The Cannabinoids:

Looking Back and Ahead

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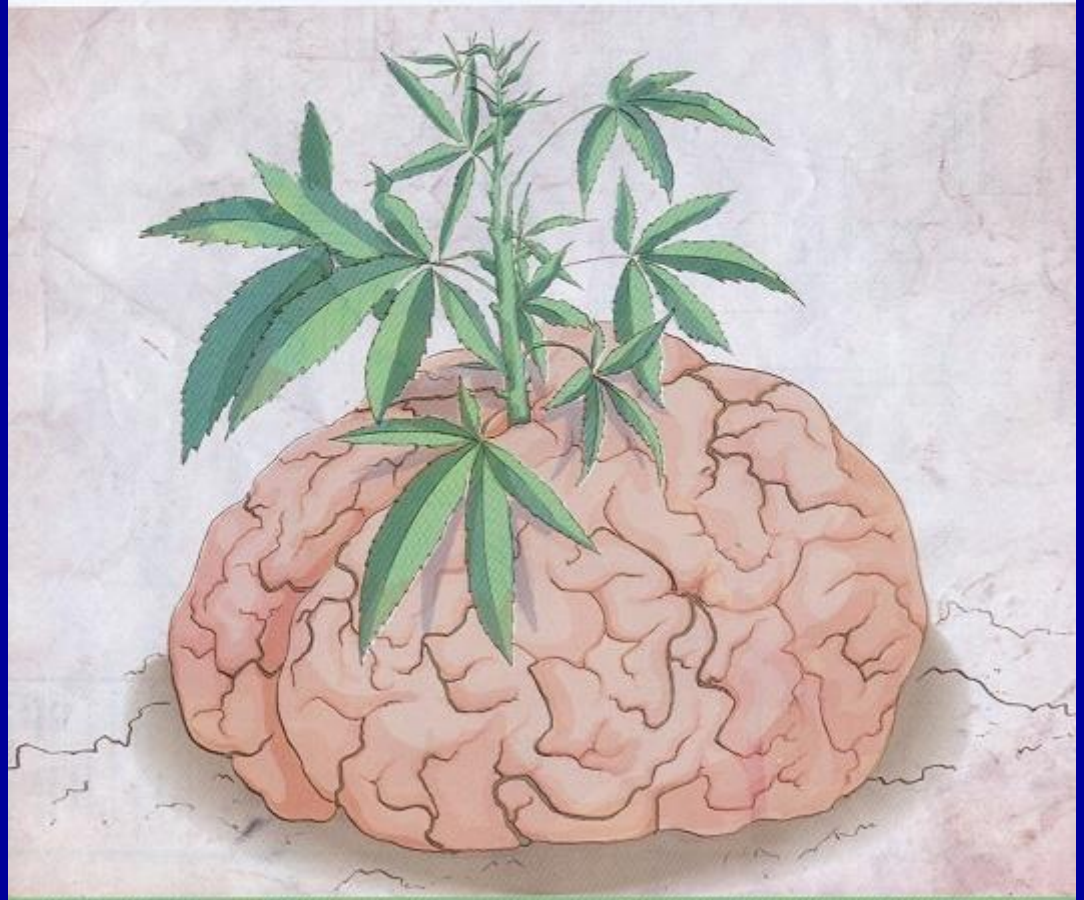
NEUROSCIENCE



FROM THE ANCIENT WORLD TO THE CLINIC
The story of cannabinoids

Hippocampal time cells
Mapping the fourth dimension

"….modulating endocannabinoid activity may have therapeutic potential

in almost all diseases affecting humans,

including obesity/metabolic syndrome, diabetes and diabetic complications, neurodegenerative, inflammatory, cardiovascular, liver, gastrointestinal, skin diseases, pain, psychiatric disorders, cachexia, cancer, chemotherapy-induced nausea and vomiting, among many others."

Pacher and Kunos review, FEBS, 2013

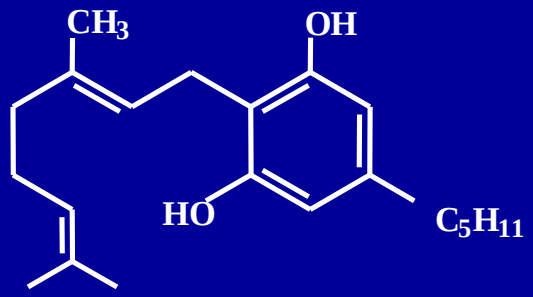
Gan-zi-gun-nu – the drug that takes away the mind
Azallu – hand of ghost, poison of all limbs (neurological diseases?)
Qunnabu – used in religious rites

Phases of cannabinoid research

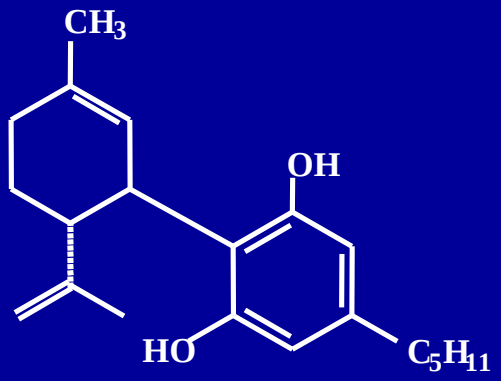
1. Phytocannabinoid research

2. Endocannabinoid research (anandamide and 2-AG)

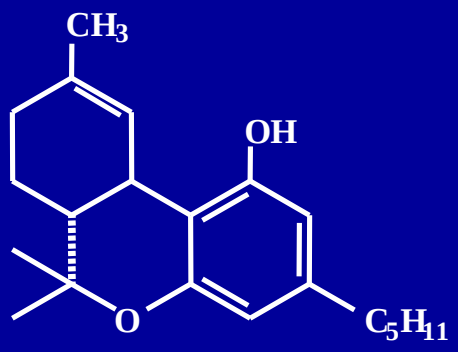
3. Endogenous, anandamide - like compounds



