Bern – Capital of Switzerland

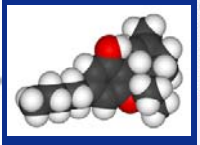
1

University of Bern

15'000 students, 8 faculties, 160 institutes
Specialities: space & climate research, artificial organs, orthopedics

2

Phyto- and Endocannabinoids: An Option for Medicine?



Rudolf Brenneisen
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rudolf.brenneisen@dkf.unibe.ch

3

Cannabis and Columbus

Has Cannabis been facilitating the discovery of America by Columbus?

Board pharmacy of „Santa Maria“

4

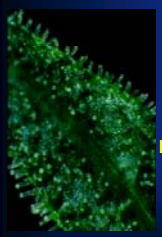
Phytocannabinoids

Cannabis sativa L.

↓

Female flowers/leaves

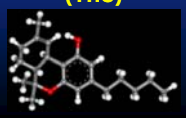
↓



Glandular hairs/resin glands

↓

Delta-9-tetrahydrocannabinol (THC)



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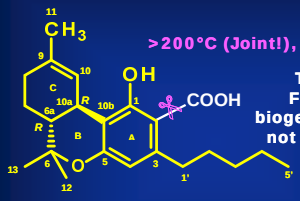
Phytocannabinoids



>200°C (Joint!), storage

THC acid B
Fresh plant, biogenic precursor, not psychoactive

Delta-9-tetrahydrocannabinol (THC)
psychoactive

6a,10a-trans-6a,7,8,10a-tetrahydro-6,6,9-trimethyl-3-pentyl-6H-dibenzo[b,d]pyran-1-ol

Isolated 1942, structure 1964

6

Phytocannabinoids

Δ⁹-Tetrahydrocannabinol, THC, THCV, THC-C3

Cannabidiol, CBD

"Drug type" Cannabis, CB 1 agonist, psychoactive

"Fiber type" Cannabis, industrial hemp

CB_1-R + CB_X-R ? antipsychotic

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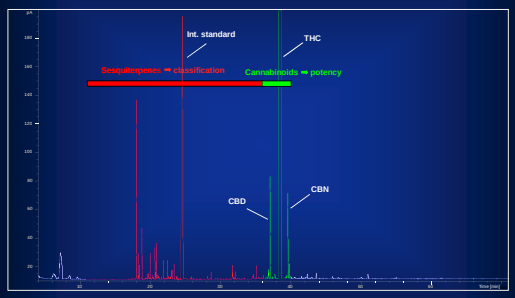
Phytocannabinoids and -noncannabinoids

Gaschromatographic fingerprints



[Brenneisen & ElSohly, J Forensic Sci 1988]

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CBMs and/~~or~~ TBMs ?!

Phytocannabinoids, CBMs

Multicomponent drugs
„Shotgun"

Synthetic Cannabinoids, TBMs and Noncannabinoids

Monocomponent drugs
„Silver bullet"

Modulation of Endocannabinoid System

Therapeutic effect

9

THC and PONV

Gynecology patients
10 mg i.v. THC just after last suture

THC

Side-effects of narcosis ↓ , sleep duration ↑

[Theiler et al., University of Bern 2009, unpublished]

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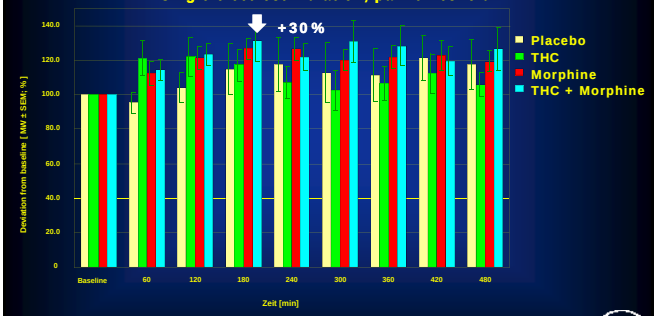
THC and acute pain

Oral THC / morphine synergism

Single electrostimulation, pain threshold



[Naef et al., Pain 2003]

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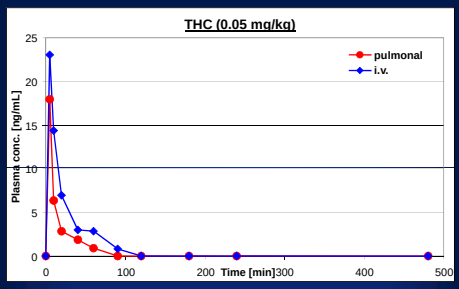
Pharmacokinetics of THC



