Institute of Experimental Medicine
Hungarian Academy of Sciences,
Budapest, Hungary

Discovery research in the field of brain disorders: the greatest demand in medicine in the 21st century

Tamás F. Freund

World Science Forum, 5th Nov. 2015, Budapest

The greatest intellectual challenge of science and mankind is:

Understanding the brain

NAP

HUNGARIAN BRAIN RESEARCH PROGRAM

NEMZETI AGYKUTATÁSI PROGRAM

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Disorders of the brain:

the greatest societal and economical challenge of mankind.

The cost of nervous system disorders in the EU in 2010:

798 billion Euro

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Gustavsson et al. (2011) Eur. Neuropsych. 21, 718-779.

Cost of Disorders of the Brain in Europe in 2010.

Comparison with the costs of other major disorders:

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Cardiovascular disorders: €192 billion (in 2008)

Cancer: € 150-250 billion (in 2010)

Diabetes: € 20-83 billion (in 2010)

Rheumatoid Arthritis: € 25.1 billion (in 2008)

Chronic pulmonary disorders: € 39 billion (in 2006)

Total (non-nervous disorders): ~ **€ 500 billion**

Nervous system disorders: **€ 798 billion**

The economical and societal burden keeps growing:

- The incidence of Alzheimers disease and other dementias increases with increasing life expectancy.
- The explosion of information and communication technologies, globalization, worldwide economical and financial crises leads to an increasing adaptational pressure on the brain, and consequent mental disorders like depression, anxiety, addiction, chronic stress and schizophrenia.
- According to WHO data, the most devastating diseases from the economical point of view during the 2020-30s will be depression, anxiety and their somatic consequences.

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High priority support of research into the mechanisms of brain disorders is an urgent political task!

New drugs, pharmacotherapies and prevention strategies can only be expected from new discoveries: support basic research!

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2013. January 28. – The European Union announces the largest single program of its history, the Human Brain Project, HBP with a budget of 1.2 billion Euros for 10 years.

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2013. April 2. – President Barack Obama announces the USA BRAIN Initiative (**B**rain **R**esearch through **A**dvancing **I**nnovative Neurotechnologies) program with a budget of 3 billion USD for 10 years.

The structure of NAP

BOARD OF DIRECTORS	
Program President	President: Tamás F. Freund
Pillar Directors / Pillar Co-Directors	

THEMATICAL PILLARS	DISCOVERY RESEARCH	CLINICAL NEUROSCIENCE	PHARMACEUTICAL RESEARCH	BIONICS, INFOBIONICS	EPIDEMIOLOGY, NEUROETHICS, LAW, SOCIETAL, ECONOMICAL IMPLICATIONS
Pillar Directors / Pillar Co-Directors	Gábor Tamás Zoltán Nusser	Tamás Dóczi István Bitter László Vécsei	Zsolt Szombathelyi György Keserű	István Ulbert Lóránd Erőss	Ferenc Oberfrank László Csiba

NAP Director

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NAP B Program

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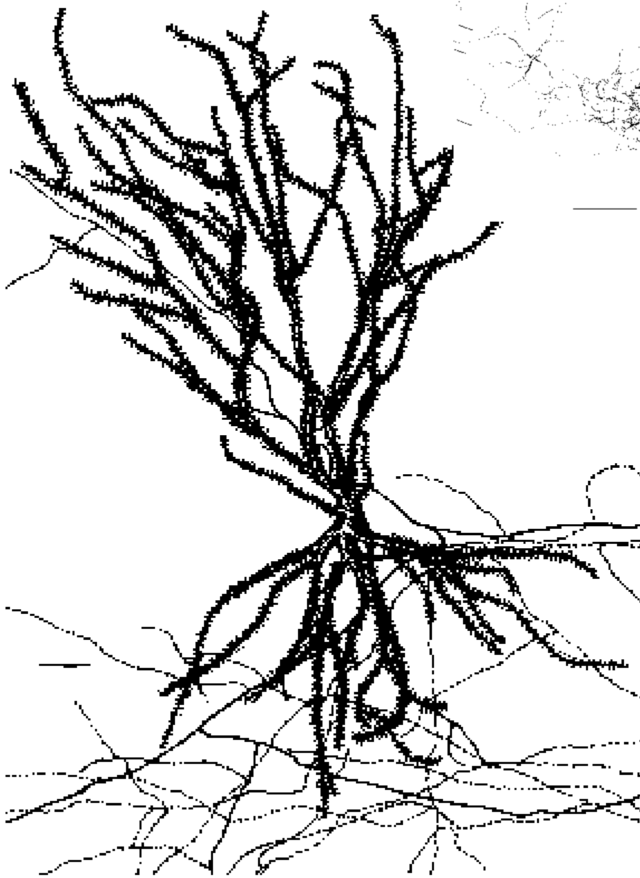
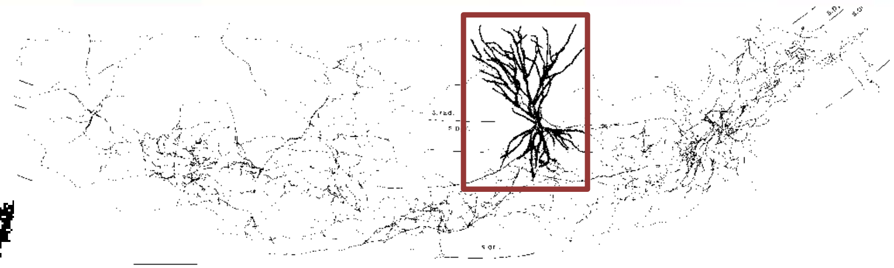
Nerve cells form complex networks



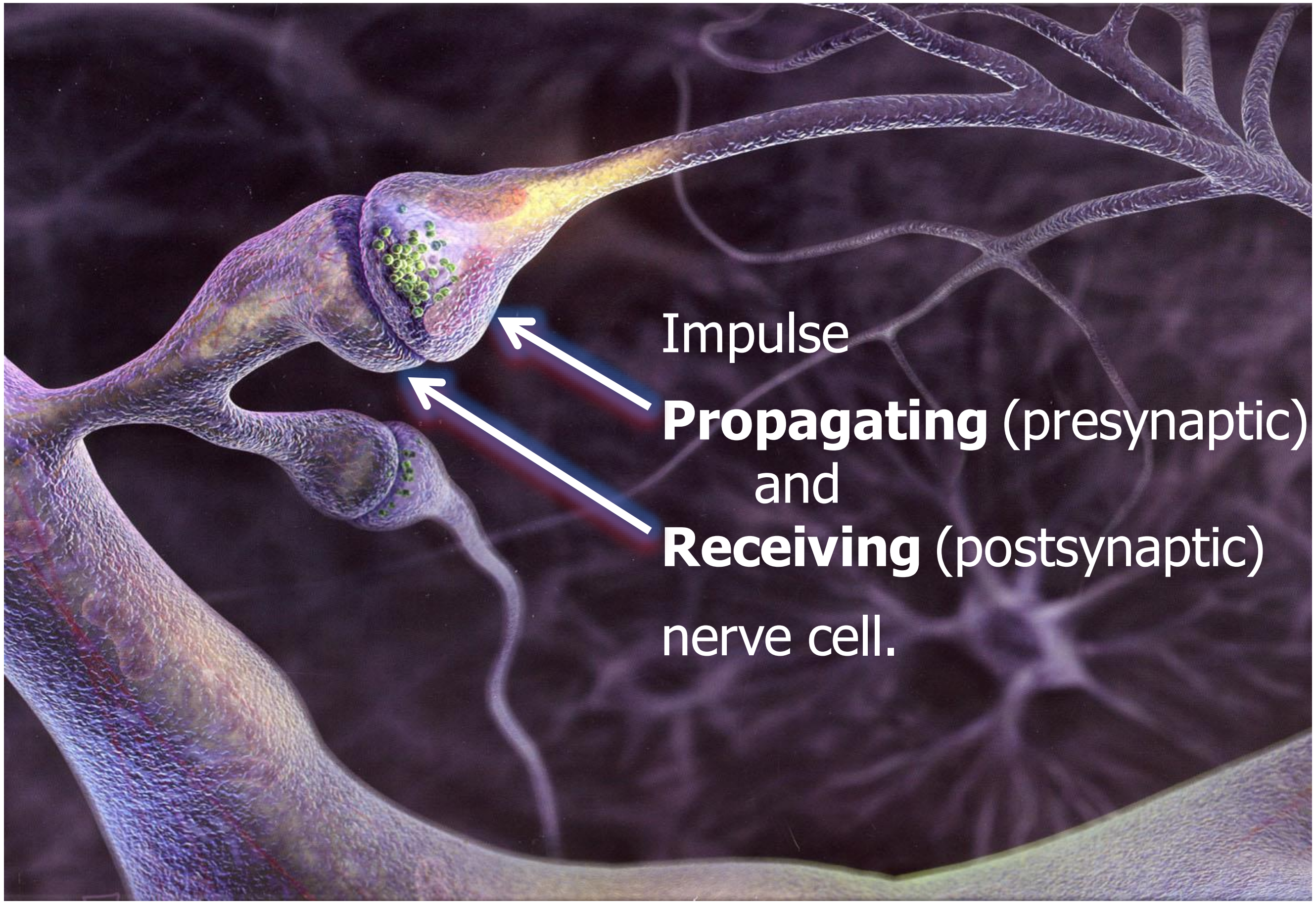


<u>The cerebral cortex has nearly 100 billion neurons, each connecting to 50-100 thousand others.</u>