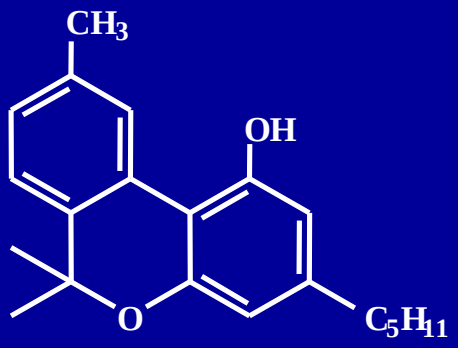
cannabigerol (CBG)
(Gaoni and Mechoulam, 1964)



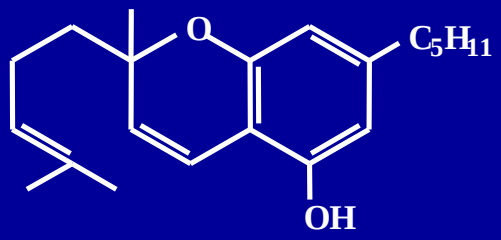
cannabidiol (CBD)
(Mechoulam and Shvo, 1963)



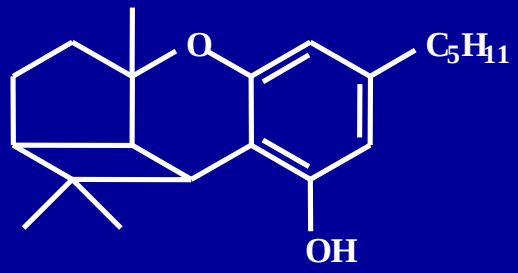
Δ^9-tetrahydrocannabinol (Δ^9-THC)
(Gaoni and Mechoulam, 1964)



cannabinol (CBN)
(Adams et al., 1940)

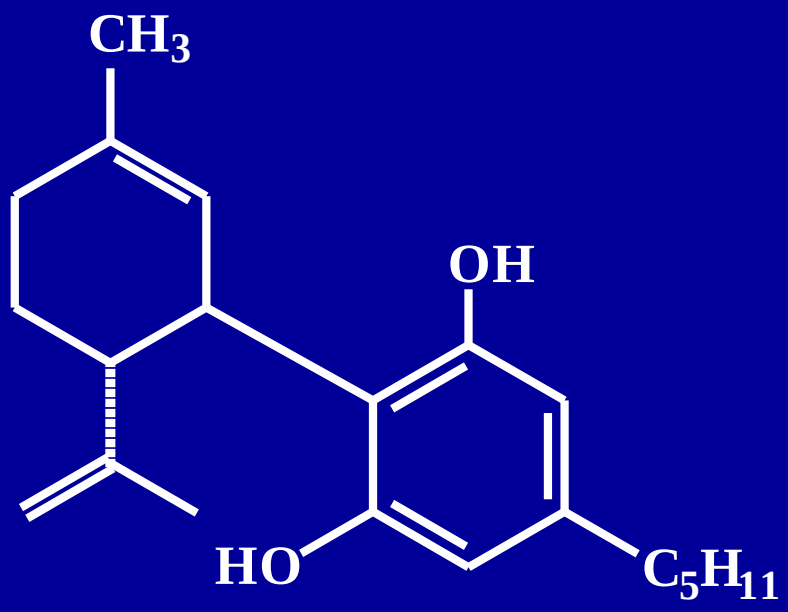


cannabichromene (CBC)
(Claussen et al., 1966;
Mechoulam and Gaoni, 1966)



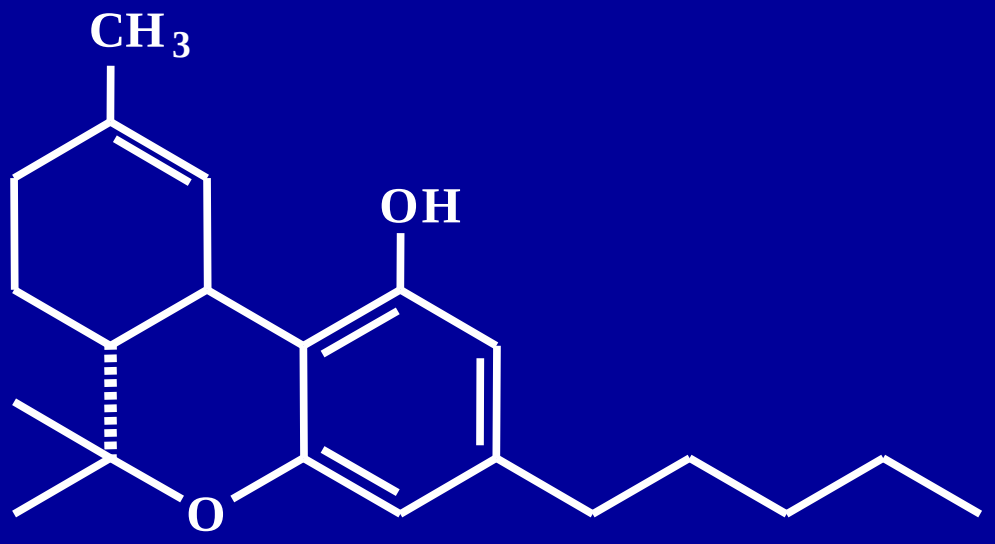
cannabicyclol (CBL)
(Crombie et al., 1968)

Representative natural cannabinoids



cannabidiol (CBD)

Mechoulam and Shvo:
Tetrahedron ***19***,2073 (1963)



Δ^9-tetrahydrocannabinol (Δ^9-THC)

Gaoni and Mechoulam:
J.Amer.Chem.Soc. ***86***, 1646 (1964)

Entourage effect – enhancement of cannabinoid effects by non-cannabinoid compounds.

