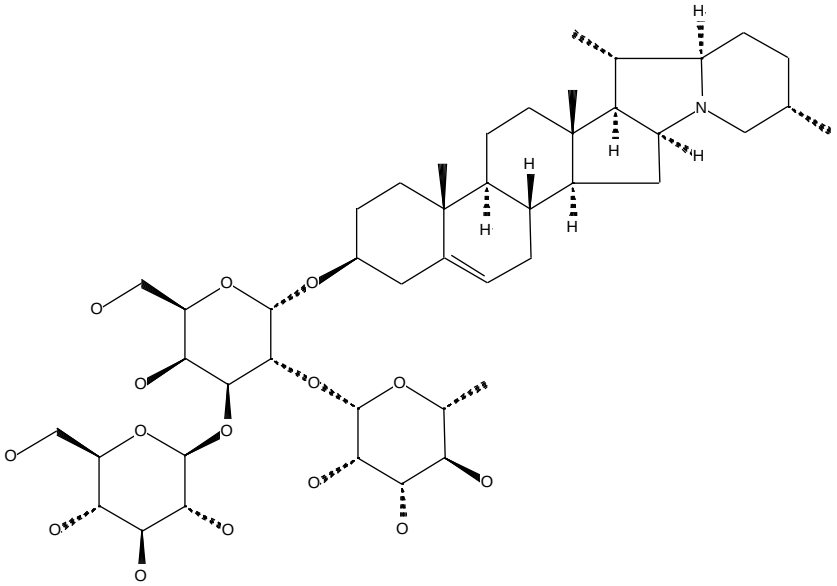
- Diterpenic alkaloids
  - Biologic precursor isoprene
    - Consequent introduction of nitrogen
  - Pseudoalkaloids
  - *Aconitum* spp., *Consolida* spp., *Delphinium* spp Helleboraceae
  - Ester alkaloids more toxic
  - Non-ester so called atisine alkaloids less toxic
  - **Aconitine**
    - Diterpenic ester compound
    - *Aconitum* spp. Helleboraceae
    - Toxic dose 3-6 mg p.o. (2-15 g of tubers)
    - Cardiotoxicity, neurotoxicity
    - Rapid absorption
      - Good transition through membrane
      - Absorption through the skin
    - Persistant opening of sodium channel of axones
    - Inhibition of repolarisation
    - Symptoma of intoxication
      - Anaesthesia of tongue
      - Nausea, vomiting
      - Diarrhea, colic
      - Parestesia
        - » „pins and needles“, chills
        - » pains
      - Mydriasis changes to miosis
      - Arrhytmia, paralysis
      - Death
        - » Ventricular fibrilation
        - » Respiratory arrest



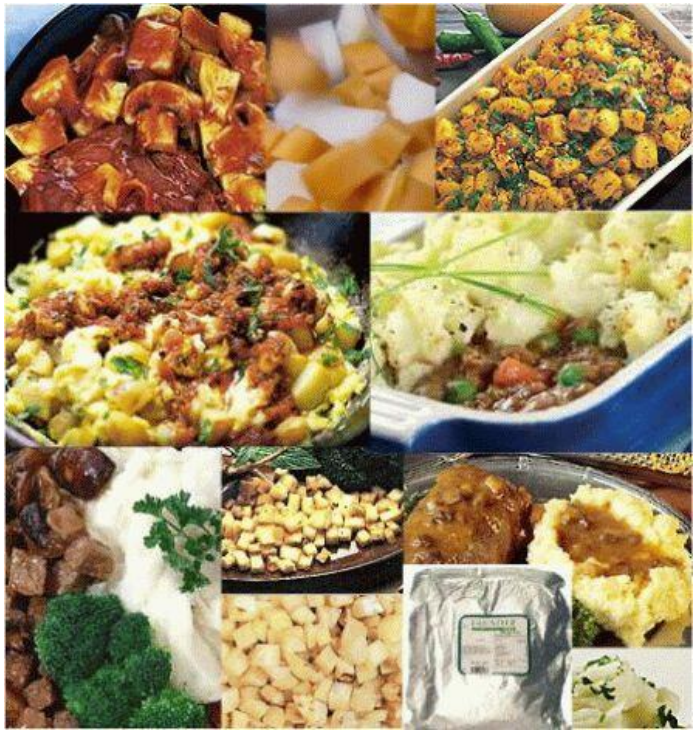
- Taxin A
  - Pseudoalkaloid
  - *Taxus baccata* Taxaceae
  - Main alkaloid of yew
  - Cattle intoxication from eating of needles
  - Suicides
    - 50-100 g of needles for adult man
  - Symptoms
    - After 30 minutes
    - Nausea, vomiting
    - Vertigo
    - Painful stomach colic
    - Shallow respiration, arrhythmias
      - » Similar to hypokalemia
    - Death
      - » Respiratory paralysis
      - » Cardiac arrest in diastole



– α-solanine, α-chakonine



- Glycosylated form more toxic than aglycon solanidine
- *Solanum* spp. Solanaceae
- Presence of alkaloids in whole plant
- In tubers variable content
  - Increased by different factors
    - » Genetic, ripening, fertilization
    - » Mechanic damage, stressors
- Heat resistance, only removal by hot water
- High glycoalkaloids content
  - Burning and bitter taste
- Low absorption from GIT – advantage, safe
  - Intoxication at more than 1 mg/kg
- Mechanism of intoxication
  - Inhibitors of acetylcholinesterase
  - Damage of mucose layer of GIT
    - » Necrosis, gastroenteritis
- Symptoms
  - Nausea, vomiting, diarrhea
  - Stomach pain, headache, vertigo
  - Hallucinations, neurologic disorders, coma



- Toxic proteins
  - Lectins (phytohemaglutinines)
    - Proteins or glycoproteins containing 4-10 % of sugar component
    - Molecules from 4 subunits
      - Connection via non-covalent bonding
    - Ability to bind the sugar residues on the surface of cell
      - D-galactose, N-acetyl-D-galactosamine
      - More binding sites
        - » Ability to li up neighboring cells - agglutination
    - Inhibition of protein synthesis of *eukaryota*
    - Some lectins
      - Inhibition of mitosis
      - Stimulation of lymphocyte maturation
      - Killing of cancer cells
    - Toxicity
      - Binding to cells of GIT mucosa membrane
        - » Inhibition of absorption of nutrients – antinutrition factors
        - » Vomiting, hemorrhagic diarrhea, loss of water and electrolytes
    - Occurrence in plants
      - Seeds and fruits of Fabaceae, Brassicaceae, Ericaceae
    - Content in plants different
      - Influenced by heat treatment