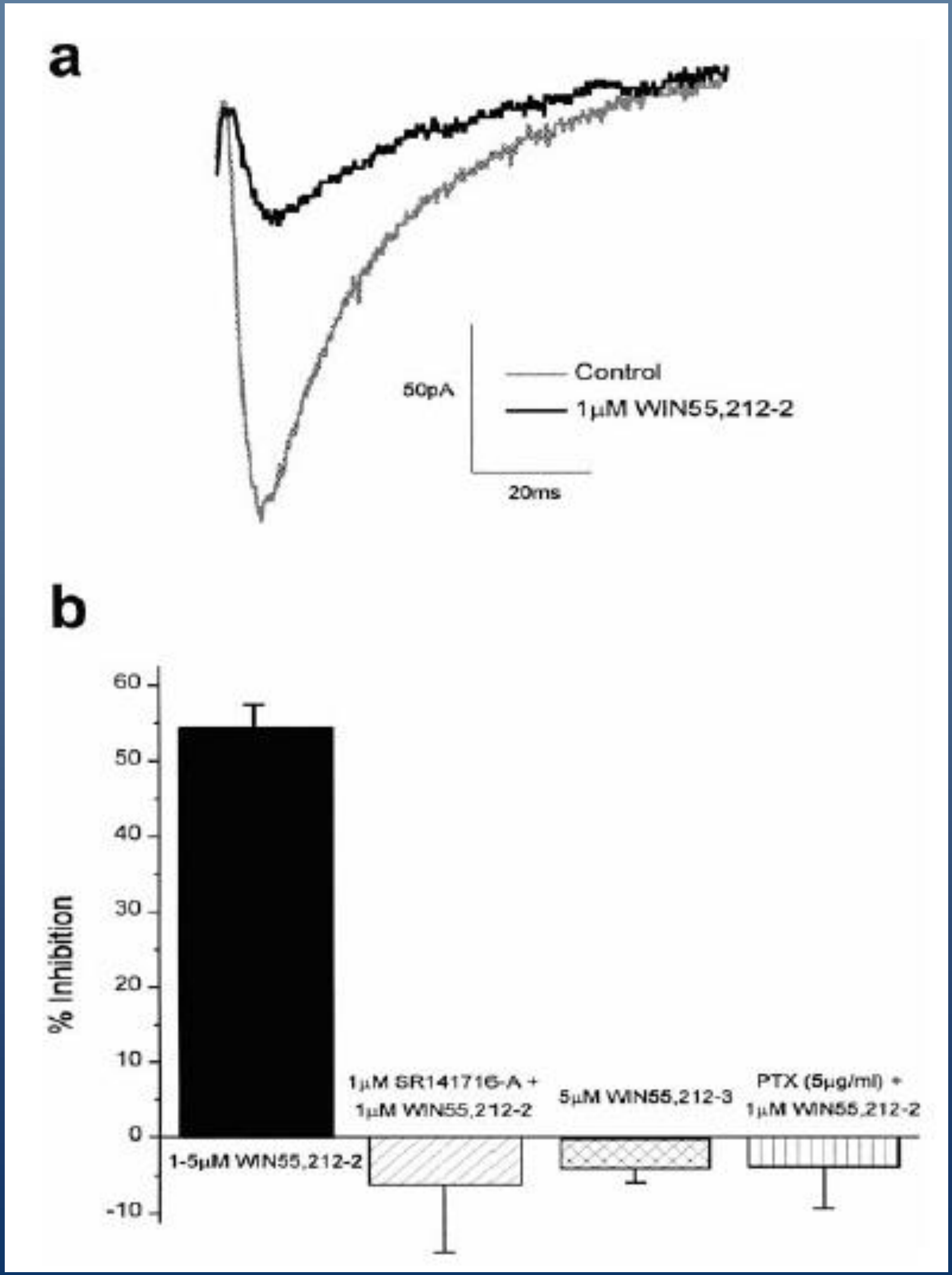
<u>Dendrites</u> receive impulses from 15-20 thousand other neurons.

<u>Axons</u> pass on impulses to 40-60 thousand other neurons.

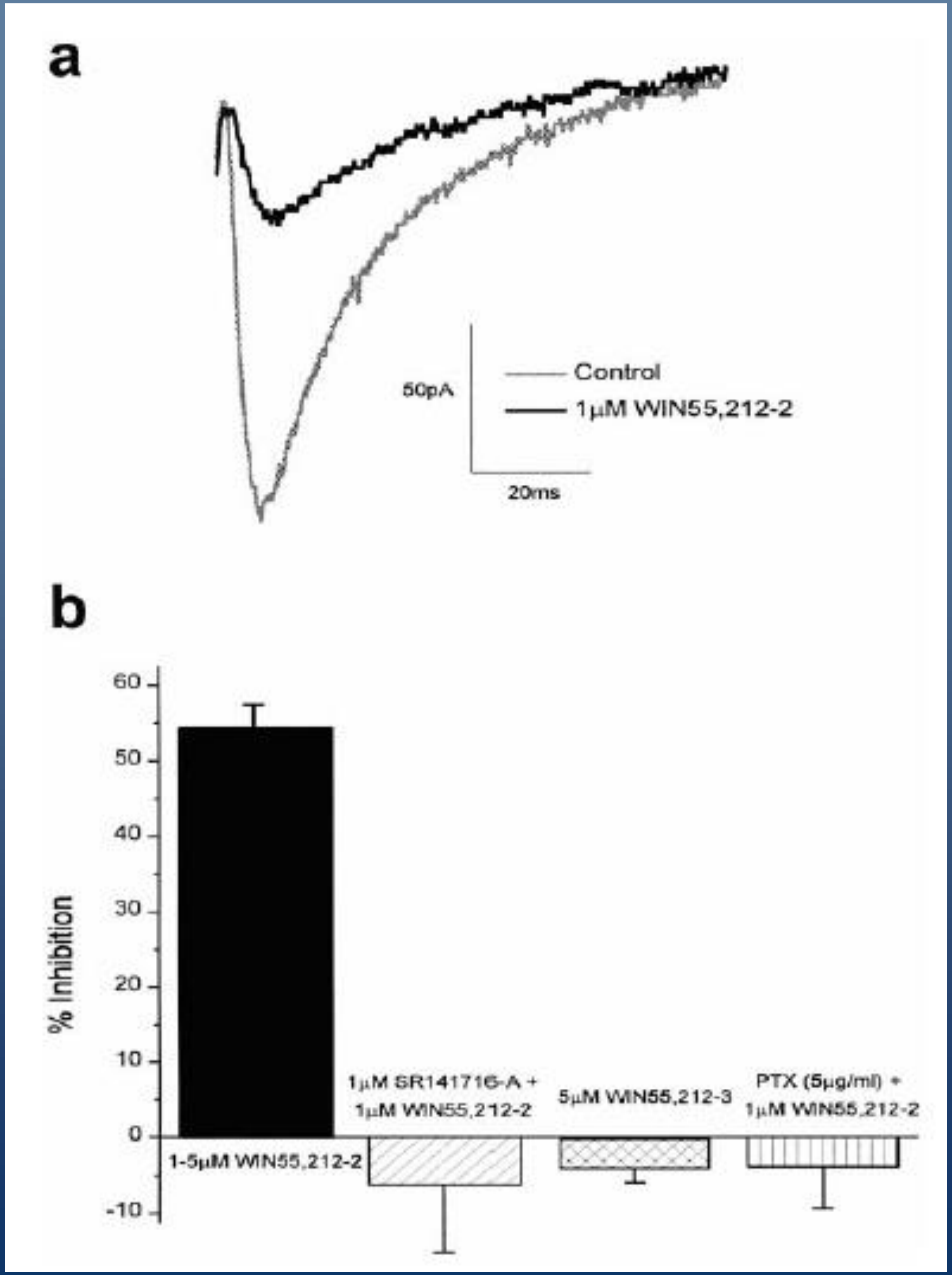
The excitatory (glutamate-containing) synapse



The strength of the synapse is regulated in a feed-back manner, but the retrograde signal molecule was unknown.