☺ Bioavailability, rapid onset of effect
☹ Psychotropic side-effects

[Naef et al., J Pharm Sci 2004]

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Cannabis and neuropathic pain

Canadian study on neuropathic pain patients
(N = 23, post-traumatic or post-operative)

⬇

Cannabis, 2.5-9.4% THC
(Prairie Plant Systems Inc., Saskatoon)

⬇

3 x 25 mg Cannabis 9.4% THC per day
for 5 days, smoked

⬇

Pain intensity ↓, sleep quality ↑,
few side-effects (headache, cough, dizziness)

[Ware et al, CMAJ 2010]

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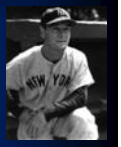
THC/Cannabis and Amyotrophic Lateral Sclerosis

- ALS mouse model:
  transgenic superoxide-dismutase („SOD1^{G93A}“)
- CB_1-R knockout mouse
- In vitro spinal marrow cultures

➡ Cannabis, THC etc.:
Spasticity ↓, excitotoxic and
oxydative cell damages ↓

➡ Neuroprotection

- Swiss clinical studies with THC
- CBMs in self-medication („Sativa-Oil“)



Lou Gehrig
(1903-41)

Stephen Hawkin
(1942-)

[Raman et al., Amyotroph Lateral Scler Other Motor Neuron Disord 2004]
[Weber et al., Univ.hospital St. Gallen & Univ. of Bern, submitted 2012]

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Cannabis and MS-induced muscle spasms

Cheryl & Jim Miller

Relevant studies (N=38)

⬇

Evaluated studies (N=11)

⬇

RDPC studies (N=6)

⬇

Meta analyses (N=1)

⬇

THC-CBD standardized extracts reduced
MS-related spasms

Evidence, that cannabinoids are also
neuroprotective und anti-inflammatoric

[Lakhan & Rowland, BMC Neurol 2009]

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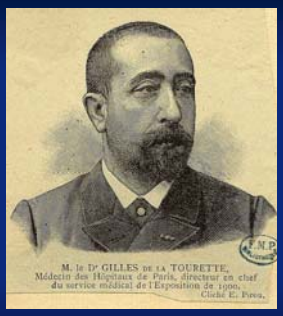
Cannabis and Tourette Syndrome



http://www.planetopia.de/magazin/news-details/datum/2012/03/19/cannabis-gegen-tourette-nur-der-joint-hilft-billy-wieschollek.html

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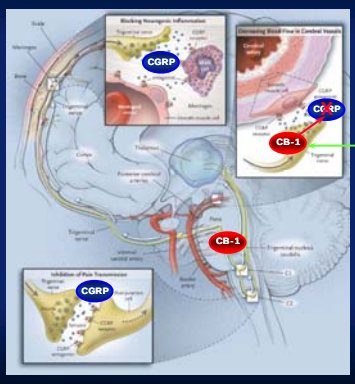
TBMs and migraine



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CBD and heroin addiction

i.v. Cannabidiol (CBD), rat

⬇

Cue-induced heroin seeking ↴

⬇

Specific effect of ECS and glutaminergic system

[Ren et al, J Neurosci 2009]

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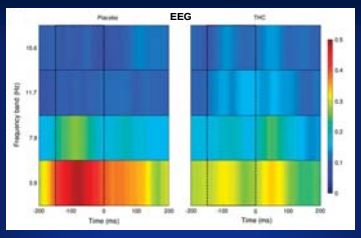
THC and schizophrenia



- Synchronisation of neural oscillations significantly disrupted after 1.25 mg i.v. THC
- Degree of disruption related to THC-induced symptoms (anxiety, persecutory ideation, perceptual abnormalities etc.)
- THC may modulate a similar neural substrate to schizophrenia
- Useful biomarker for development of novel antipsychotics?

[Stone et al, Mol Psych 2011]

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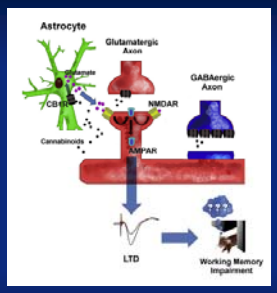
THC and memory impairment



- Impairment of working memory by Cannabis/THC is due to the activation of astroglial CB_1-R

[Han et al, Cell 2012]

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THC + CBD ?