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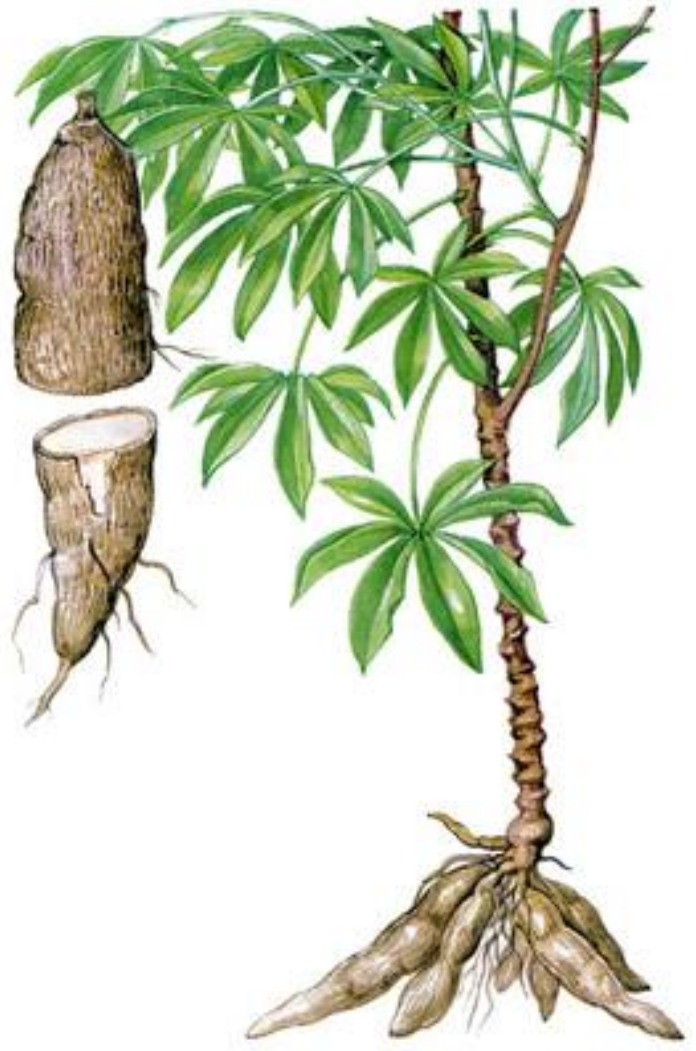
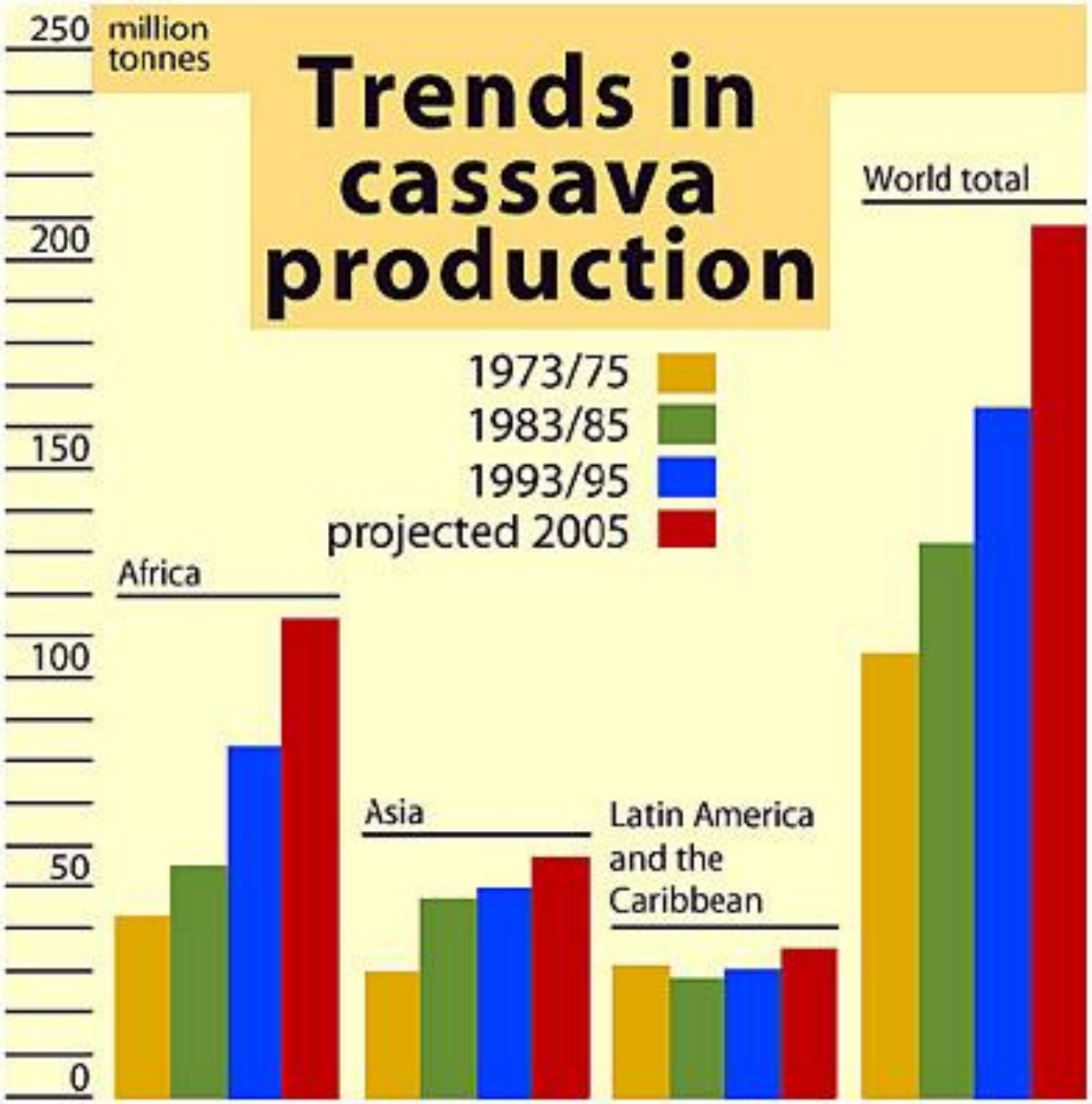
- **Ricine D**
  - *Ricinus communis* Euphorbiaceae
  - Component of ricine
  - 4 lectines
    - » RCL_I and RCL_{II} non-toxic
    - » Ricine D and RCL_{IV} toxic
  - Dimeric
    - » Chains A and B connected by disulphide
    - » B enables linkage to cell
    - » A is a cytotoxin
  - High toxicity
    - » 1 mg in 1 g of seeds is a lethal dose
  - Interference with protein synthesis and inactivation of ribosomal subunit 28S
  - Very sensitive are glial cells
  - Oral intoxication – ricinism
    - » Nausea, headache
    - » Bloody diarrhea, dehydratation
    - » EKG changes
    - » Liver necrosis
    - » Coma, death

- Cyanogennic glycosides
  - 2-hydroxynitriles + β-D-glucose
  - Hydrolysis produces:
    - HCN
    - Sugar
    - Residue (acetone, benzaldehyde)
  - Widely distributed
    - Rosaceae
    - Fabaceae
    - Euphorbiaceae
    - Passifloraceae
  - Toxic concentration of HCN 0.5-3.5 mg/kg
    - Massive consumation
    - Hydrolysis in GIT
  - Rapid detoxication in organism
    - Production thiocyanate
  - Toxicity
    - Cytotoxic anoxia
      - Bonds at cytochrome c
      - Disabling of O_2 utilization

- Three phases of intoxication:
  1. Dispnoe and irritation
  2. Convulsions
  3. Terminal adynamy
- Mild intoxication
  - Headache
  - Anxiety and respiratory distress
  - Vomiting, palpitation
  - Tachycardia, dyspnoe
- Higher doses
  - Peripheral anesthesia
  - Insane mind
  - Cyanosis, stupor, tonic-clonic convulsions
  - Respiratory arrest, death
- Alimentary intoxications
  - Manioc
  - Sorghum
  - Bitter almonds
  - Several Asian and American species of beans

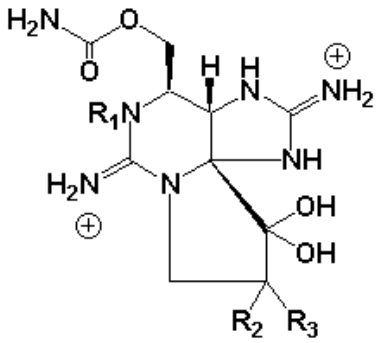
- Manioc
  - *Manihot esculenta* Euphorbiaceae
  - Linamarine, lotaustraline
  - Inhibition of Na+/K+ ATPase
    - Loss of potassium, ion disbalance
  - Damage of kidneys and liver
  - Acute intoxication
    - Stomach pain, diarrhea
    - Coma, cardiopulmonary failure
  - Chronic intoxication
    - Tropical neuropathic ataxia
      - Damage of skin and mucosa
      - Damage of optic and auditory nerve
      - Depletion of sulphur-containing AMA



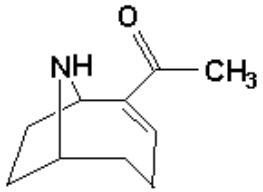

250
million tonnes
200
150
100
50
0
Trends in cassava production
1973/75
1983/85
1993/95
projected 2005
Africa
Asia
Latin America and the Caribbean
World total

Neurotoxins and paralytic poisons (Paralytic shellfish poisons)

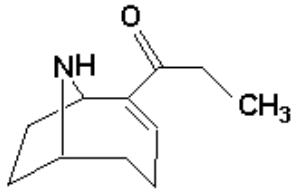
- Representative compounds:
  - anatoxin a, anatoxin a(s), anatoxin b, homoanatoxin
  - saxitoxin, neosaxitoxin
  - aphantoxins 1-5
  - gonyautoxins
  - Chemical structure:
    - Purine derivatives
      - Saxitoxins, aphantoxins, gonyautoxins
      - Tricyclic perhydropurine
      - Different substitution
    - Derivatives of cyclic *N*-hydroxyguanine
      - Anatoxin a(s)
    - Simple bicycles
      - Anatoxin a, homoanatoxin a



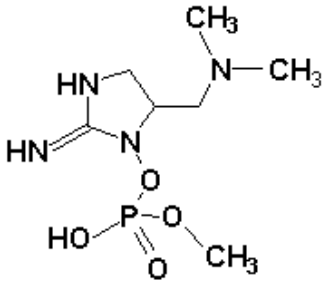
STX	R_1	R_2	R_3
STX	H	H	H
GTX-II	H	H	OSO_3^-
GTX-III	H	OSO_3^-	H
NeoSTX	OH	H	H
GTX-I	OH	H	OSO_3^-
GTX-IV	OH	OSO_3^-	H



ANATOXIN-a



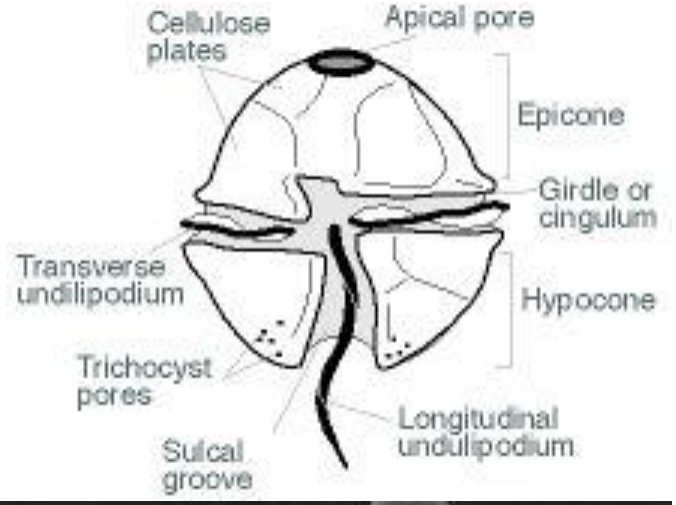
HOMOANATOXIN-a

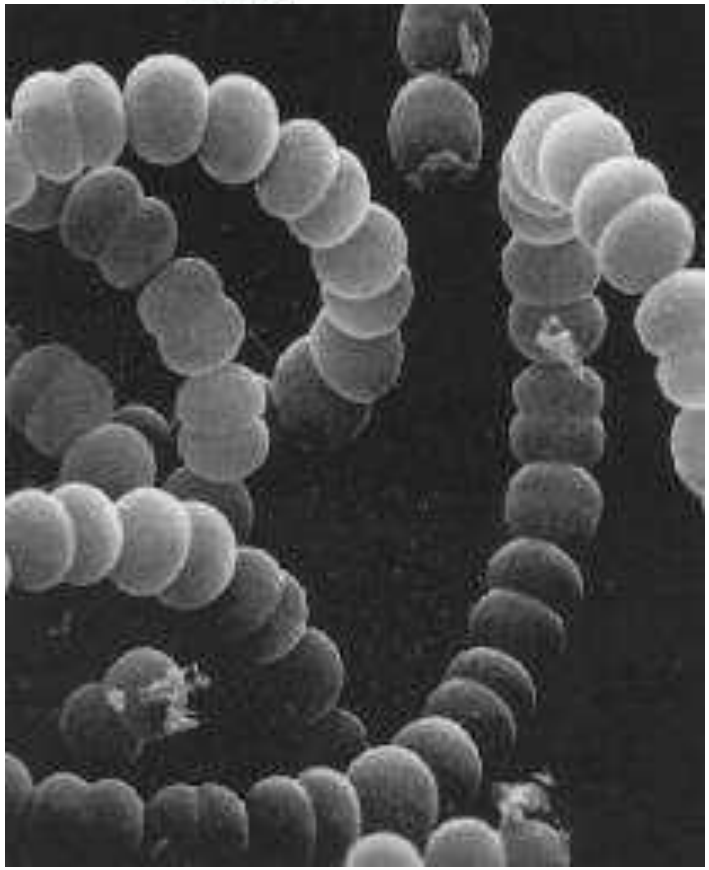


ANATOXIN-a(s)