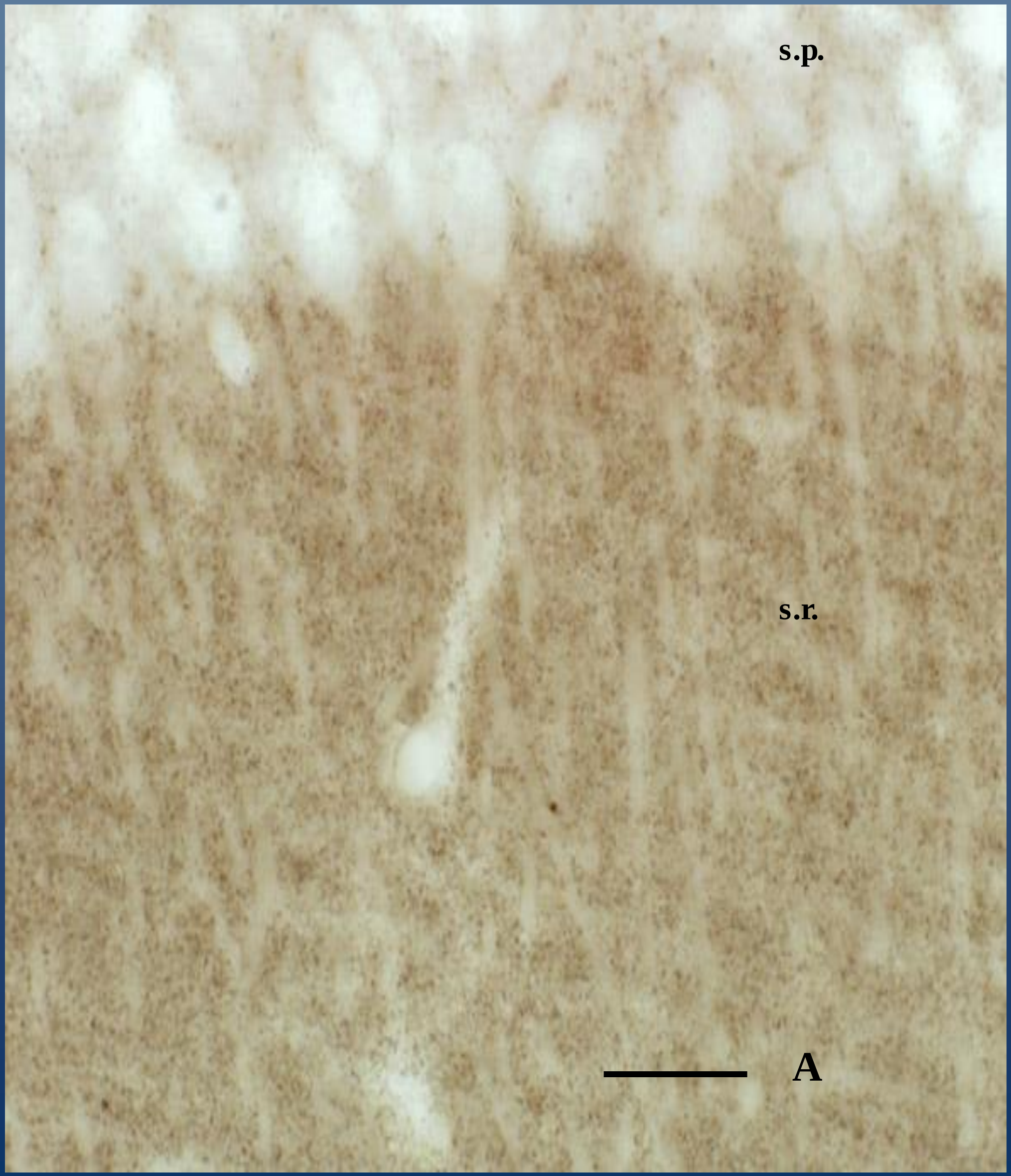
Cannabinoids, e.g. THC, the psychoactive compound of marijuana, and the endocannabinoid 2AG reduce glutamate release.



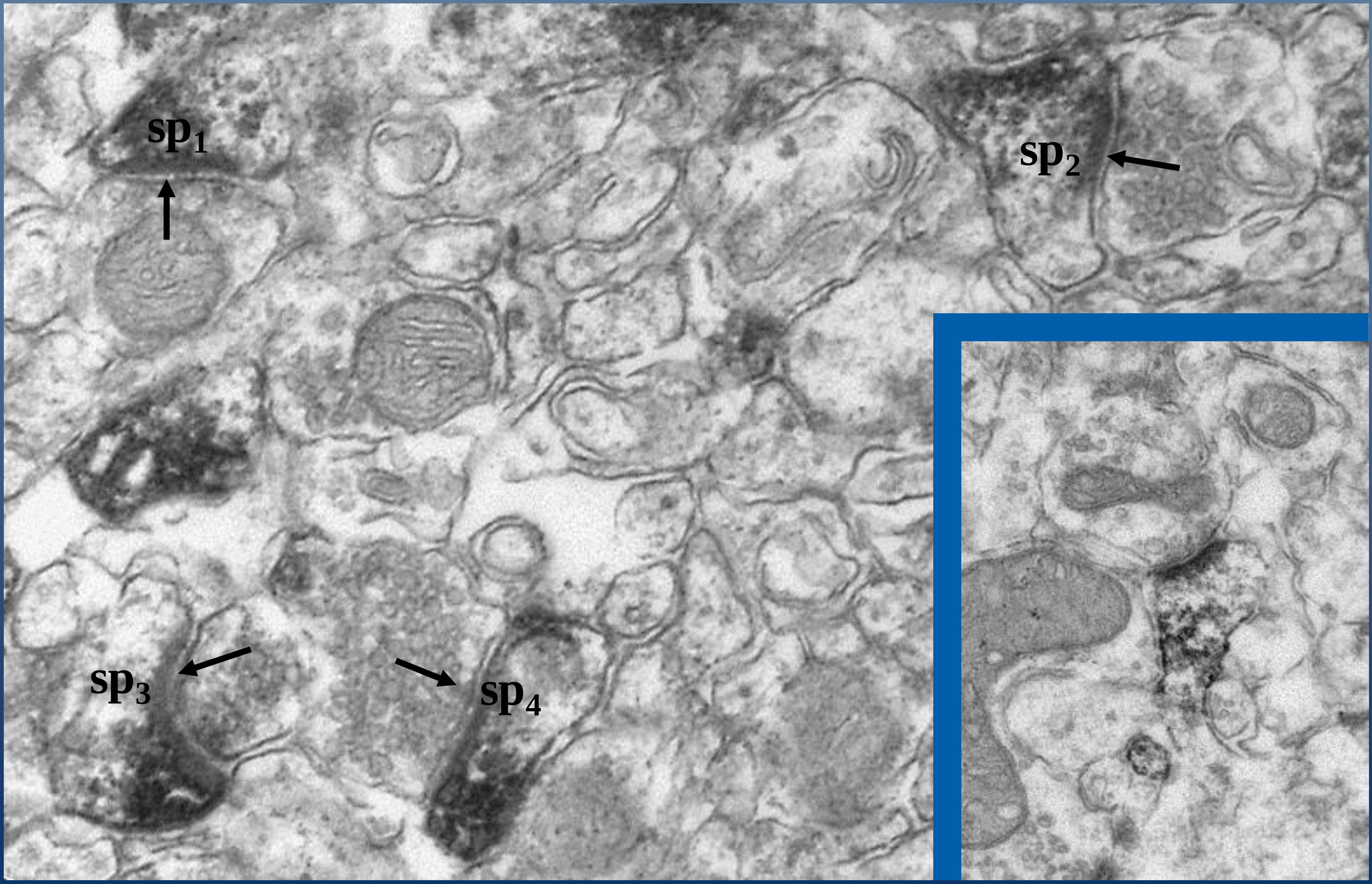
Cannabinoids, e.g. THC, the psychoactive compound of marijuana, and the endocannabinoid 2-AG reduce glutamate release.

Where do, cannabinooids, endocannabinoids act (i.e. where are the receptors), and where are they synthetised?

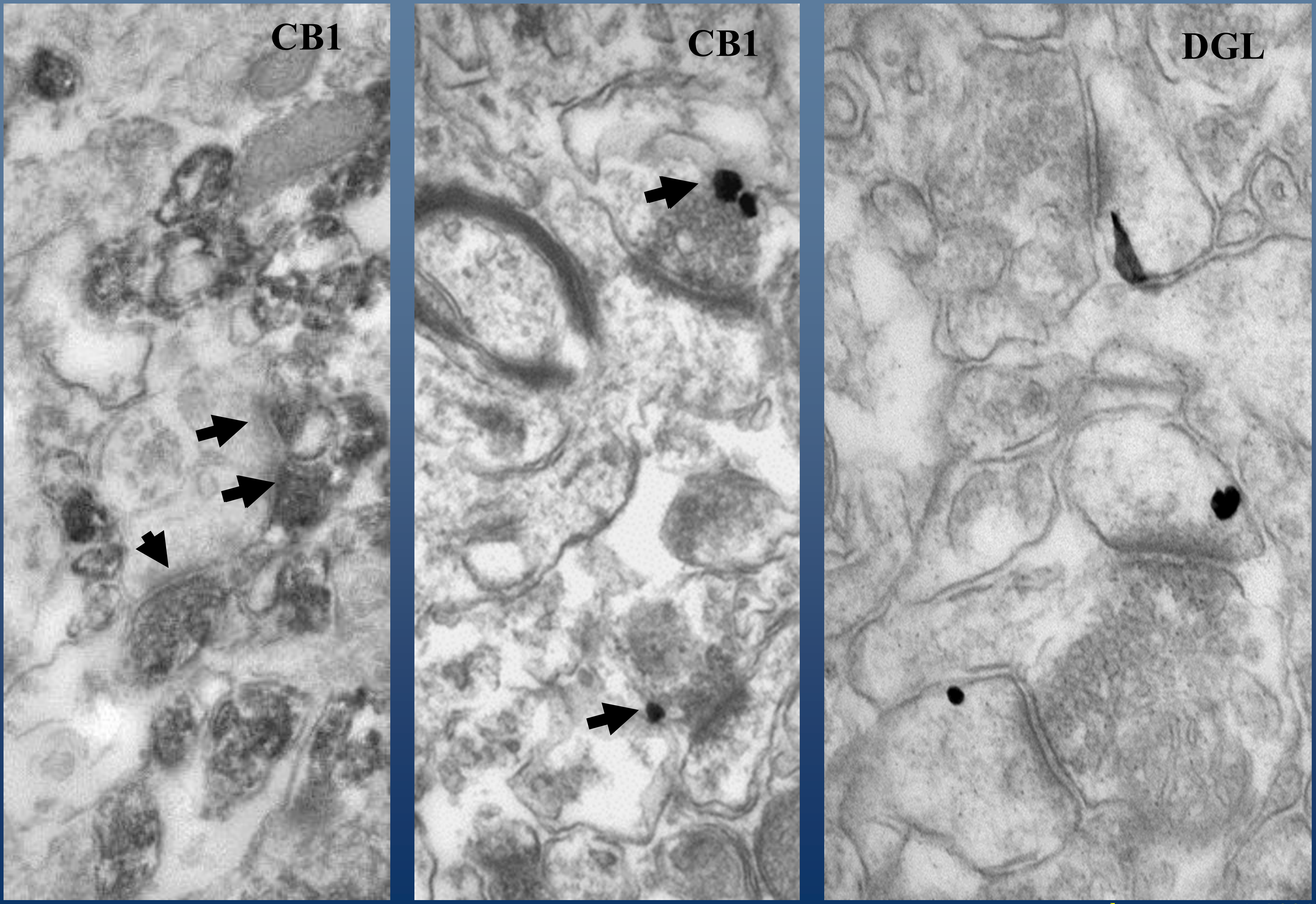
CB1 receptor as well as DGLα-immunreactivity reveals a dense granular labeling pattern