Study on 134 Cannabis users (16-23 yr., min. 1x/month for 1 year)

Group A: THC-rich, CBD-poor drug

Group B: THC-rich, CBD-rich drug

- In contrast to group A subjects of group B did not show acute cognitive deficits and memory impairment.
- Psychotomimetic symptoms equal in both groups.

[Morgan et al, Br J Psych 2010]

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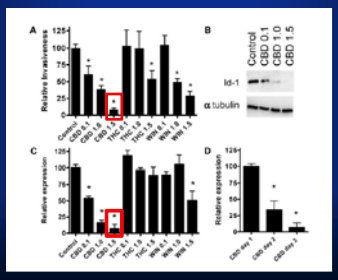
CBD and breast cancer

- „Id-1“ protein: keyplayer in the development of breast cancer metastases, also upregulated in many other tumors.
- CBD ➡ Id-1 gene expression ⤵ ➡ tumor agressivity ⤵ ; low toxicity ➡ ideal candidate for chronic application.



[McAllister et al, Mol Cancer Ther 2007]

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Approved indications for Cannabis in USA

Table 1. Diseases and Conditions for Which Medical Marijuana Use Is Permitted According to State Laws.*

Qualifying Diseases and Debilitating Conditions	Alaska	California	Colorado	Hawaii	Maine	Michigan	Montana	Nevada	New Jersey	New Mexico†	Oregon	Rhode Island	Vermont	Washington
Cancer	X	X	X	X	X	X	X	X	X (if terminal)‡	X	X	X	X‖	X
Glaucoma	X	X	X	X	X	X	X	X	X‡	X	X	X		X‡
HIV-AIDS	X	X	X	X	X	X	X	X	X	X	X	X	X‡§	X
Hepatitis C						X						X		X‡
Alzheimer's disease						X					X	X		
Nail-patella syndrome						X								
Amyotropic lateral sclerosis						X			X					
Cachexia, or wasting syndrome‖	X	X	X	X	X¶	X	X	X	X¶		X	X	X	X‡
Severe or chronic pain‖	X	X	X	X		X	X	X	X¶		X	X	X	X‡
Severe nausea‖	X	X	X	X	X¶	X	X	X	X¶		X	X	X	X‡
Seizures‖	X	X	X	X	X	X	X	X	X‡	X (epilepsy)	X	X	X	X
Intractable spasticity									X‡					X‡
Anorexia		X												X‡
Severe muscle spasms	X	X	X	X	X	X	X	X			X	X		X‡
Multiple sclerosis									X	X			X	X
Spinal cord damage, with neurologic indication of muscular spasticity										X				
Appetite loss					X¶									X‡
Cramping														X‡
Arthritis		X												
Migraine		X												
Muscular dystrophy									X					
Inflammatory bowel or Crohn's disease						X			X					X‡
Admission to hospice care or terminal illness									X‡	X				
Any other chronic or persistent medical condition		X**												
Any other medical condition approved by state agency	X		X	X	X	X	X	X	X	X	X	X		X

[Hoffmann & Weber, N Engl J Med 2010]

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Cannabis and glaucoma

NIDA Cannabis 3.56% THC
US Cannabis IND Program
Only anecdotal evidences, no RDPC studies

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Cannabis as doping agent

- 2004: Cannabis banned by WADA at competion (THC-COOH ≥15 ng/mL).
- ≈ 50 % of positive doping cases due to Cannabis consumption (Switzerland, Germany, ...). Team players (ice hockey, handball), X-treme sports athletes (snowboard), table tennis, ...
- Cannabis sensu stricto not a doping agent, as cognition and physical performance impaired!
- Motivation for use:
  - Therapeutic: stress reduction before competition, pain killer, sleep enhancer, appetizer, etc.
  - Social: recreational activities and contacts (excuse: passive inhalation).