Thus, Cannabis indica differs from Cannabis sativa although their cannabinoid content may be the same.

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THC medical actions:

Pain

Elimination of side effects of cancer chemotherapy

Post trauma

CBD actions

Epilepsy

Double blind.
Drug: CBD in capsules
Patients: 15 epileptic patients, who did not benefit from known antiepileptic drugs.
Dose: 200-300 mg/day for 4.5 months.
Results: 4 patients (out of 8) remained almost completely free of seizures.
3 patients had partial improvement
1 patient showed no improvement
Placebo patients: only one showed improvement

Cunha, Carlini, Mechoulam, 1980

Graft-versus-host disease

Graft-versus-host disease (GVHD) is a complication that can occur after a bone marrow transplant in which the newly transplanted donor cells attack the transplant recipient's body.

M. Yeshurun et al., (2014) administered CBD (300mg/day) to 46 patients with hematological malignancies for 30 days and followed them for 8 months.

Chronic GVHD (after 100 days)

	101 patients control	46 patients (with CBD)
2-4 grade	46%	12%
3-4 grade	10%	5%

Schizophrenia

In a double-blind, anti-schizophrenia clinical trial of CBD vs amisulpride (a potent antipsychotic) both treatments led to significant clinical improvement, but CBD displayed a superior side effect profile. Moreover, CBD treatment was accompanied by a significant increase in serum anandamide levels (Leweke et al., 2012)

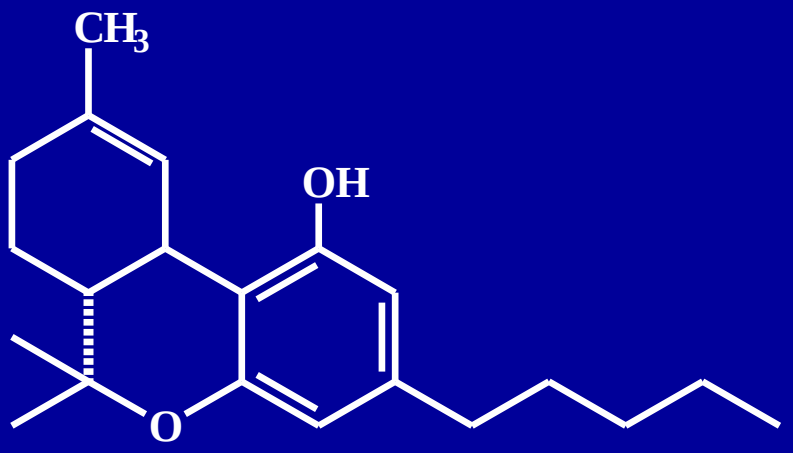
Diabetes type 1

Histological analysis of pancreas tissue from mice treated with CBD and untreated.

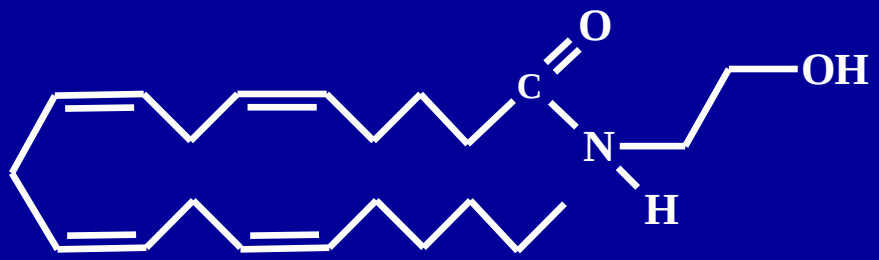
Untreated	**5% intact cells**
CBD	**77% intact cells**

Brain regions in which cannabinoid receptors are abundant

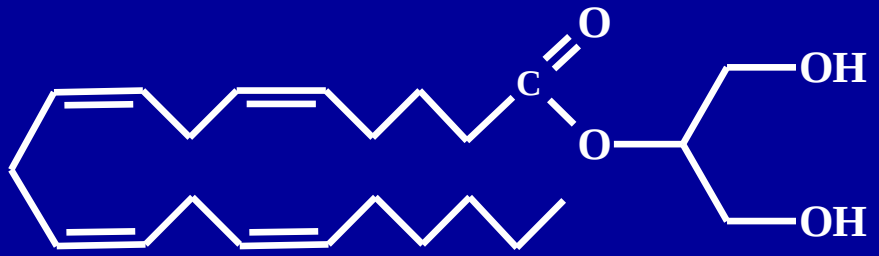
Basal ganglia	Movement control
Substantia nigra pars reticulata	
Enteropeduncular nucleus	
Globus pallidus	
Putamen	
Cerebellum	Body-movement coordination
Hippocampus	Learning and memory, stress
Cerebral cortex, especially cingulate, frontal, and parietal regions	Higher cognitive function
Intrabulbar anterior commissure	Link between cerebral hemispheres
Nucleus accumbens	Reward pathway