Immunoperoxidase labeling for DGLα visualizes dendritic spines



Presynaptic CB1 and postsynaptic DGL in glutamatergic synapses

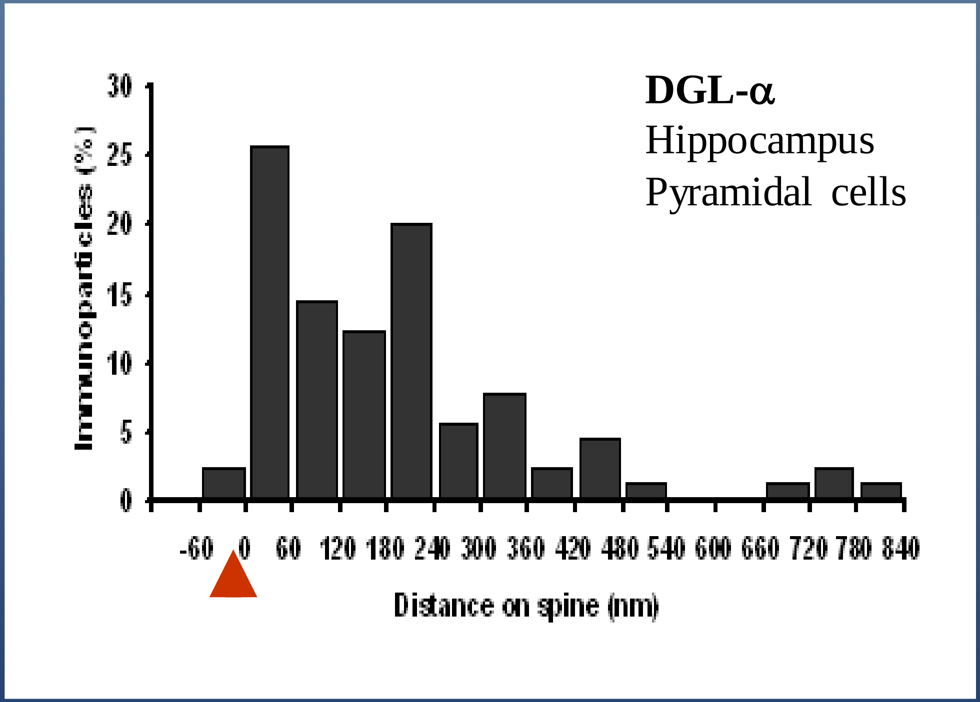


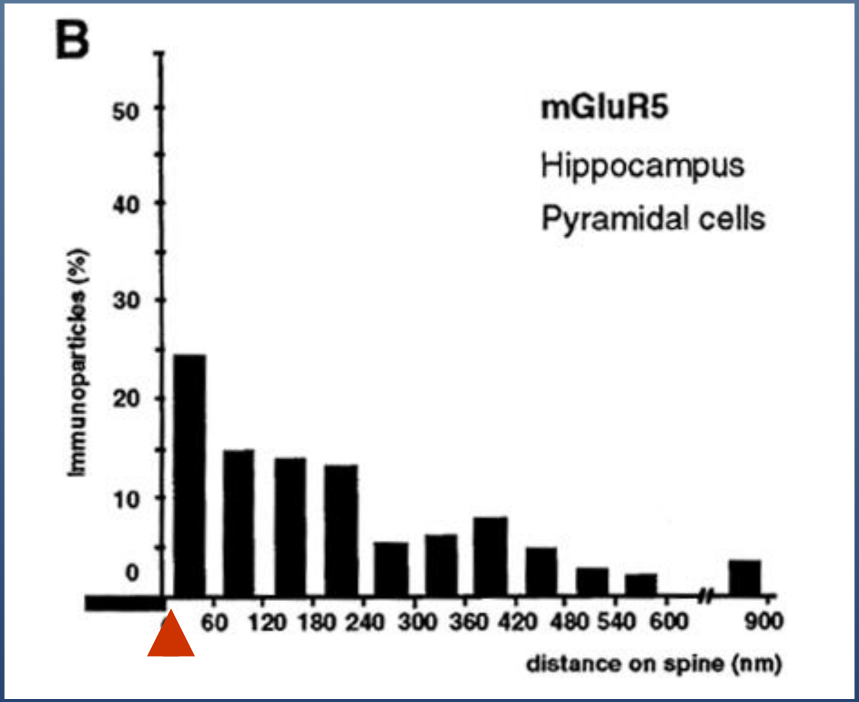
Katona et al., J.Neurosci. 2006

DGL-α is localized in the perisynaptic annulus

25% of the immunogold particles is localized in a 60 nm wide perisynaptic annulus, 75% is found within 240 nm

This ditribution shows striking similarity to the subcellular distribution of mGluR5