[Saugy et al, Br J Sports Med 2006; Lorente et al, Addict Behav 2005]

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Cannabis as doping agent

Dutch State Medicinal Cannabis as clinical preparation

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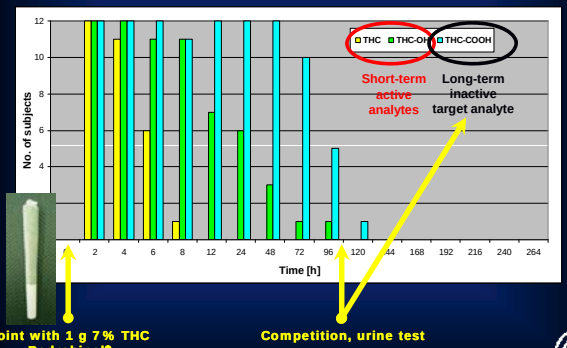
Cannabis as doping agent



[Brenneisen et al, ABC 2010]

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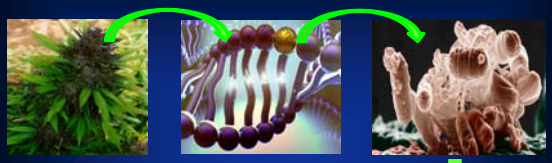
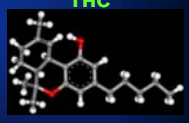
Logistic shortage - THC from E. coli



THC



- Need Germany: 1 t THC per year.
- Extraction from fiber-type Cannabis: 20 kg, 50‘000 €/kg
- Synthesis: xx kg, >>50‘000 €/kg
- Biotechnological production E.coli: xx kg, 2‘500 €/kg.

[Technical University Dortmund 2010]

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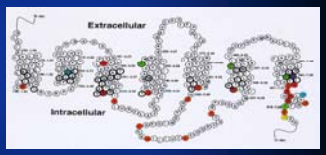
Endocannabinoid System - Discovery

Milestones

1988: Discovery of endogenous cannabinoid system ➡ CB_1 receptor



All mammals, but also leeches, birds, amphibians, fishs, see urchins, mussels, etc.; not insects.

[Devane et al, Mol Pharmacol 1988]

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ECS - Discovery

Milestones (cont.)

1992: First CB_1-R ligand from pork brain: arachidonylethanolamide, „anandamide“, AEA
[Devane et al, Science 1992]

1993: CB_2 receptor (rat spleen)
[Munro et al, Nature 1993]

1994: First synthetic CB_1-R antagonist (SR 141716A, rimonabant, Acomplia®; Sanofi)
[Rinaldi-Carmona et al, FEBS Lett 1994]

1997: Second CB_1-/CB_2-R ligand: arachidonylglycerol, 2-AG
[Stella et al, Nature 1997]

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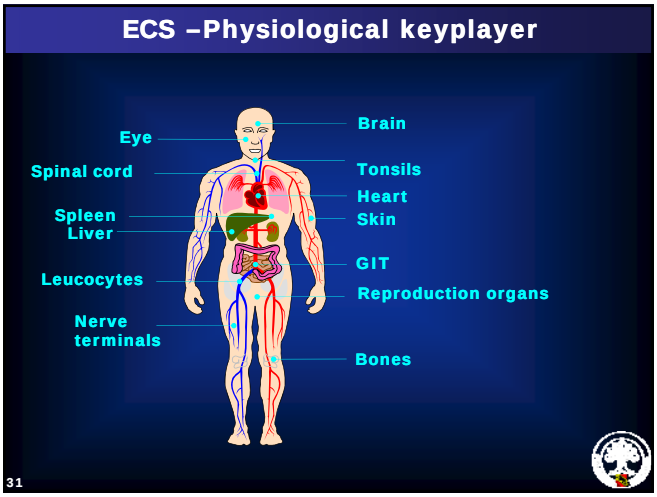
ECS –Physiological keyplayer



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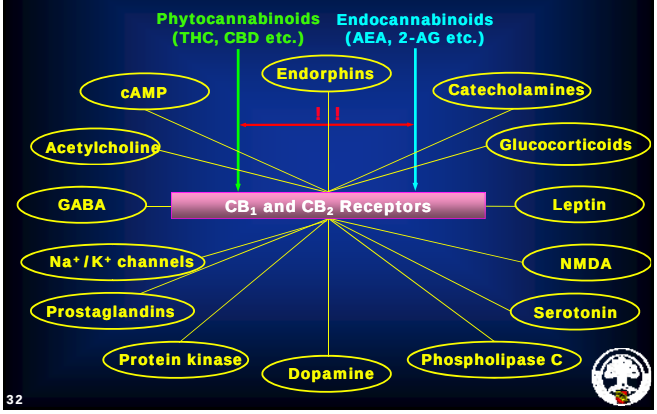
ECS – Physiological keyplayer