Δ^9-tetrahydrocannabinol
(Δ^9-THC)



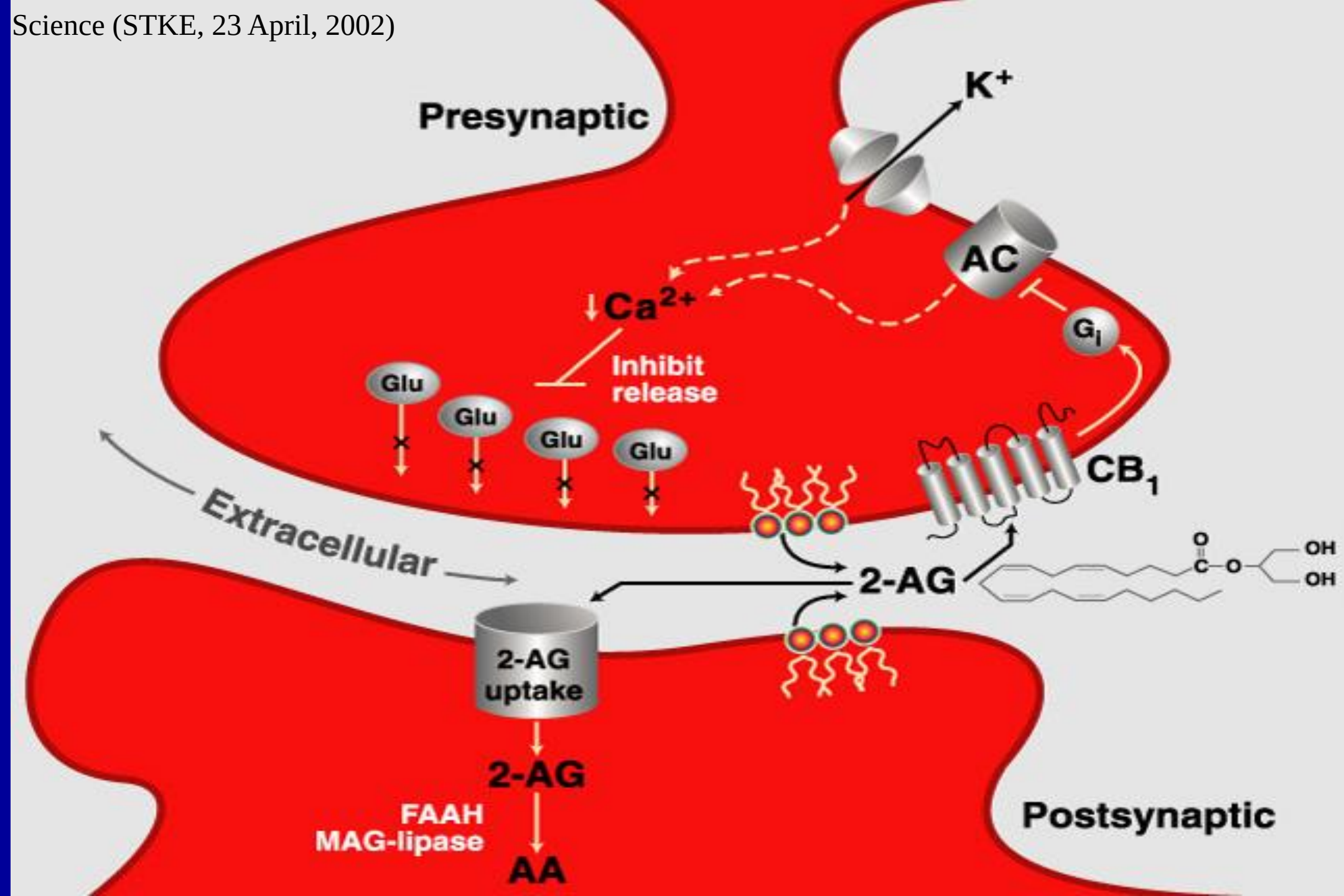
anandamide



2-arachidonoyl glycerol
(2-AG)

Science, 258, 1946-1949 (1992)

Science (STKE, 23 April, 2002)