▲ = **edge of postsynaptic density**

Luján et al (1997) *J. Chem. Neuroanat.*

2-AG release evoked by mGluR5 activation

mGluR5 activation

↓

Gq/11

↓

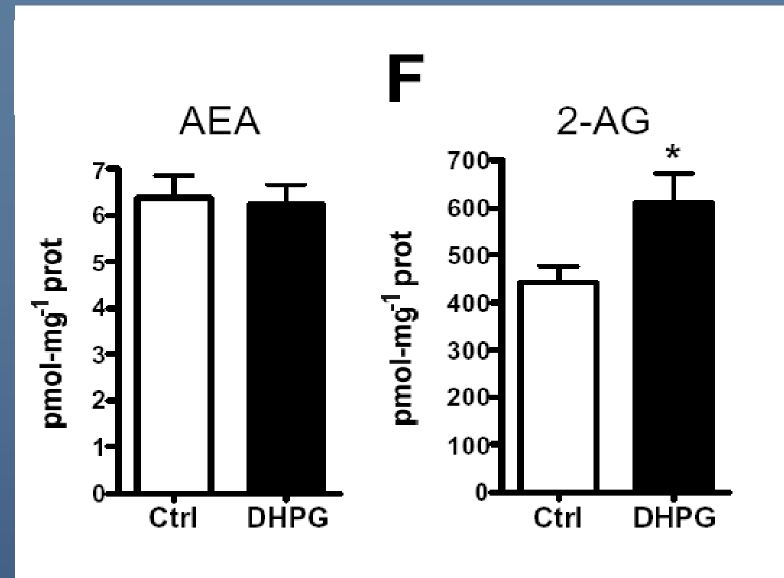
PLCβ

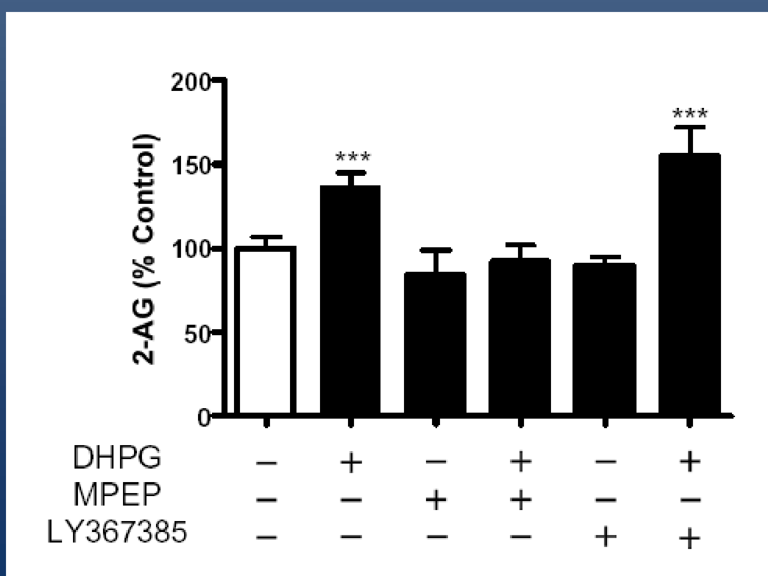
↓

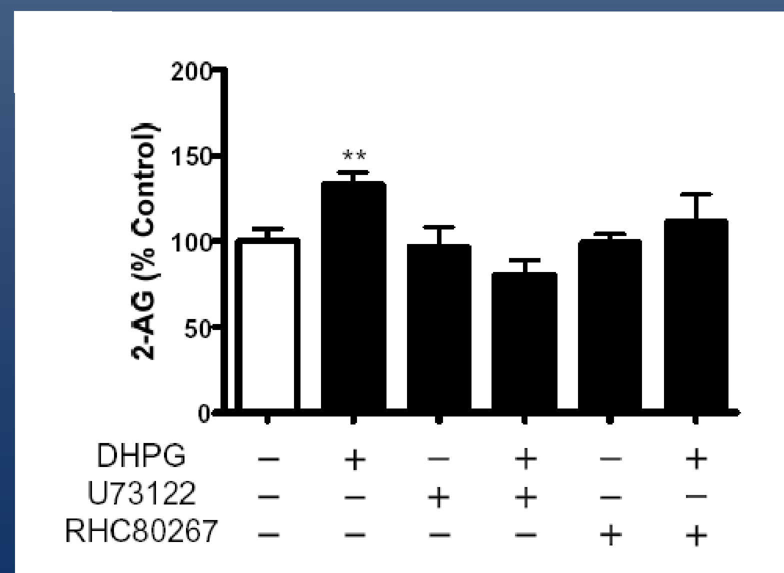
DAG

DGLα ⟶ ↓

2-AG

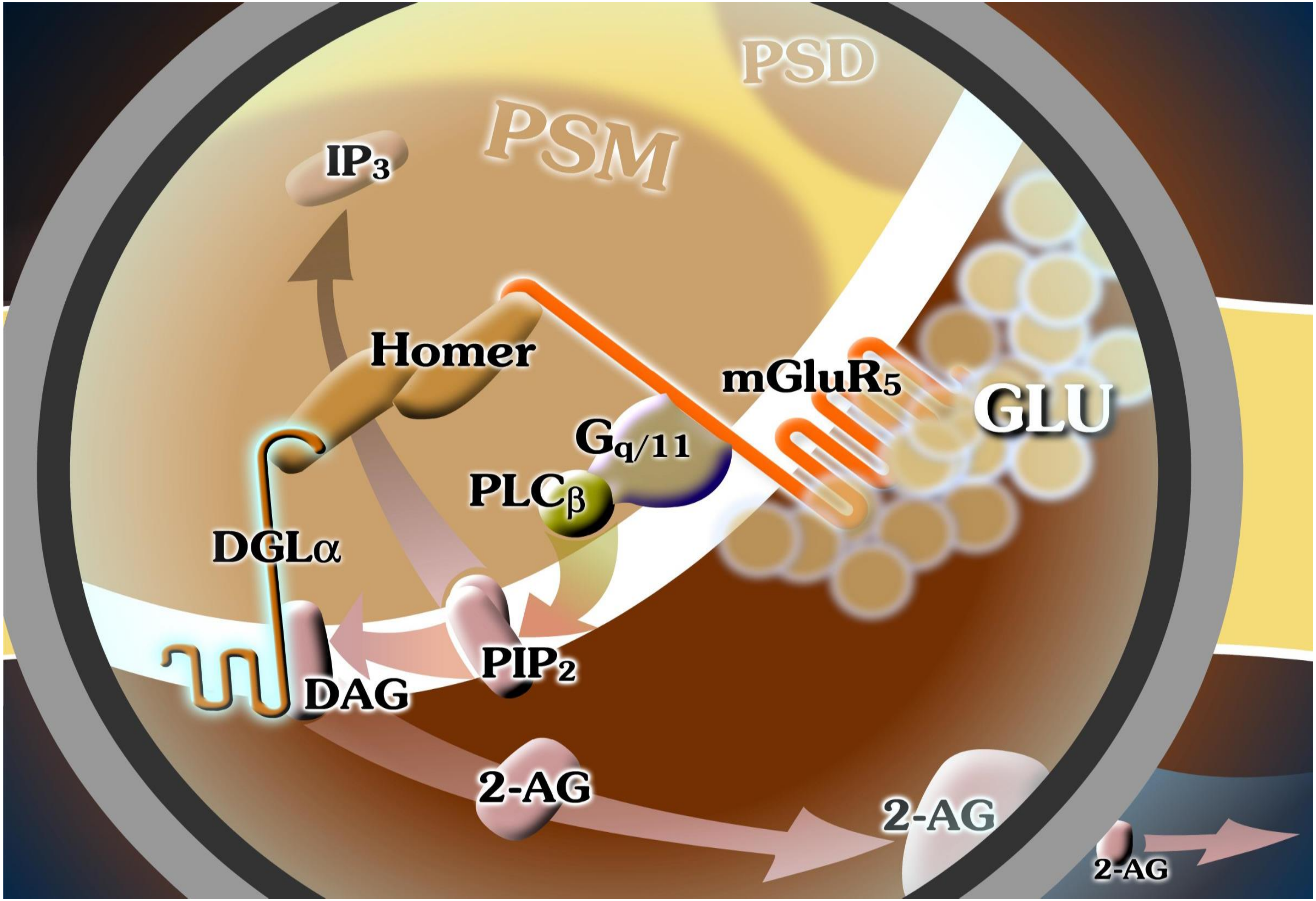




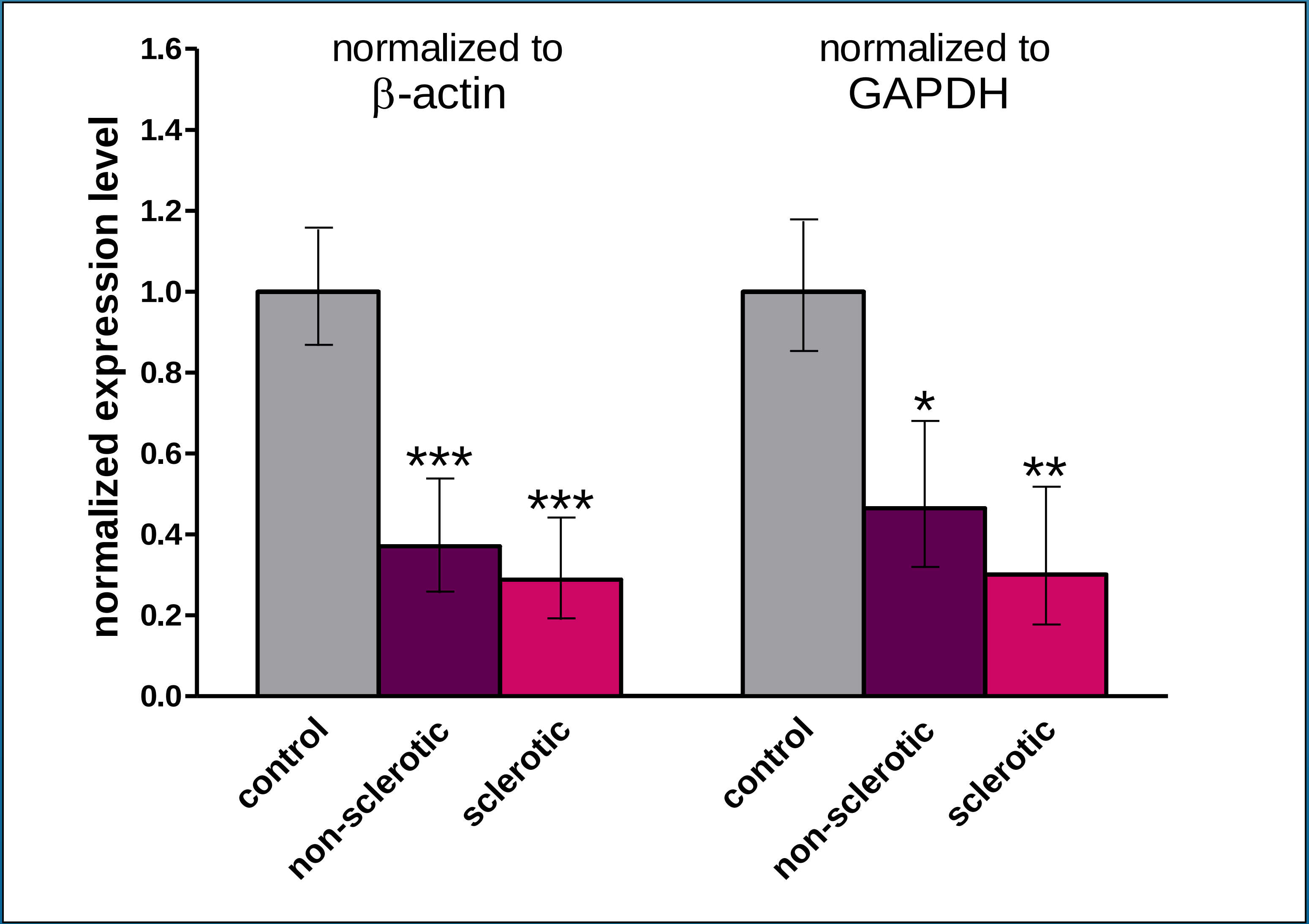


Jung et al. (2005) *Mol Pharmacol*

The Perisynaptic Signaling Machinery (PSM)