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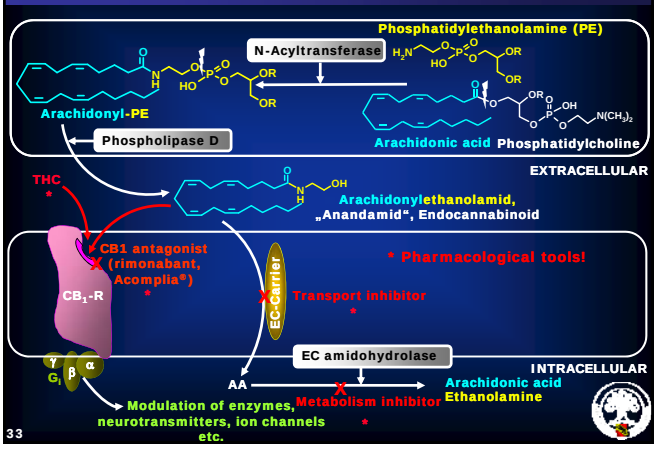
ECS – Target for therapeutic tools



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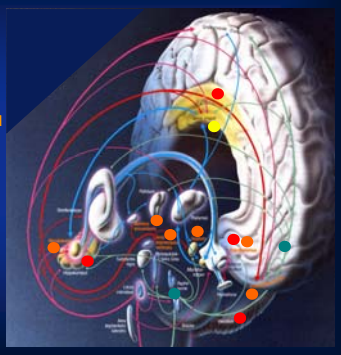
ECS and addiction

- CB_1-R
- Limbic system
- Mesolimbic „Reward System“
- Serotonergic system



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ECS and appetite

Appetite ↑ after Joint (CB_1-R agonism of THC)
Therapeutic option „Waisting Syndrom“

Appetite ↓ after rimonabant (Acomplia®), CB_1-R antagonism
Therapeutic options overweight, metabolic syndrome, nicotine withdrawal symptoms
Risk of depression and suicide!

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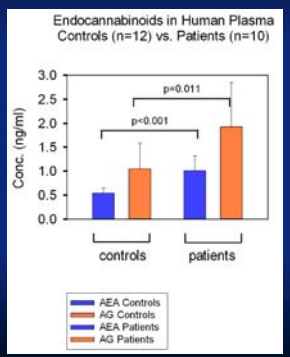
ECS and liver diseases

Endocannabinoid plasma levels in cirrhotic patients



[Lanz et al, unpublished]

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ECS – Essential to survive ?

ECS directly or indirectly involved in:

- Effects of THC
- Processing of negative memories, traumas, stress
- Mental diseases, psychiatric disorders (schizophrenia, depression)
- Drug abuse
- Modulation of anxiety
- Sleep control
- Perception of pain
- Control of movement
- Control of food intake, appetite
- ...

Vincenzo di Marzo:
"The endocannabinoid system is essential to life and it relates messages that affect how we relax, eat, sleep, forget and protect"

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Summary, Conclusions (1)

- Discrepancy between empirical folk medicine and evidence-based modern medicine.
- Ethnomedical bonus usually not accepted by modern medicine.
- Uncritical, non-controlled self-treatment results in risk of patient's criminalization.
- Cannabis is a safe but highly potent therapeutic drug without risk of dependency if used under strict medical control.
- The endocannabinoid system is a most interesting target for the development of innovative new drugs.

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Summary, Conclusions (2)

Therapeutic potential:

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Summary, Conclusions (3)

- Very broad indication spectrum, however not a wonder drug.
- Narcotic, therefore not to be sold over-the-counter.
- In competition with established drugs of „school medicine“.
- Stigmatization as „illicit drug“ and not yet fully available clinical evidence still inhibit justified remedicinalization.
- Further RDPC trials needed.

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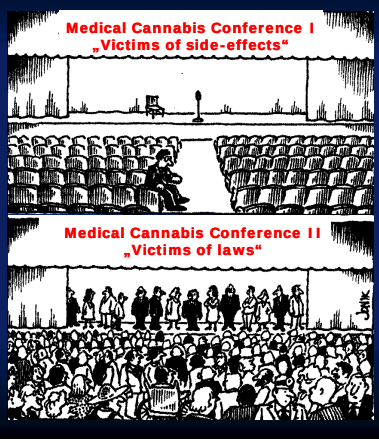
Summary, Conclusions (5)

41

Thank you !



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