Sources:

- ***Gonyaulax*** Dinophyta
  - Marine algae
- ***Anabaena, Aphanizomenon***
  - Cyanobacteria
- **Principles of effect:**
  - **Aphantoxins, saxitotin, neosaxitoxin** – blockade of transfer of neural excitements via blocking of Na+ channels. No influence on K+ channels
  - **Anatoxin A and homoanatoxin** causes change of function in preganglial neural terminations, acetylcholine receptors, increases the flow of Ca2+ ions into cholinergic neural terminations
  - **Anatoxin a(s)** acts as blocker of cholinesterase, causes depolarisation of postsynaptic terminations, affects nicotinic, muscarinic and acetylcholine receptors
  - **Saxitoxin** is je blocker of Na+ channels (first toxin with essential influence for explanation of Na+ and K+ channels function and neurobiology), tetrodotoxin disrupts action potential of neural and muscular fibers



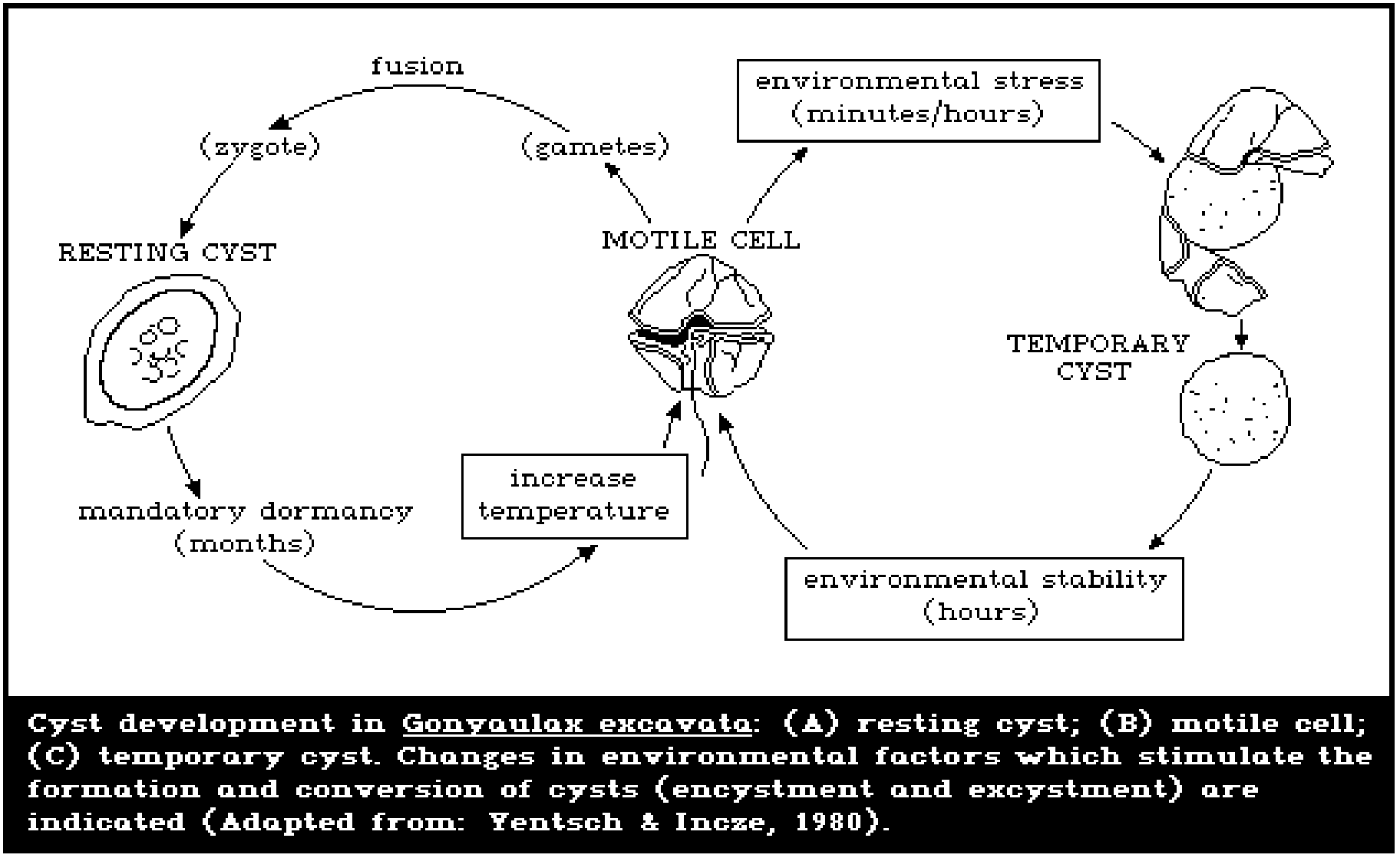


- **Symptoms of intoxication by anatoxins**
  - **Anatoxin-a, homoanatoxin-a, anatoxin-a(s)**
    - *Anabaena flos-aquae*
    - postsynaptic depolarizing neuromuscular blockers
    - inhibitors of acetylcholinesterase
    - Strong interaction with nicotine receptor
    - Hypersalivation
    - Diarrhea
    - Paralysis
    - Death caused by respiratory failure

- **Potential war poisons (chemical warfare)**
  - Absorption
    - Inhalation
    - Intact skin
    - Per oral

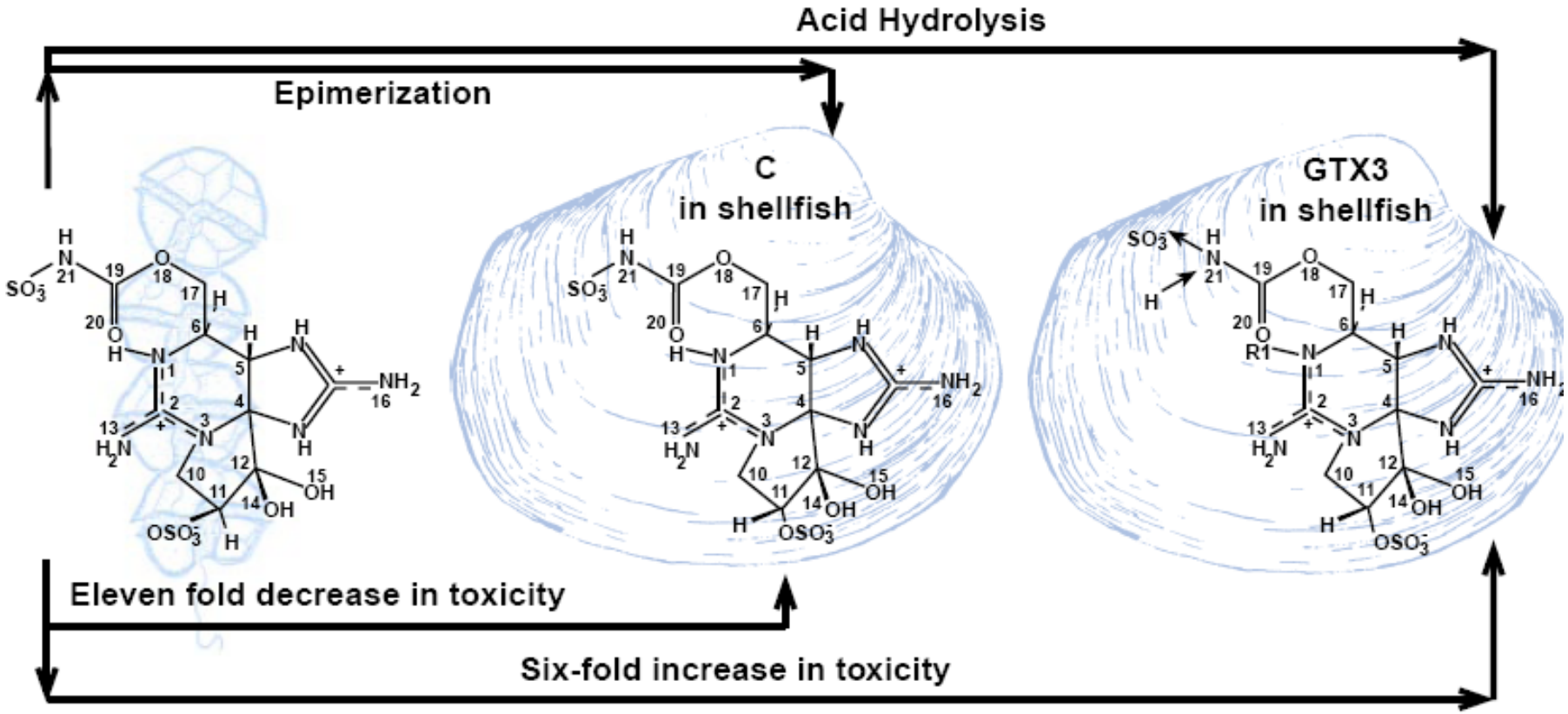
- Introduction into food chain
  - Accumulation in Crustaceans and fishes
  - Both dependent and independent on climate
- Intoxication PSP
  - Relaxation of smooth muscles
  - Depression of action potential in heart
  - Block of sodium channel
    - Guanidine ring condition of effect
    - Block from outer side of channel
    - Blocked both open and closed channel

http://www.pac.dfo-mpo.gc.ca/ops/fm/shellfish/Biotoxins/closures/default_e.