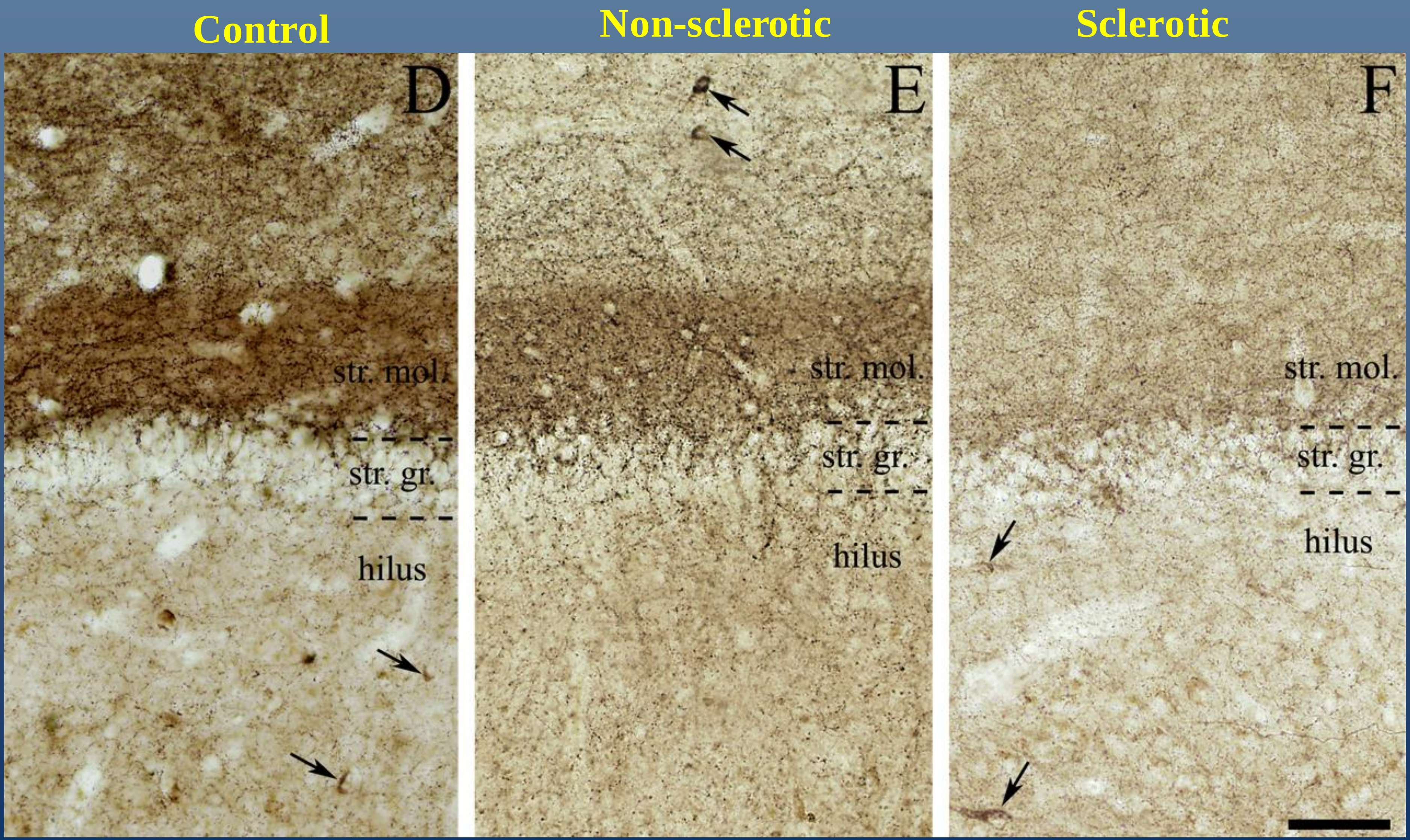


CB_1 cannabinoid receptor expression level is reduced in the epileptic hippocampus



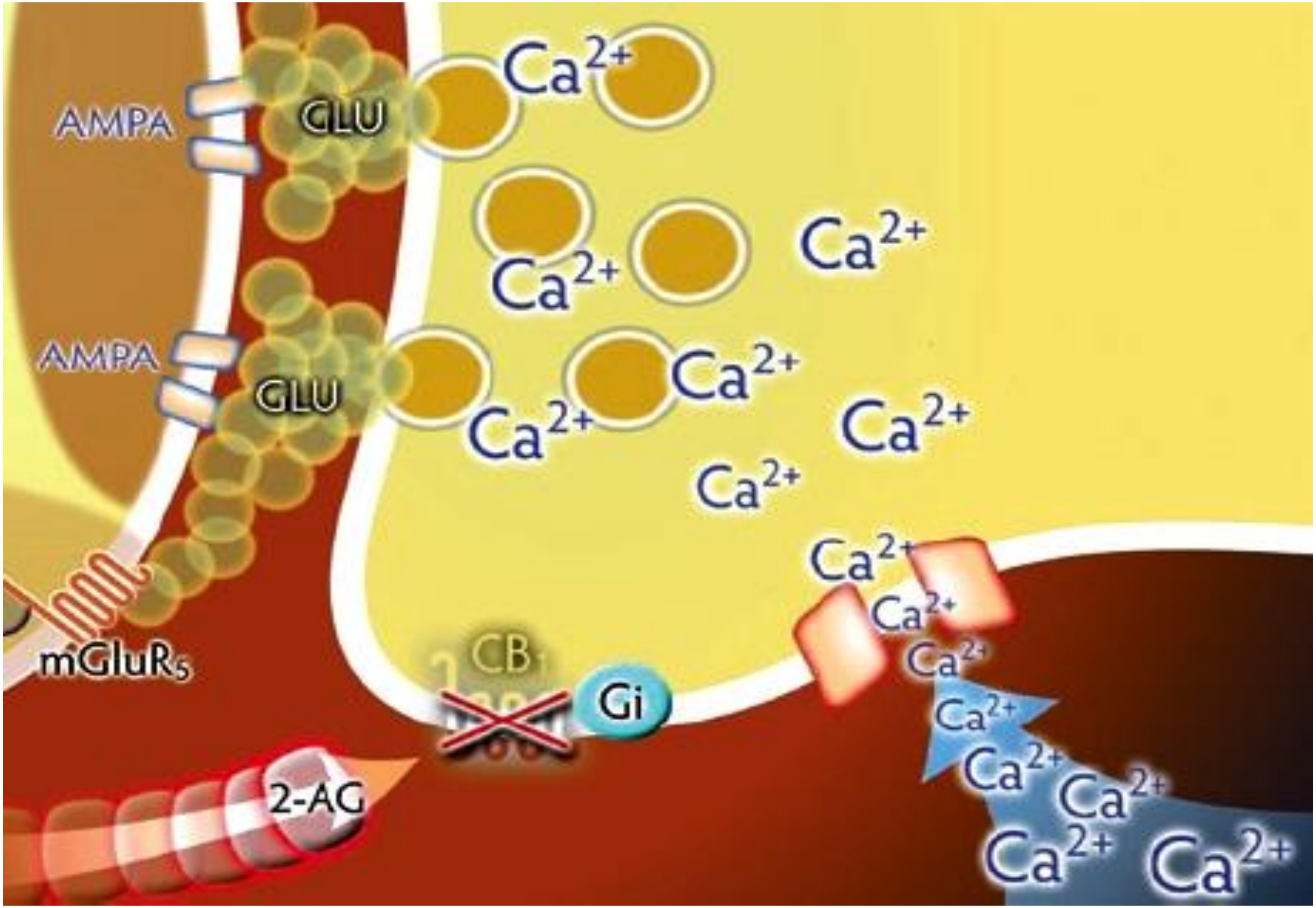
Ludányi et al. (2008) J. Neurosci.

Reduced CB_1-immunostaining in the dentate gyrus of epileptic patients

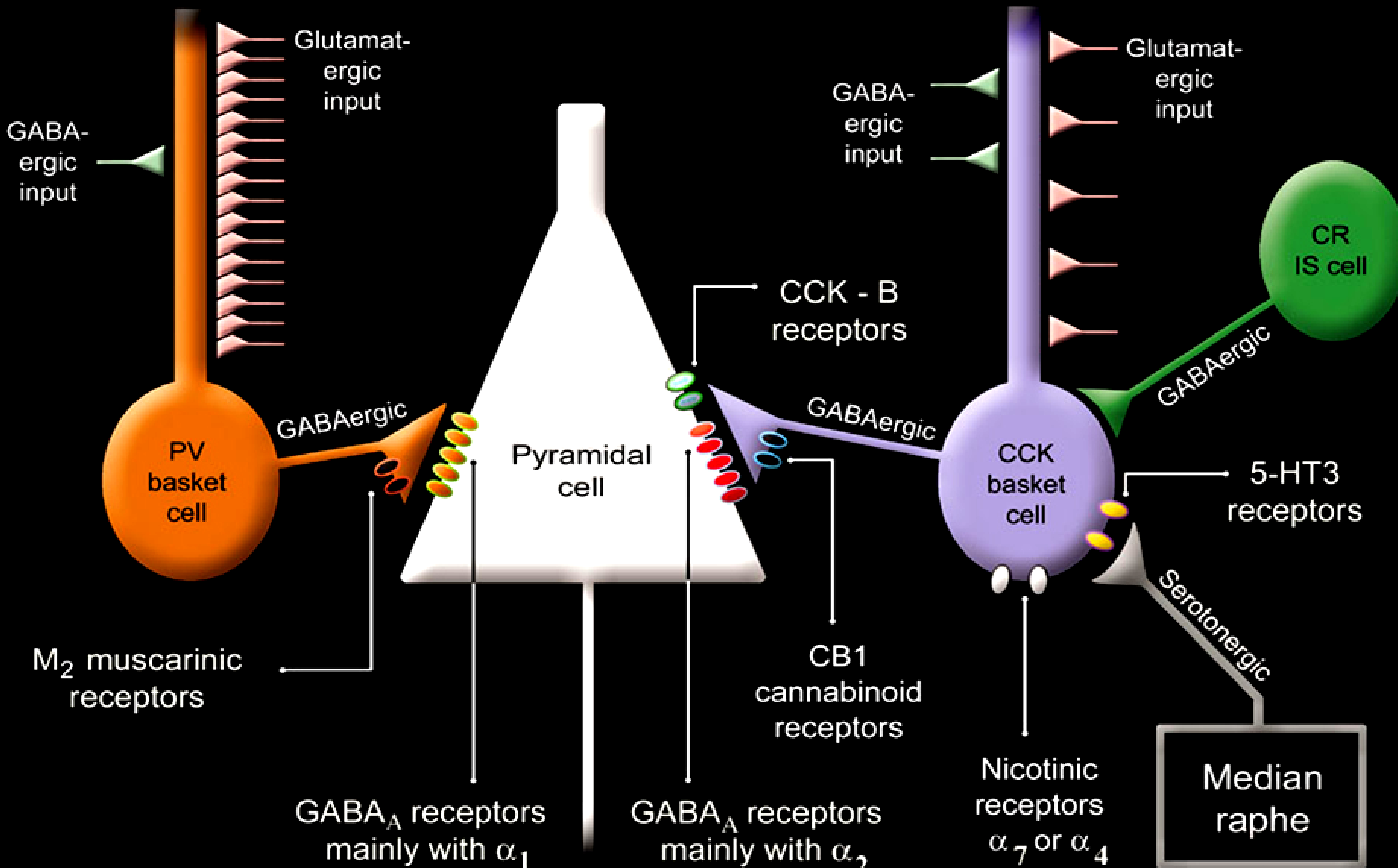


Ludányi et al. (2008) J. Neurosci.