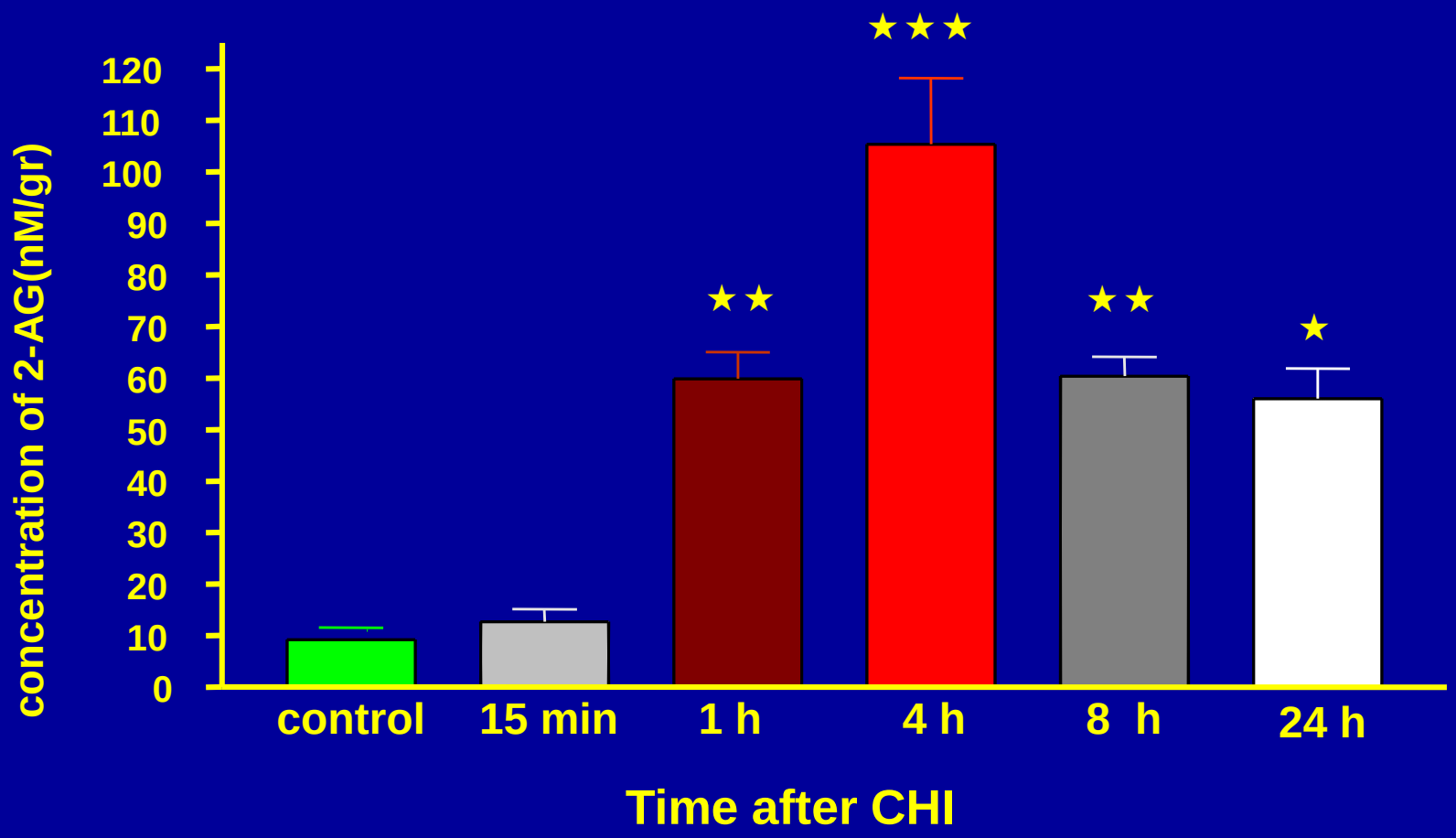


Physiological systems and conditions affected by cannabinoids (a partial list)

Anxiety
Appetite/feeding
Blood pressure
Bone formation
Cerebral blood flow
Digestive system
Emesis and nausea
Immune system
Inflammation
Memory
Mood
Movement
Neuroprotection
Pain
Reproduction
Stress