Cyst development in Gonyaulax excavata: (A) resting cyst; (B) motile cell; (C) temporary cyst. Changes in environmental factors which stimulate the formation and conversion of cysts (encystment and excystment) are indicated (Adapted from: Yentsch & Incze, 1980).

Cysts contain possible 1000 times higher amounts of toxines



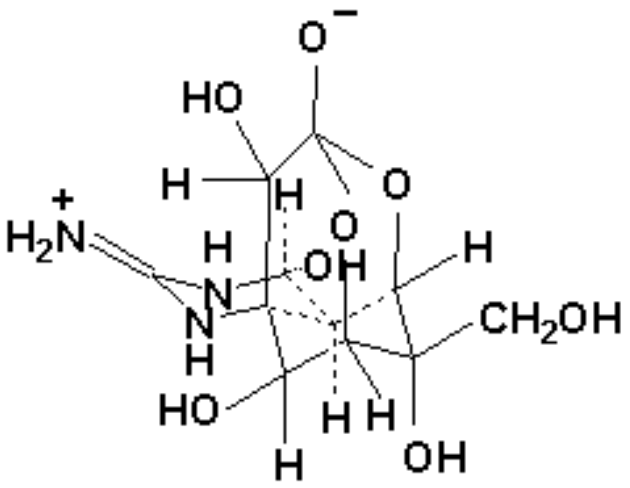
Paralytic Shellfish Poisoning: The Alaska Problem

Raymond RaLonde, Marine Advisory Program, Aquaculture Specialist

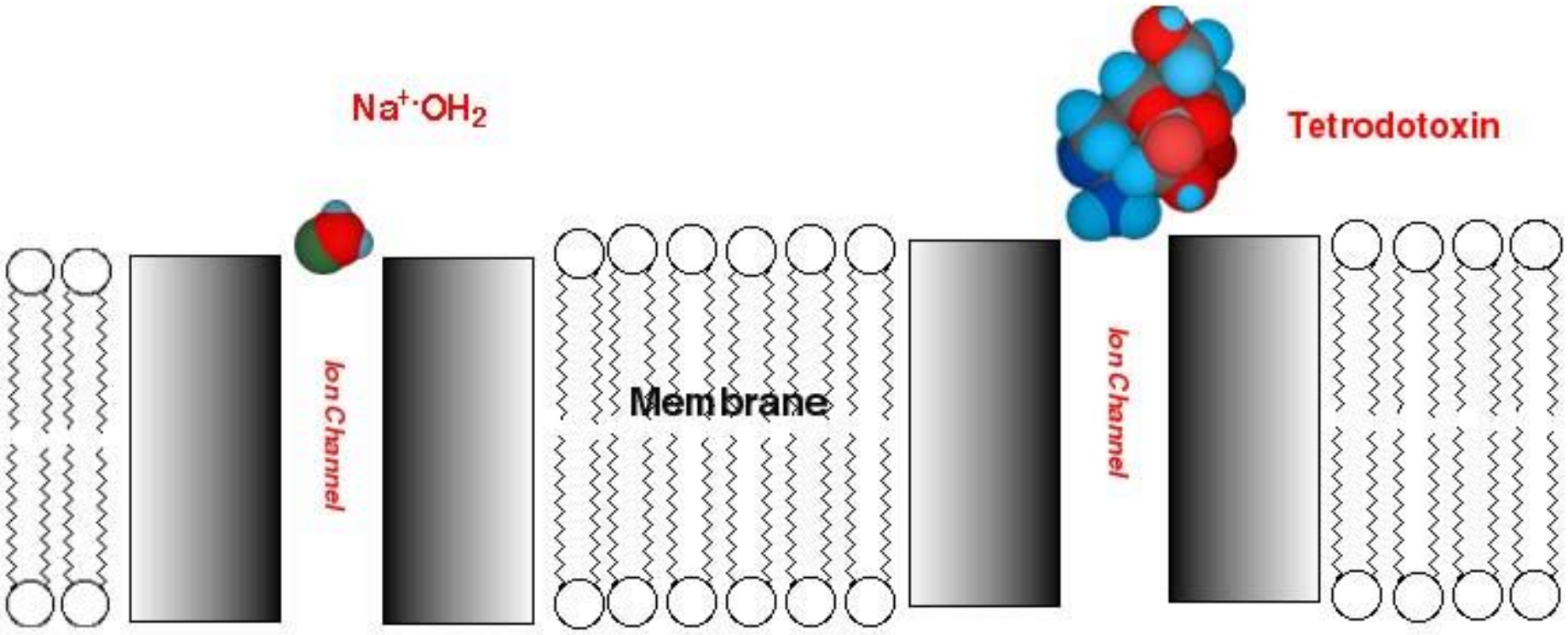
- Symptoms of saxitoxin intoxication
  - Consumption of contaminated food
    - Oysters, Crustaceans
    - Very rapid onset
  - LD *p.o.* 0.5 mg, *i.v.* 0.05 mg
  - Anesthesia and immobility of tongue and fingers
  - Sense of thirst
  - Pain in tips of fingers
  - Massive intoxication
    - GIT disorders
    - Headache
    - Disorder of movement coordination
    - Ascendant type of paralysis
    - Disorders of cognitive functions
    - Respiratory paralysis
- For differential diagnostics absence of hypotension
- PSP compounds
  - saxitoxin, neosaxitoxin, gonyautoxin I, gonyautoxin III, and decarbamoyl saxitoxin
    - Toxicity similar
  - gonyautoxins II, IV, V, VI, VIII, VIII-epimer, sulphocarbamoyl gonyautoxin I, IV
    - Substantially less toxic
  - Toxicity strongly dose-dependent
- Usage
  - Chemical warfare
  - Experimental compounds

Tetrodoxin TTX

- Potent and rapid action
- *Tetraodontiformes*
  - tetraodon, pufferfish
  - ovaria, liver, guts highest content
  - skin traces only
  - In Japan 646 of cases between 1974 nda 1983 (179 mortal), in present time 30-100 per year
- Some frogs, octopuses, snails and slugs
- Unusual tricyclic structure
  - guanidinium toxins
  - aminoperhydroquinazoline
- Specific blocker of Na+ channels of neurons
  - Tetrodotoxin – Na+ binding site extremely narrow
  - TTX acts as hydrated Na^+
  - Inters the channel orifice, binding to a glutamate residue in channel peptide
  - Conformation changes
  - Electrostatic binding to an open channels