The 2-AG mediated negative feed-back on glutamate release is impaired when CB1 receptor number decreases

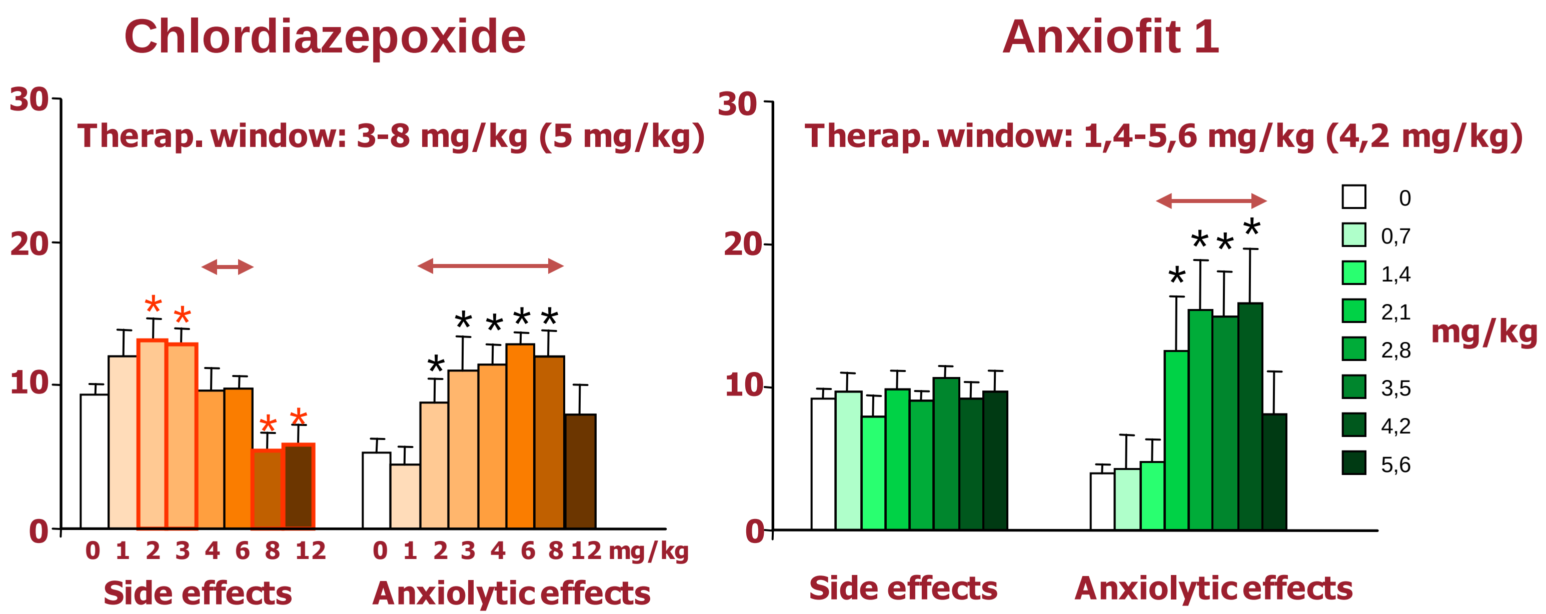


Katona and Freund, Nature Med., 2008



Freund (2003) TINS

A plant extract acting via the eCB system



The efficacy of Anxiofit is similar to the best anxiolytic drugs, but without the side effects!

TUDOMÁNY ÜNNEPE
A MAGYAR
2012

Haller, Hohmann and Freund, Phytother Res., 2010

A plant extract acting via the eCB system

Collaborators

Institute of Experimental Medicine, Hungarian Academy of Sciences

Neuroanatomy and Molecular biology:

István Katona
Gábor Nyíri
Eszter Szabadits
Zsófia Maglóczky
Anikó Ludányi
Gabriella Urbán
Csaba Cserép
Attila Gulyás

Behaviour:

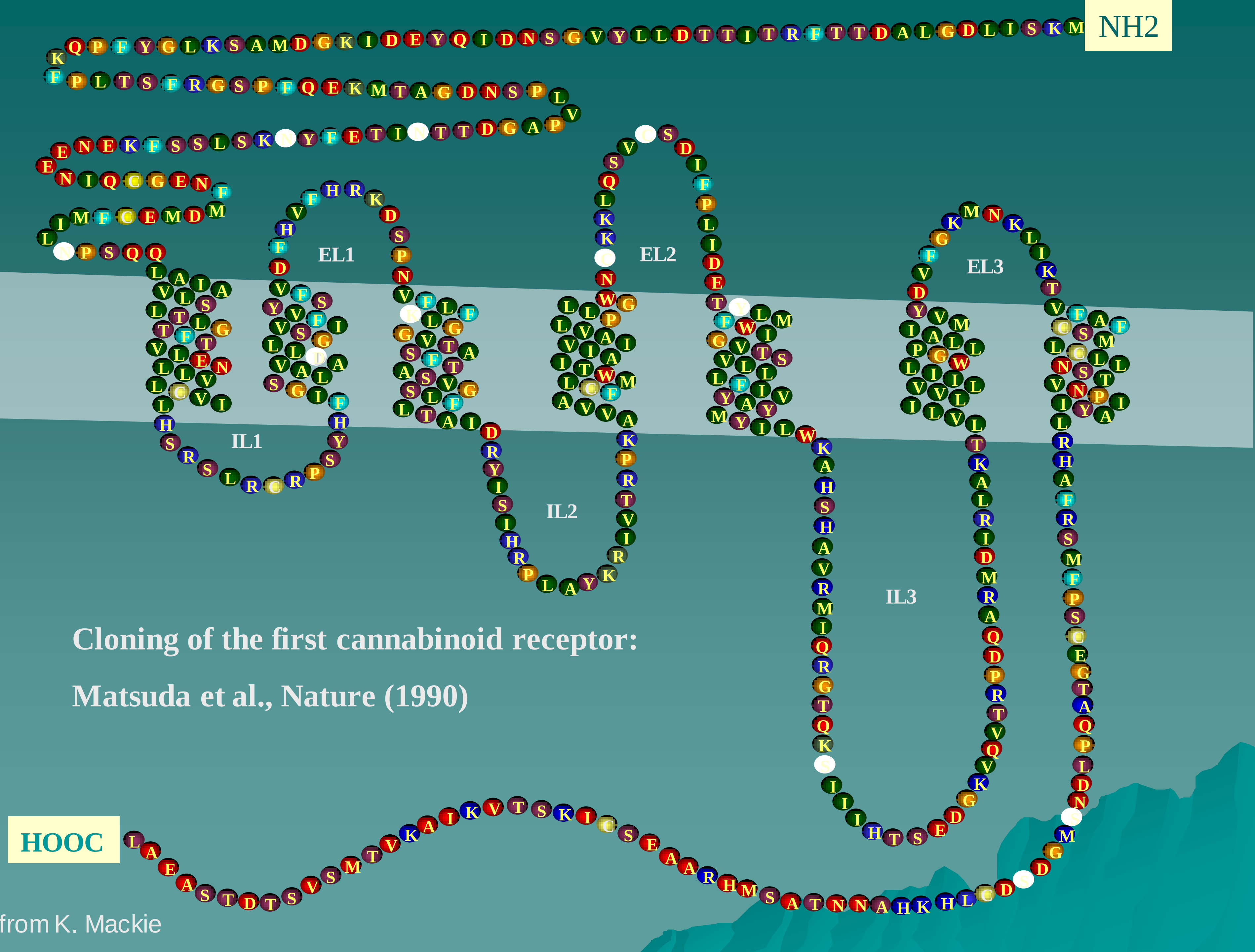
József Haller
Nikolett Bakos
Balázs Varga

Electrophysiology:

Judit Makara
Norbert Hájos
István Mody

Antisera: Kenneth Mackie (Univ. Washington, Seattle)
Masahiko Watanabe (Hokkaido Univ. Japan)

CB1 KO mice: Catherine Ledent (Brussels), Andreas Zimmer (Bonn)