Neuroprotection

Levels of 2-AG in mouse brain after CHI



Anova with Tukey post-test:P<0.0001, F=36.01

★★★ -P<0.001 vs. control

★★ -P<0.01 vs. control

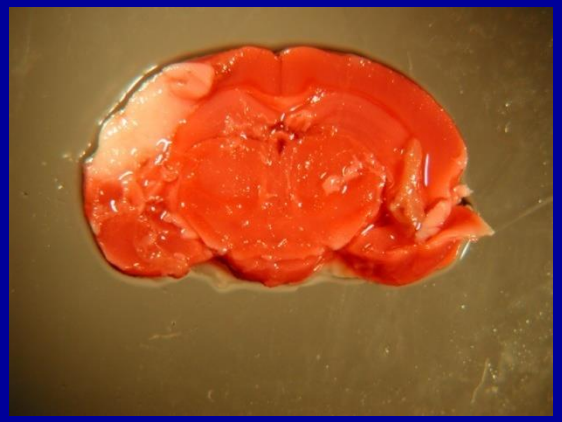
★ -P<0.05 vs. control

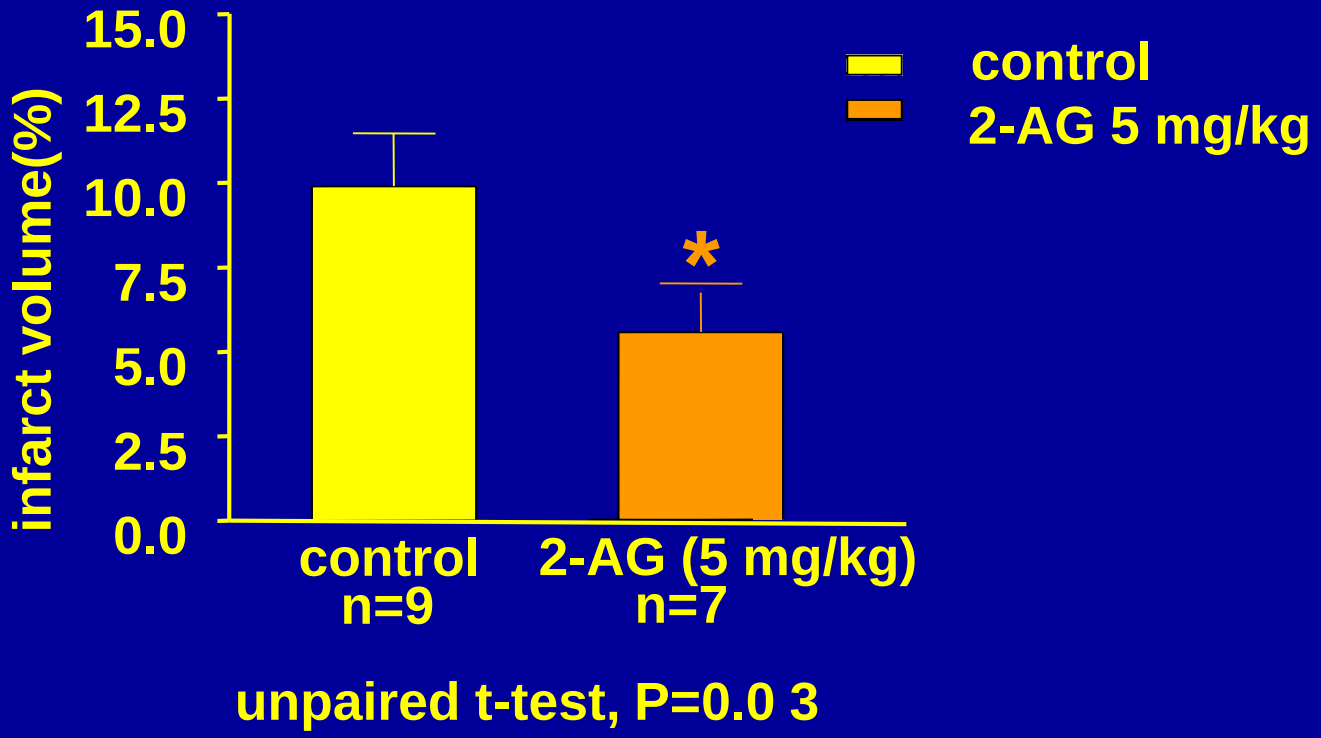
Nature 413, 527 (2001)