TETRODOTOXIN

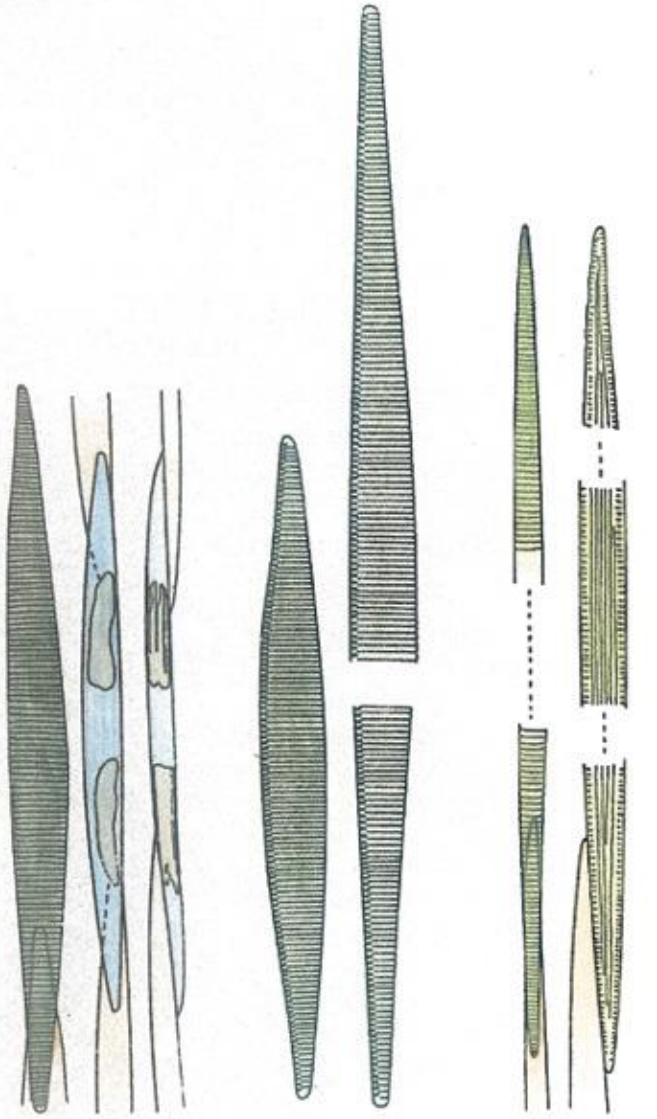


http://www.life.umd.edu/grad/mlfsc/zctsim/ionchannel.html

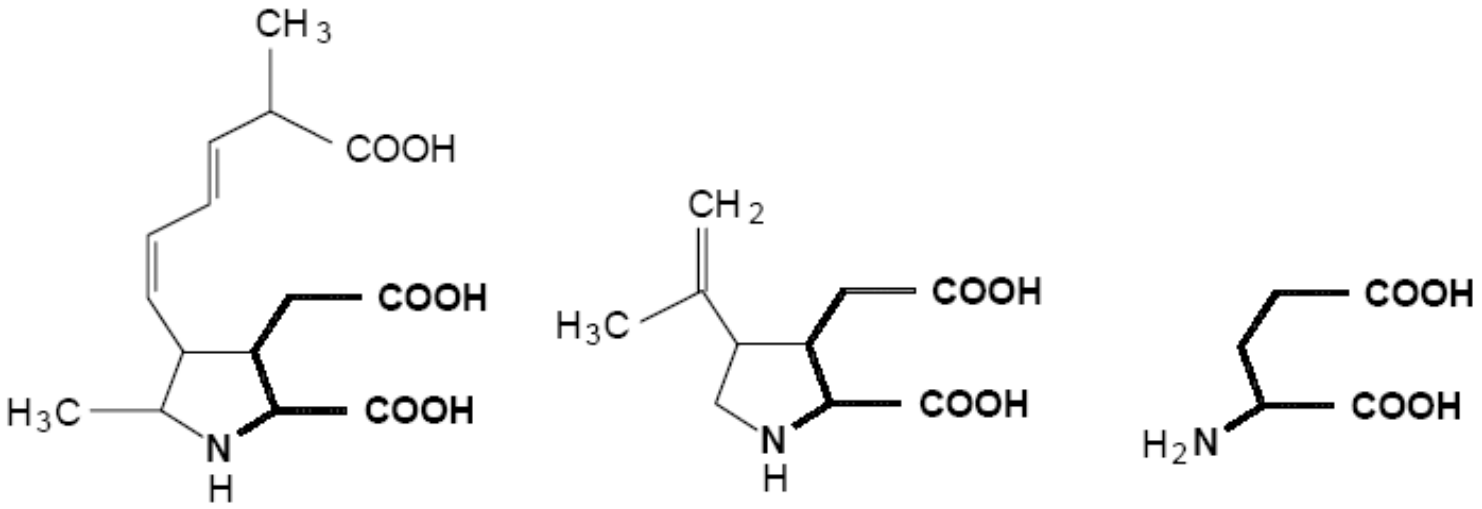
- Extreme toxicity TTX
  - Minimal *p.o.* is 30 µg/kg
    - Decomposition in acidic environment in stomach
  - Termostable, decomposition in acids and bases
- Symptoms of intoxication
  - In minutes or hours
  - Trembling, tingling and paresthesia of tongue, lips and tips of finger
  - Headache, nausea, vomiting, diarrhea
  - Second degree
    - Continuous paresthesia
    - Paralysis
    - Impossibility of movements
    - Convulsions, arrhythmia, mental confusion
  - Death caused by respiratory arrest aprox. In 8 hours
    - Possible full consiousness close before death

Domoic acid

- *Nitzchia pungens*
- Amnesic shellfish poisoning (ASP)
  - Intoxication accompanied by neurologic disorders
    - Hallucination, time-space disorientation
    - Loss of short-term memory
- Symptoms of intoxication
  - Vomiting, stomach convulsions, diarrhea, headache
  - ASP
- Accumulation of toxin in hepatopancreas, branchiae, so called siphon of pelecypods
- Pelecypods resistant, meat becomes toxic
- New Zealand, coast of Canada, Mexico
- Red tide
- Structure:
  - Tricarboxylic acid
  - Derivative of proline
  - Structural similarity with excitation aminoacids (cainate, glutamate)
- Mechanism of effect:
  - Excitation AMA
  - 100times higher effect then glutamate
    - Rigidity of ring
  - Binding to a NMDA receptor
    - Influence on Ca2+ channels, entry of calcium into cell
      - » Stimulation of many proceses → damage of neurons
    - Mediation of loss of memory



http://www.regione.emilia-romagna.it/laguna/immagine_dettaglio.asp?id_img=1



kyselina domoová kyselina kainová kyselina glutamová

Obr. 1: Strukturální podobnost neurotoxinů ze skupiny excitačních aminokyselin (domoové a kainové) s kyselinou glutamovou, přirozeným agonistou NMDA-glutamátových receptorů.

KYSELINA DOMOOVÁ, NEBEZPEČNÝ NEUROTOXIN

Plk. v zál. prof. MUDr. Vratislav HRDINA, CSc., [1,2]prof. RNDr. Jiří PATOČKA, DrSc.,
plk. v zál. doc. RNDr. Vladimír MĚRKA, CSc., [3]doc. MUDr. Radomír HRDINA, CSc.

- Doses:
  - 0.9-1.9 mg/kg GIT disorders
  - 1.9-4.2 mg/kg neurotoxic to lethal
- Clinical symptoms:
  - neurotoxic symptoms predominating
    - Headache, vertigo, confusion, time-space distortions
    - Disorders of motoric coordination, hallucinations, loss of short termed memory
  - gastrointestinal difficulties
  - excessive secretion of mucus into respiratory tract
  - tachycardia, peripheral vasodilatation and hypotension
  - cardiac arrhythmia and coma.
  - Intoxication can terminated sudden death 12 to 14 hours caused by respiratory paralysis
- Therapy:
  - antagonists of NMDA
  - prophylactic administration of melatonin

Toxin of *Bacillus anthracis*

- *Bacillus anthracis*
  - Gram-positive rods
  - *In vivo* in short chains
  - Encapsulation
  - Formation of resistant spores
    - autoclaving

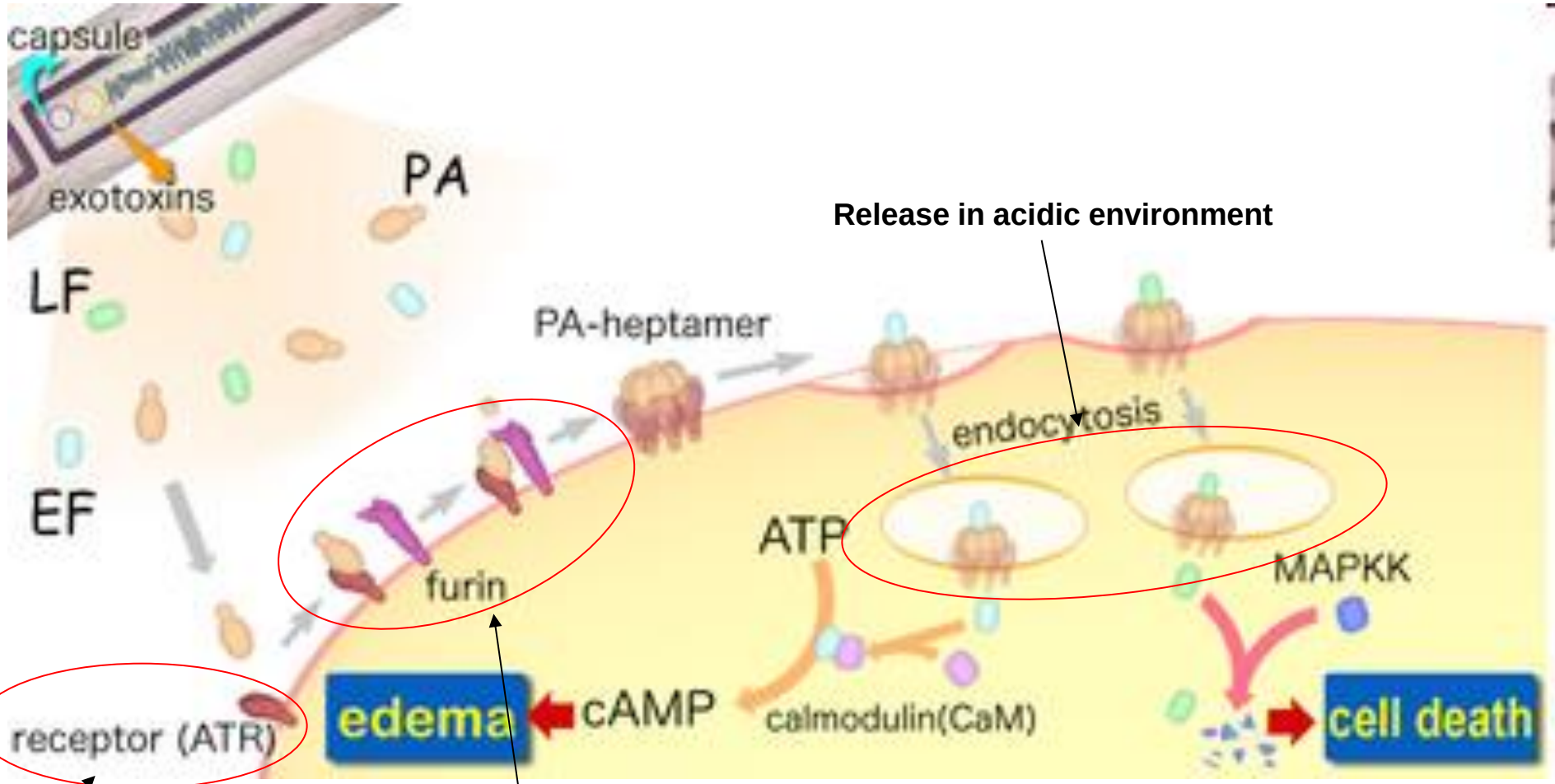
Bacillus anthracis

- **To 30thies worlwide**
  - Today Afrika, middle Asia, south America
  - Pasture × industrial form of anthrax
- **Lower incidence, but possibility of attack**
  - Vaccination, sterilisation of sources, hygiene
  - Ames, Vollum, Sterne
- **Full virulence**
  - Encapsulation + toxin
- **Disease – anthrax – sněť slezinná**
  - After infection **local necroses**
  - **Invasion via lymphatic system into blood circulation**
  - Localisation directly in capillaries
  - **Toxin increases the capillary permeability**
    - „densification" of blood
    - Leakage of liquids into tissue
  - **Septicaemia**
    - **Sudden death becouse of cardiopulmonary failure**
  - Infected perosns spreads the bacillus via extcrets and non-coagulated dark blood leaking all body holes
  - **Skin**
    - Hemorhagic necrosis with pustules and edems, co called pustula maligna - uhlák
  - **Pulmonary**
    - Pneumonia and strong effect on mediastinum
      - Import of bacilli into lymphatic system mediated by macrophages
      - 92% $\rightarrow$ 45% mortality
  - **Gastrointestinal**

Toxin of *Bacillus anthracis*

- Three components
  - Protective antigen (PA or also factor II)
    - Binding to a specific receptor of eukaryotic cell
    - Formation of secondary receptors for further two proteins
  - Edemogenic factor (EF, factor I)
    - Adenylylcyclase dependent on calmoduline
    - Together with protective antigene lower activity of neuthrophiles
  - Lethal factor (LF, factor III)
- Attack of especially macrophages
  - After internalisation transfer to cytosol
  - Disruption of cellular signal pathways
  - Disruption of cell migration
  - Cell lysis
  - Damage of immune fuction

Effect of anthrax toxin



Anthrax receptor

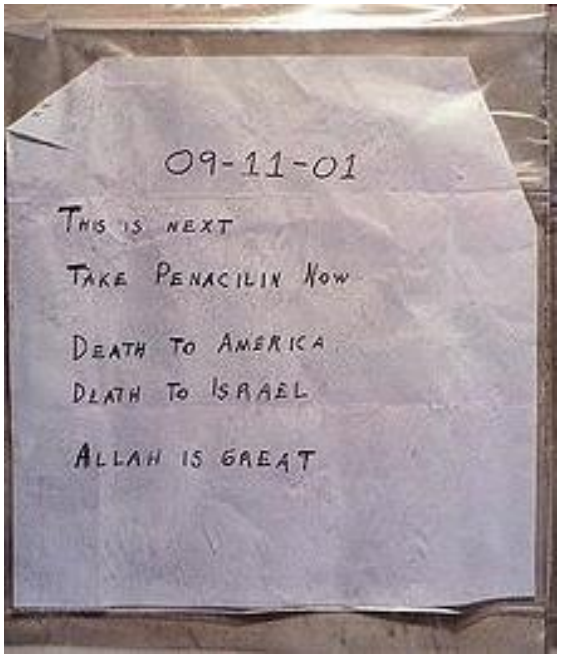
Cleavage with endoprotease from furin family

Blockade of calmoduline for further processes

LF- endoprotease activity on mitogen-activated protein kinase kinases

Induction of apoptosis

Gruinard Island



Toxins of *Staphylococcus aureus* types

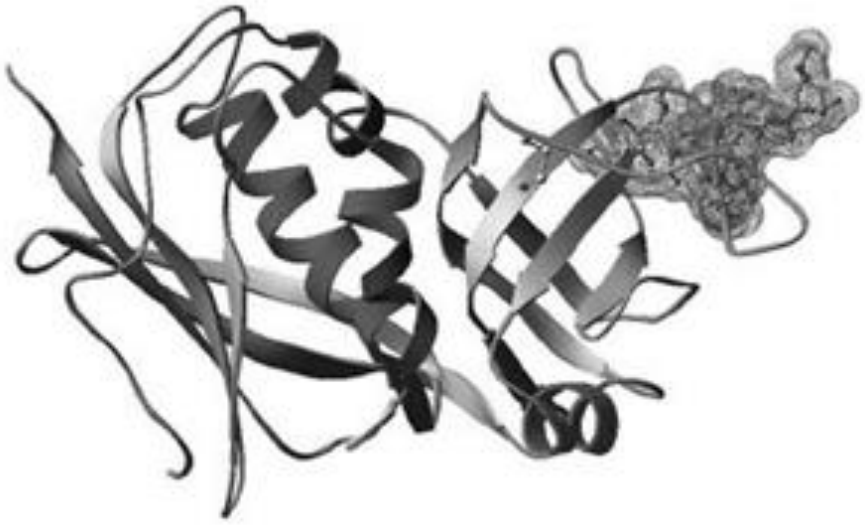
- Enterotoxins
- Exfoliatins (epidermolytic toxins)
- Hemolysin α (alpha toxin)
- Hemolysin β
- Hemolysin γ
- Hemolysin δ
- Hyaluronidase
- Leukocidin (Panten-Valentin toxin)
- Plasmocoagulase (PK)
- Staphylokinase (fibrinolysin)
- Termorezistant nuklease
- Toxin of toxic shock syndrom (TSST-1)

Toxins of *Staphylococcus aureus* types

Enterotoxin B

- 10 antigenic differences A-E G-K
- In Czech mainly A and D

- Protein 28.5 kDa, no sugars and lipids
- Thermostabile
- Pyrogennic toxin
- Alimentary intoxications
  - Mayonnaise, eggs, ice-cream, salads, sweets
- Staphylococcal enterotoxicosis



- Source of infection/intoxication
  - Human carrier (up to 40 % of population in nosohltanu)
  - Person with purulent disease
- Sites of entry
  - Perorally or inhalation
  - Different symtoms of intoxication
    - Inhalation
      - 3-12 hours
      - Strong fever 39-40°C
      - Tremor
      - Headache and pain of muscles
      - Respiratory distress, non-productive expectoration, sternal pain
    - Peroral entry
      - Interaction with parasympathic ganglia of stomach
        - » Nausea, vomiting, stomach pain, diarrhea
      - Incubation time 1-6 hours
- Complication
  - Hypotension, septic shock, death

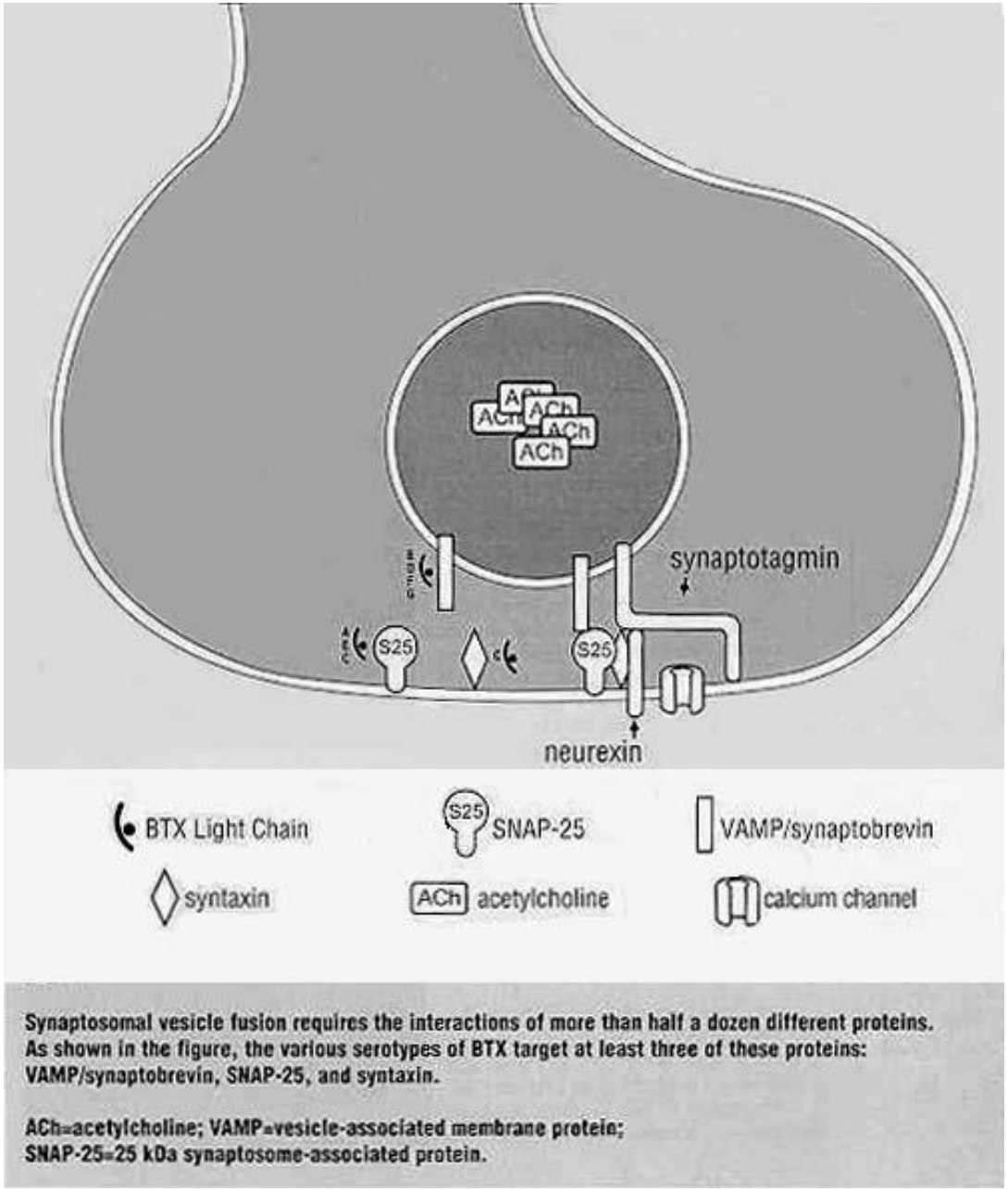
- Toxicity
  - ED_{50} 27 µg/kg for monkeys
  - Ten times lower dose can disable human
    - Potential biologic weapon
    - Contamination of water or food
    - Heating kills staphylococcus, but toxin stays resitant
- Mechanism of effect
  - Interaction with immune system
    - Binding to MHC, stimulation of T-lymphocytes proliferation
    - Bacterial superantigen
      - Secretion of cytokines
        - » Interferon, interleukin 1 and 2
- Therapy of disease
  - Supporting
    - Lowering of body temperature
    - Peroral rehydration
    - Supplementaion of electrolytes
- Prevention
  - Hygienic návyky
  - Suppression of risky food