2-AG Reduces Infarct Volume 24 h After CHI

2-AG

control





Role of CB2 receptor signaling in disease

Myocardial infarction

Atherosclerosis

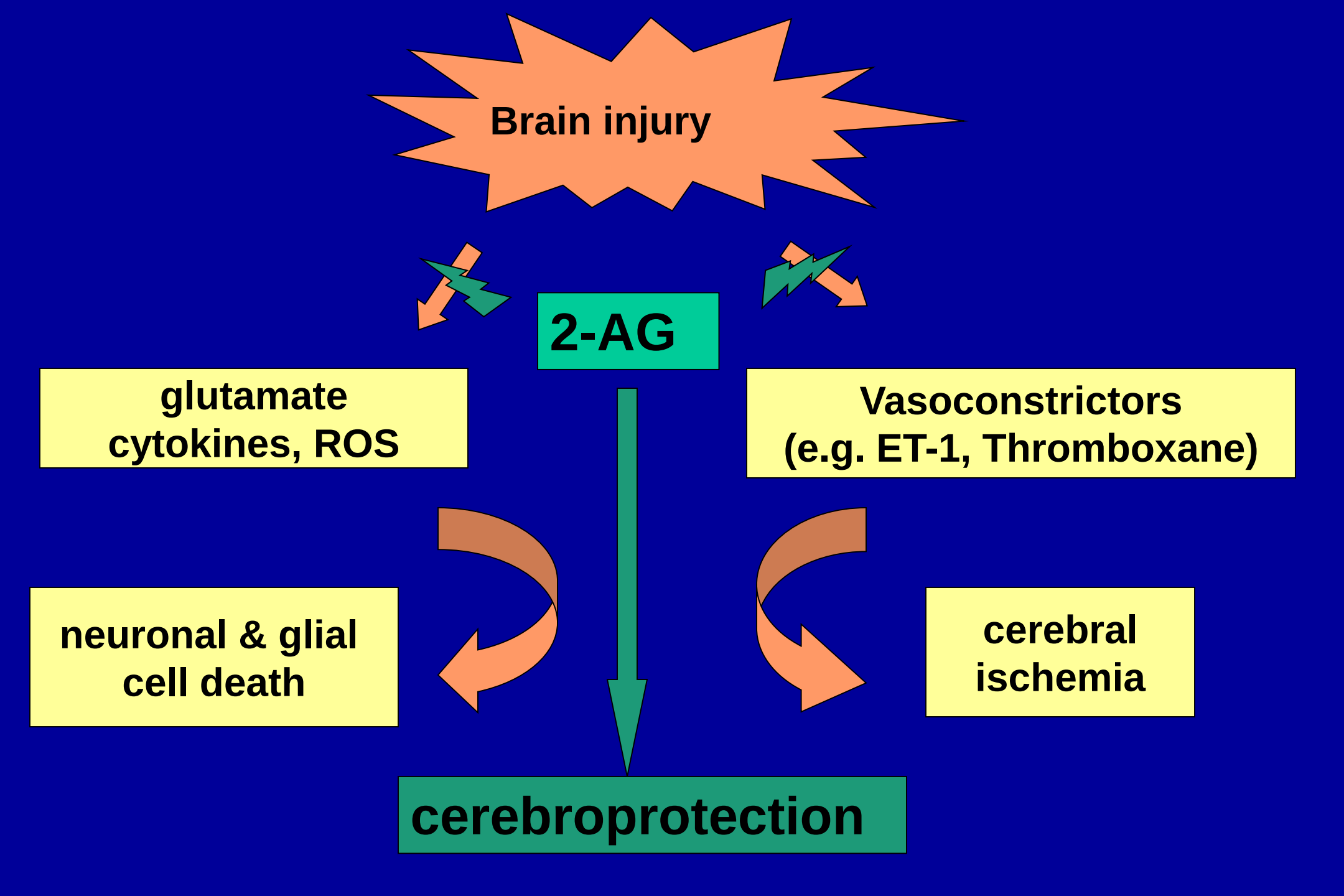
Stroke

Liver fibrosis

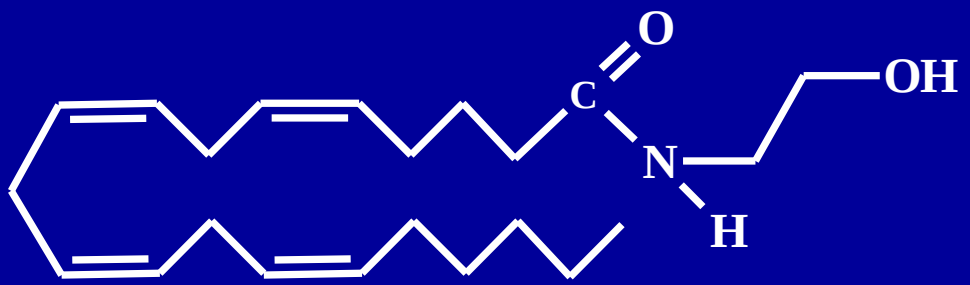
Rheumatoid arthritis

Neurodegenerative diseases

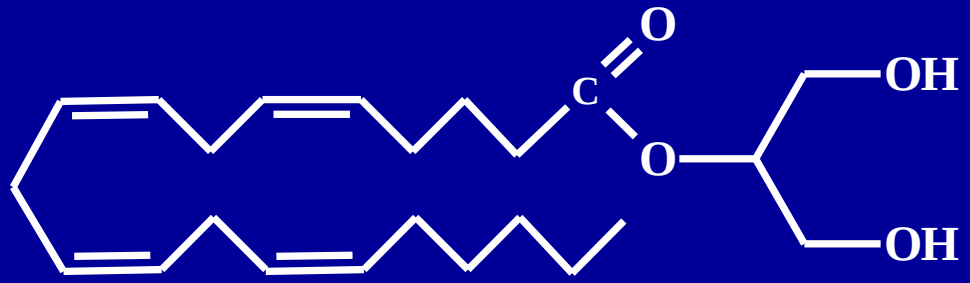
Pain


Brain injury
2-AG
glutamate
cytokines, ROS
Vasoconstrictors
(e.g. ET-1, Thromboxane)
neuronal & glial
cell death
cerebral
ischemia
cerebroprotection

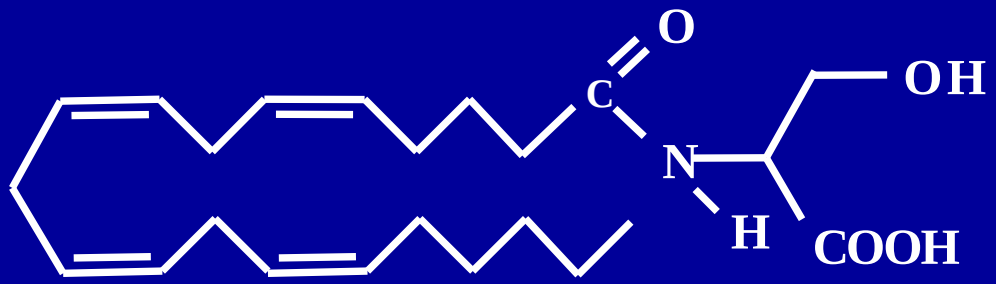
Regulation of vasodilation



anandamide

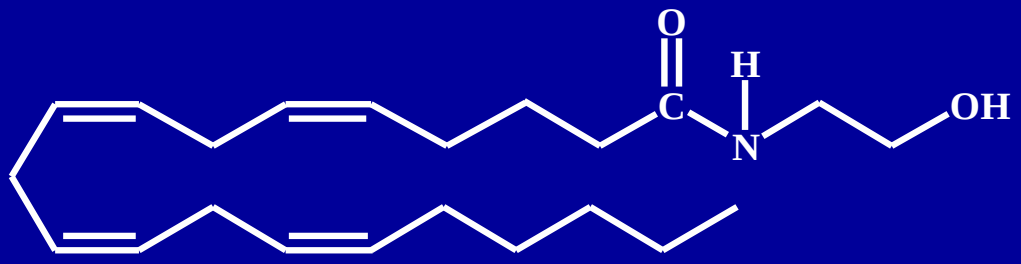


2-arachidonoyl glycerol
(2-AG)