Botulotoxin

- Group of seven antigenic-different neurotoxins A-G
- Proteins with molecular weight 150 kDa
- Heavy (H) and light (L) chain, disulphidic bridge
- L chain toxic, H chain binding to receptors at presynaptic membrane
- Product of *Clostridium botulinum*
  - Gram positive strictly anaerobic rod
  - Moving
  - Common occurrence in GIT and in dung-fertilized soil
  - Spores resist against several hours of boiling
- Thermolabile toxin
  - 10 minutes of boiling enough for deactivation
- „Sausage poison“ (lat. *botulus* = sausage)
  - Not enough sterilized meat and vegetable canned food
- Intoxication called botulism
  - For human important subtypes A, B, E
  - Classification of intoxication
    - Alimentary
    - New born
    - Early
    - Wound botulism
    - Inhalation botulism
    - Iatrogenic botulism

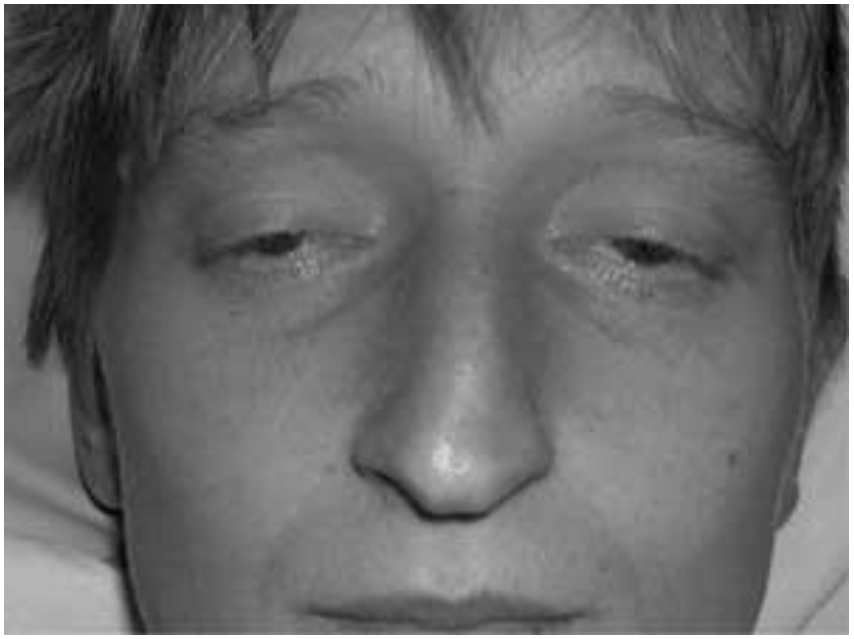
Botulotoxin

- **Mechanism of action**
  - After absorption transport in blood
  - Peripheral neural terminations
    - Binding, inhibition of acetylcholine release from vesucules
  - Serious disruption of peripheral cholinergic transmission
- **Incubation time** 18-36 hours, based on the infection dose
- **First symptoms**
  - Bulbal muscles
    - Mydriasis, diplopia, accomodation disorder, photophobia
- **Progressive development**
  - Vertigo (caused by hypotension)
  - Dryeness in mouth, muscular weakness or paralysis
  - Nausea, vomiting, stomach pain
  - Consiousness stays preserved
  - Death caused by respiratory muscles paralysis



Synaptosomal vesicle fusion requires the interactions of more than half a dozen different proteins. As shown in the figure, the various serotypes of BTX target at least three of these proteins: VAMP/synaptobrevin, SNAP-25, and syntaxin.

ACh=acetylcholine; VAMP=vesicle-associated membrane protein; SNAP-25=25 kDa synaptosome-associated protein.



WALSH COUNTY RECORD

TEN PAGES

VOLUME XXI — GRAFTON, NORTH DAKOTA, THURSDAY, FEBRUARY 5, 1931 — NUMBER 24

TWELVE DINE WITH DEATH IN GRAFTON FARM HOME

CITY IS SCENE OF MOURNING AS 12 DEAD ARE BURIED

MRS. WILL HAVE LAST RITES AT 9 FRIDAY

Eleven of Twelve Victims in Poison Food Tragedy

PARTY GIVEN THURSDAY NIGHT AT HOME OF MR. AND MRS. EDWARD HEEN HAS TRAGIC ENDING

FIVE IN ONE FAMILY ARE VICTIMS OF RARE MALADY

Botulotoxin

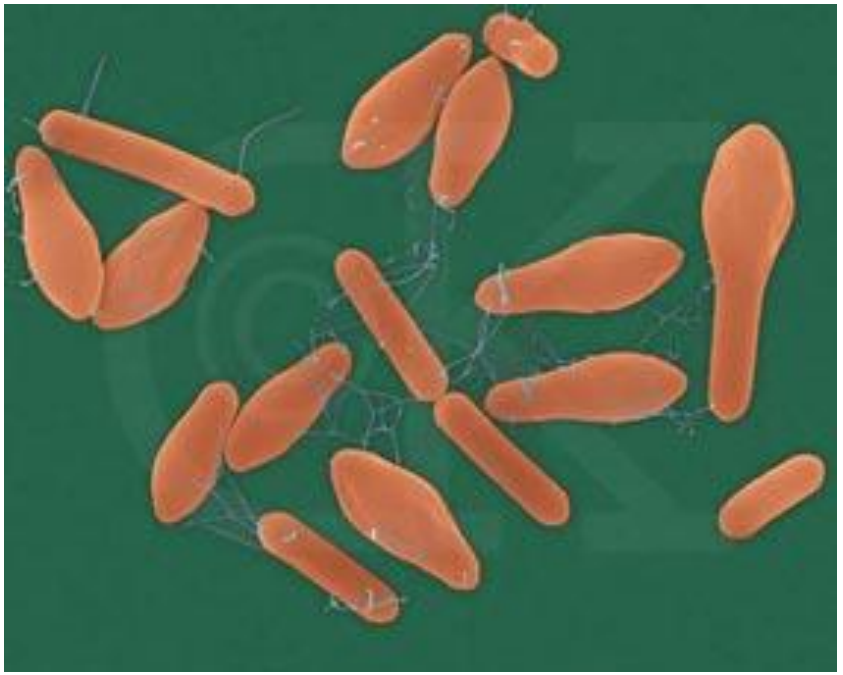
- The most redoubtable war poison
  - Toxicity 1 ηg/kg
  - Inhalation of aerosol
    - Similar symptoms as alimentar itoxication
    - Paralysis comes later
  - Asassination of Heydrich
  - War in Gulf
- Usage:
  - Cosmetics
  - Therapy of convulsive neuromuscular diseases
- Therapy of intoxication:
  - Vomiting, gastric lavage
  - Complication is respiratory failure
    - Several weaks of arteficial respiration
    - Guanidin or 3,4-diaminopyridin as support of acetylcholine release
    - Botuline antitoxin
      - Heptavalent equine

Tetanospasmin

- Production organism *Clostridium tetani*
- Two components of tetanotoxin:
  - Neurotoxic component tetanospasmin
    - Disease tetanus
  - Haemolytic component tetanolysin
    - In ethiology of tetanus does not play a role
- Tetanospasmin
  - Polypeptid 150 kDa
  - Two chains
    - Light α-chain
    - Heavy β-chain
    - Disulphidic bridge
  - Penetration to cell
    - Acidic pH - fragment of heavy chain is binding to receptor, formates pores
    - Light chain penetration to cell - neurotoxicity

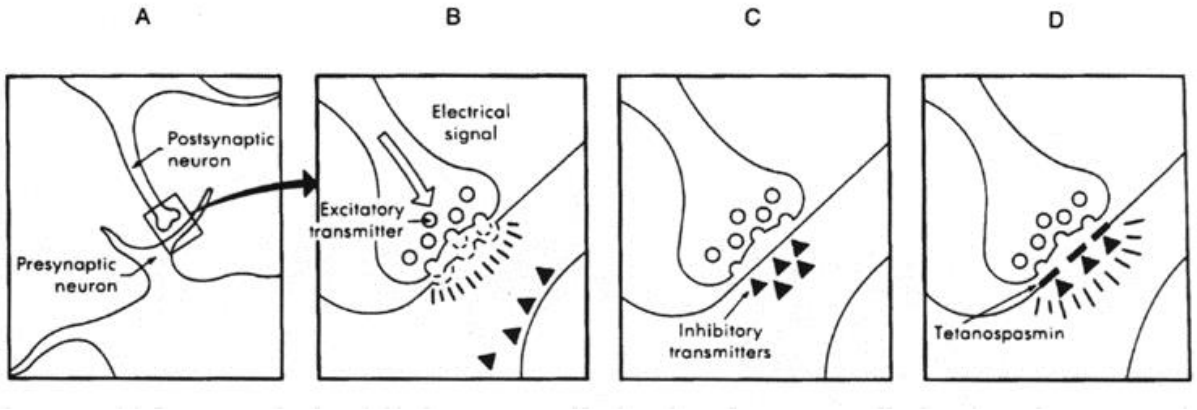
Tetanospasmin

- Highly toxic
  - LD50 for mice 0.002 µg/kg
- Thermolabile
- *C. tetani* sporulates
  - In soil can persist for years
  - For elimination necessary 4 hours of boiling
- *C. tetani*
  - Saprophytic in guts of cattle and other home animals
  - Spores via fertilization into soil
  - Wound contamination
- Disease called tetanus
  - Early infection with serious prognosis
  - After possibility of vaccination on decline in western countries
  - Factor for tetanus manifestation
    - Necrotic tissue, purulent process
    - Presence of strange body inside wound
  - Decreased red ox potential
    - Spores germination
    - Vegetative form
    - Production of toxin