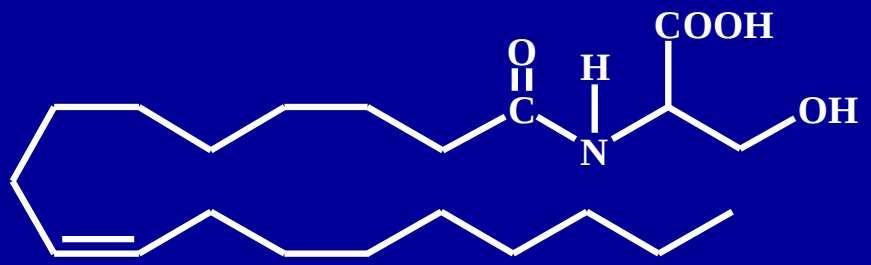


arachidonoyl serine

Bone Remodeling



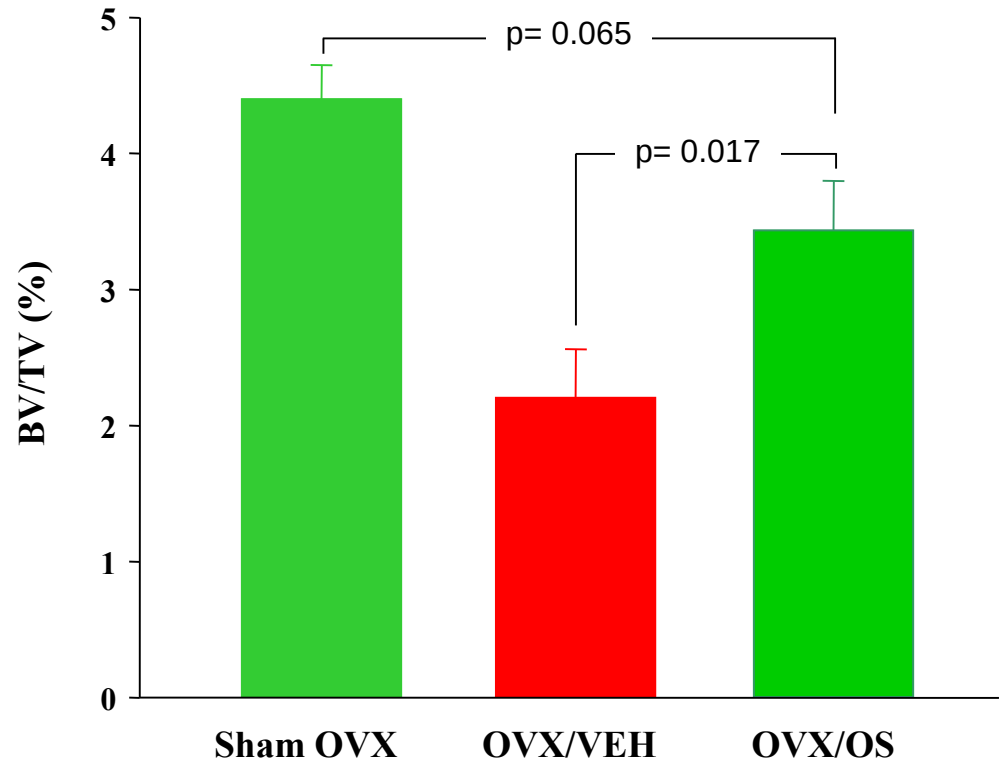
arachidonoyl ethanolamide (anandamide)

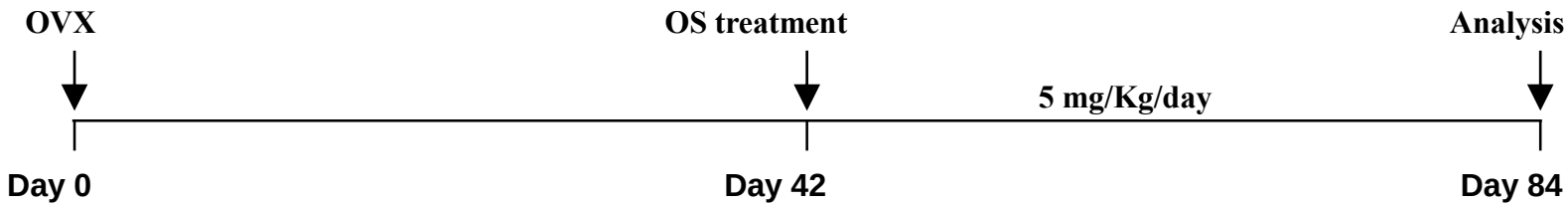


oleoyl serine (HU-639)

PNAS, 2010

Oleoyl Serine Rescues Ovariectomy-induced Bone Loss





Oleoyl glycine blocks nicotine addiction in mice

and (possibly) in addicted humans.

SUMMARY

1. Endocannabinoids are involved in a large number physiological processes. THC – a plant cannabinoid – mimics their actions.

2. CBD derivatives – may lead to a wide spectrum of novel drugs.

3. Endocannabinoid-like compounds may lead to better understanding of biological processes as well as to novel drugs.

4. CB_2 specific agonists – may lead to a wide spectrum of novel drugs. May be part of a general protective system

Collaboration in Israel

Jerusalem

Prof. L. Hanuš
Prof. E. Fride
Dr. W. A. Devane
Dr. A. Breuer
Dr. S. Ben-Shabat
Dr. D. Panikashvili
Dr. G. Milman
Dr. N. Kogan

Jerusalem

Prof. I. Bab
Prof. E. Shohami
Prof. R. Gallily
Prof. E. Berry
Dr. R. Durst

Haifa

Prof. A. Mandelbaum

Rehovot

Prof. Z. Vogel

Tel Hashomer

Dr. S. Almog

Collaboration abroad

Aberdeen
R. Pertwee

Bonn
M. Karsak
A. Zimmer

Brno
A. Šulcová

Greece
C. Simeonidou

Richmond
B. Martin
A. H. Lichtman

Canada
L. A. Parker

Bethesda
G. Kunos
M. Spatz

Napoli
V. Di Marzo

Rome
M. Maccarrone

Siberia
L. Maslov

London
M. Feldmann
A. M. Malfait
P. F. Sumariwalla