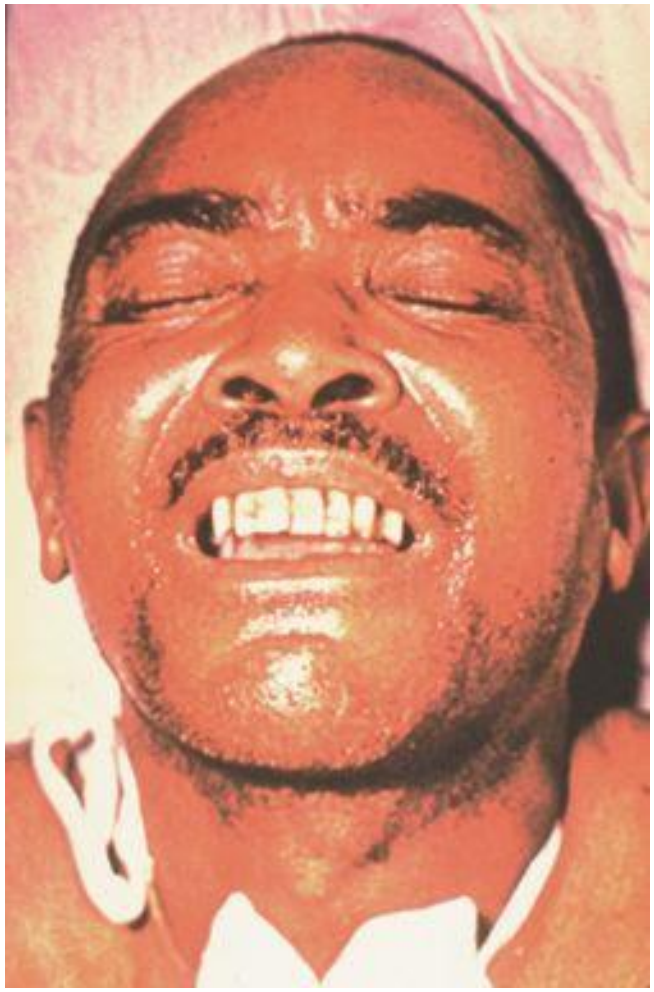
Tetanospasmin

- Transportation of toxin via vegetative nerves to neurons of spinal cord
  - 250 mm per day
- Binding to presynaptic receptors
  - Block of release of glycin and GABA
    - Responsible for inhibitory transmission to aferent motoric neurons
  - Irreversible binding
  - Unlimited muscular contraction
- Affecting also sympathicus
  - Sweating, hypertension to hypotension, arrhythmias
- Incubation period 1-3 weeks
  - Shorter incubation → worse prognosis
    - Dependent on distance of wound from spinal cord and amount of toxin



Tetanospasmin

- 4 clinic forms
  - **Generalized tetanus**
    - Most common
    - Can be triggered from very small wounding
    - Starting
      - Convulsions of chewing muscles (trismus)
      - Increased irritability anxiety, sweating, swallowing problems
    - Progression
      - *Risus sardonicus*
      - Convulsion of dorsal muscles into typical curve
      - Clenched fists
      - Triggering of convulsions by light or touching
      - In full consciousness very painful
    - Terminal stadium
      - Fractures of vertebrae and long bones
      - Laryngospasm, respiratory arrest
      - Lethality ca 50 %
  - **Localized tetanus**
    - Only surrounding of wound, good prognosis
  - **Cephalic tetanus**
    - Head wounds
    - Infection of middle ear
    - Probability of surviving minimal
  - **Tetanus neonatorum**
    - Developing countries
    - Bad hygiene during taking care about umbilical cord
    - 0.5 million of death newborns per year

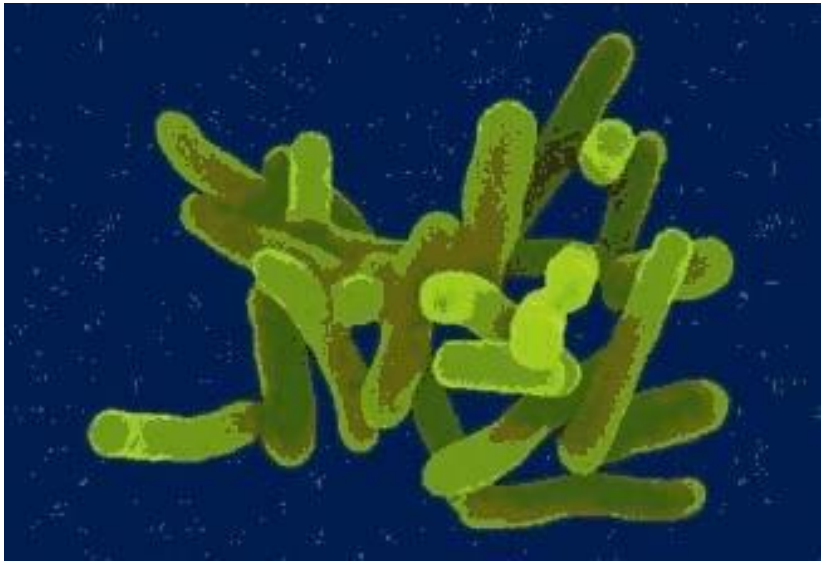


Tetanospasmin

- Therapy
  - Surgical cleaning of wound
    - Does not close
  - Antitoxin
    - Neutralization of toxin before its entry into neuron
  - Myorelaxants
  - Controlled lung ventilation
  - Preventive vaccination
    - 3 doses after months
    - 4th dose in 20th month
    - Re-vaccination in 5th and 14 year
    - Adult each 10 years
    - Booster after wounding

Shigatoxins

- Production organism *Shigella disenteriae*
- Toxic bacterial protein
  - Similar toxicity as botulotoxin 0.002 µg/kg
  - Potential biologic weapon
- Similar toxins produced by *E. coli*
  - Verotoxins
    - Synonyms
      - Verotoxigennic tribes of *E. coli*
      - Shiga-like toxin of *E. coli*
      - Shigatoxin produced by *E. coli*
    - Verotoxin 1 and verotoxin 2
      - Production conditioned by presence of speciphic bacteriophage
- Shigatoxins
  - Proteins coagulatting under heating
  - Sensitive to red ox agents
  - Two chains:
    - A unit
      - Enzymatically active, inhibitor of proteosynthesis
    - B unit
      - Binding to a surface of cell
  - Cytotoxic effects



Shigatoxiny

- Initiators of serious diarrheal diseases
  - Potentially lethal
- Cytotoxic effect
  - Endothelium of gut capillaries
  - Kidney glomerules
  - Endothelium of brain veins
- Formed changes – pathologic base for
  - Hemorrhagic colitis
    - Abdominal convulsions, watery diarrhea, blood in faeces
  - Hemolytic-uremic syndrome
    - Complication of *E. coli* infection
    - Diarrhea transferred to bloody diarrhea
    - Uremia, thrombocytopenia, hemolytic anemia, kidney failure
    - Lethality 5 %
    - Possibility of chronic kidney damage
- Infection
  - Reservoir home animals
  - Bacteriophages encoding transfer of genes responsible for toxin production are present in sewage and waste water
  - Alimentary intoxications
    - Badly prepared food (meat) – hamburgers
    - Orofecal transfer possible for children
  - Incubation 2-7 days

Toxic lipopolysaccharides

- **Peptidoglycane layer**
  - Wall of **Gram-negative** and **Gram-positive** stained bacteria
- **Gramnegative bacteria**
  - Peptidoglycane layer
  - Surface layer of outer membrane
    - phospholipids, lipopolysaccharides
    - acidic polysaccharides and proteins (ca 50%)
- Biologically active – **lipopolysaccharide complex**, assigned as **endotoxin**
- Lipopolysaccharide is arranged as double layer, with hydrophilic part composed of polysaccharide, hydrophobic part is lipidic.
- **Structural areas of lipopolysaccharides**
  - **specific polysaccharide (I.)**
    - polymers of several millions of molecular weight
      - polymer composed from oligosaccharides
    - it bears antigenic determinants and determines serologic specifity of bacterial species
  - **Medullar area (II.)**
    - Common for whole group
  - **Lipid A (III.).**
    - medullar oligosaccharide is covalently bonded to lipid A
    - skeleton composed from two molecules of glucosamine, which are connected by phosphate bridges
    - hydroxyl groups are esterified by higher fatty acids
- Single bacterial species are different both in composition of polysaccharide chains and in composition of lipid A
- Polysaccharide part – virulence of bacteria (can contribute to adhesion, activation of complement)
- Lipid A - toxicity