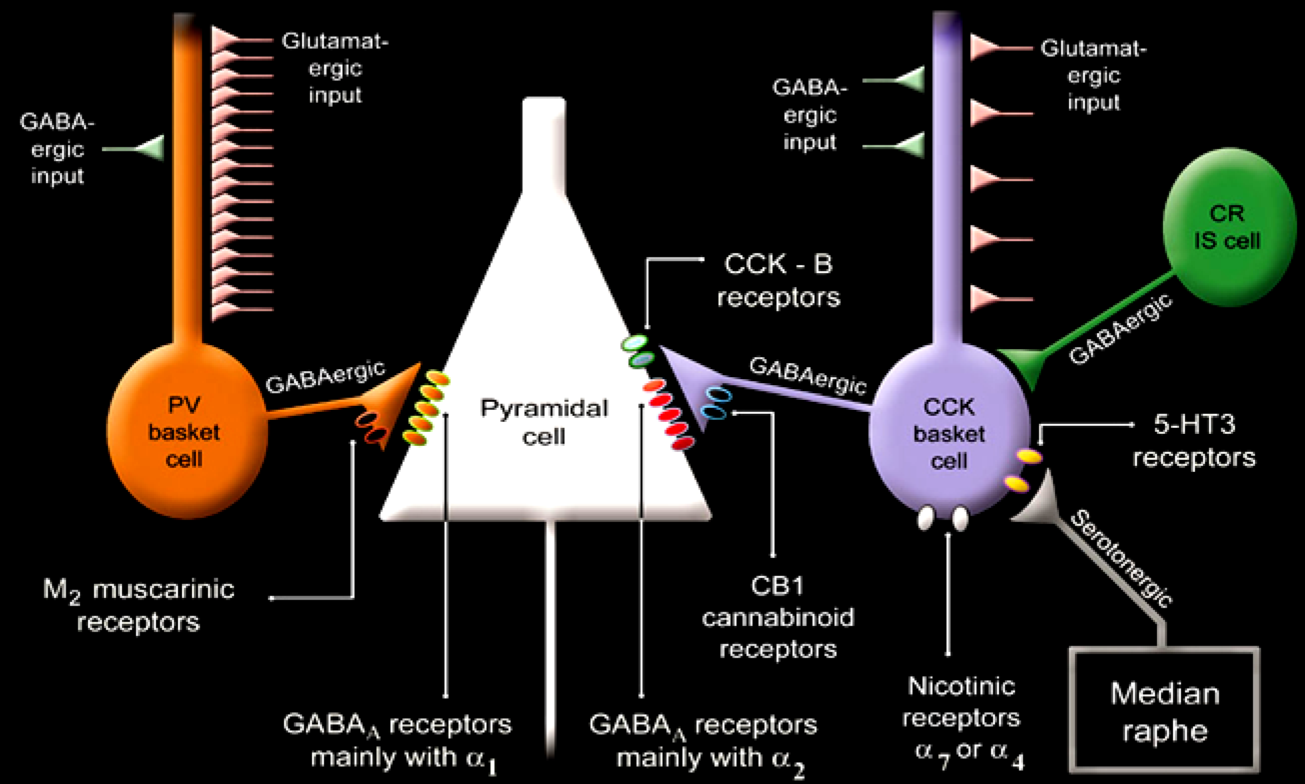


Cloning of the first cannabinoid receptor:

Matsuda et al., Nature (1990)

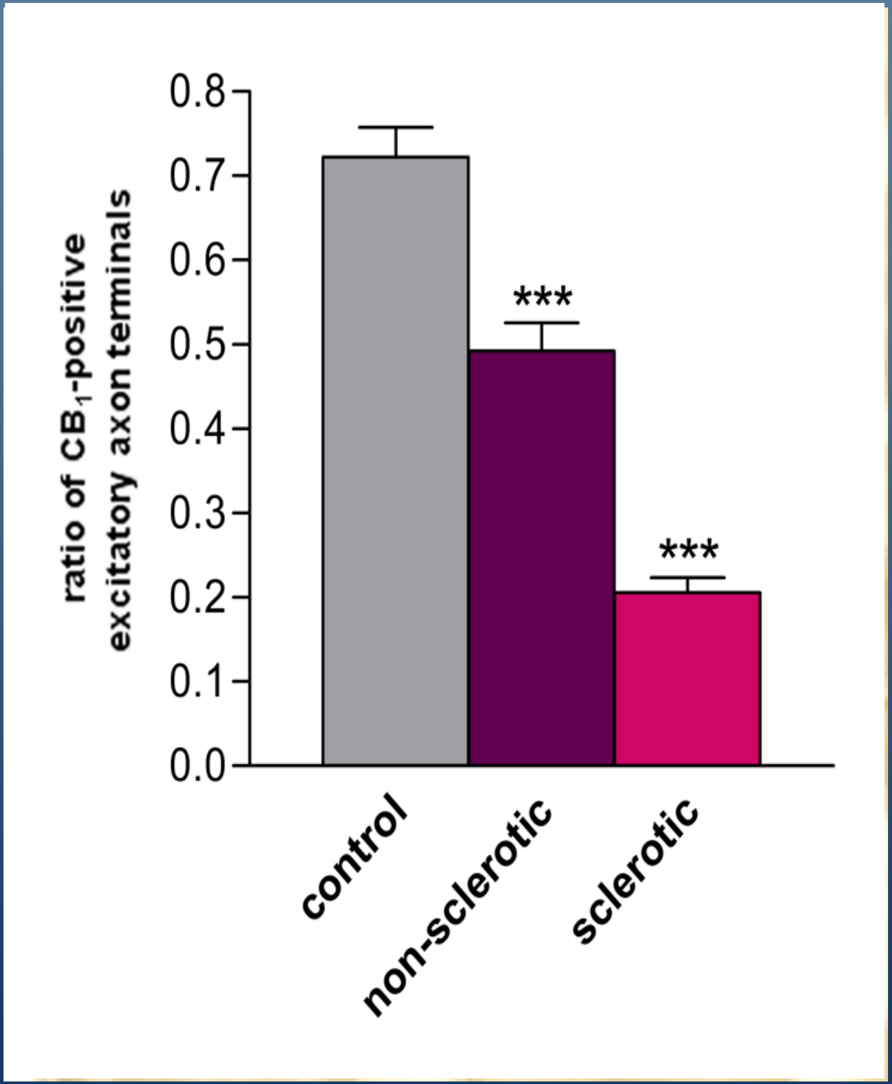
from K. Mackie

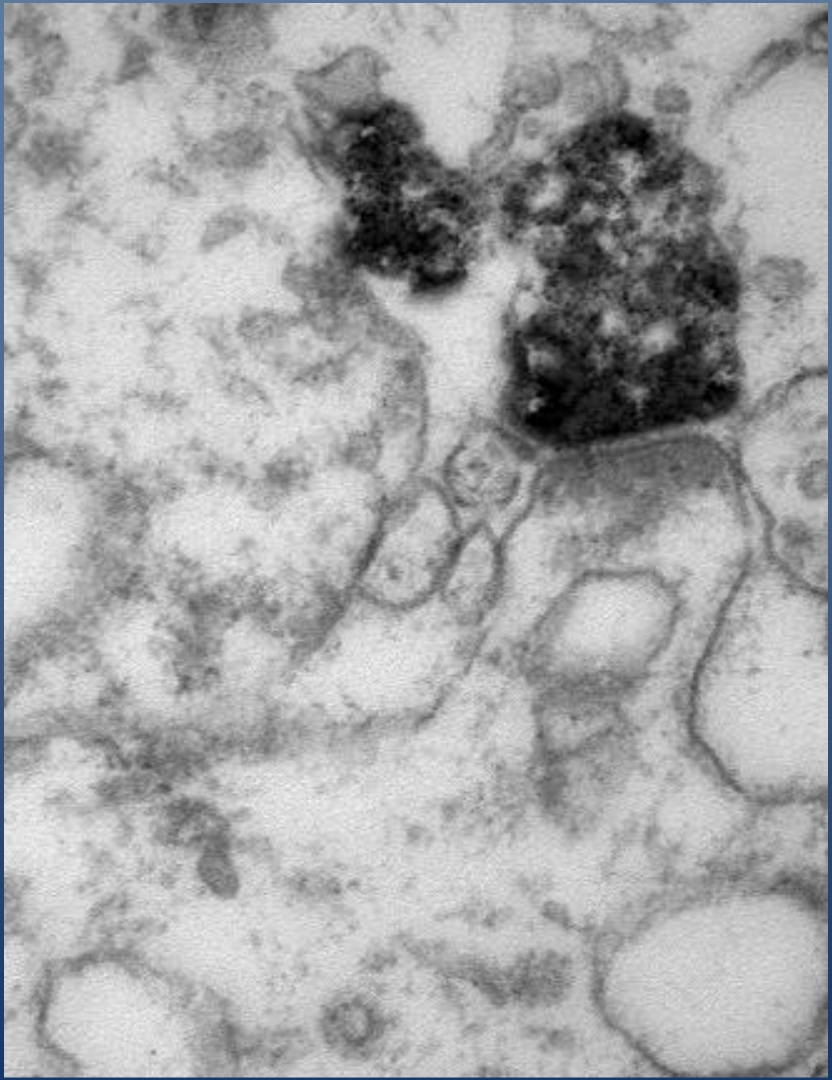
Could individual cell types with all their complexity – rather than individual receptors or enzymes – be considered as drug targets?



Freund T.F. and Katona I. (Neuron, 2007); Freund T.F. (TINS, 2003)

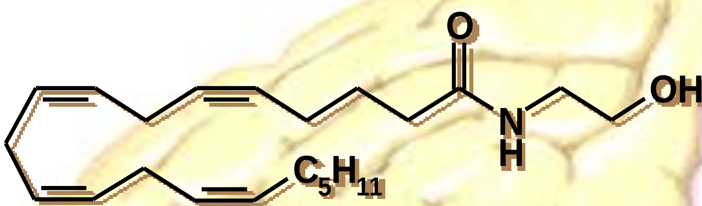
Reduced ratio of CB_1-positive excitatory axon terminals in the dentate gyrus of epileptic patients



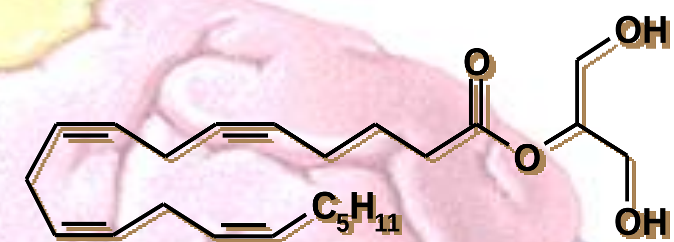


Ludányi et al. (2008) J. Neurosci.

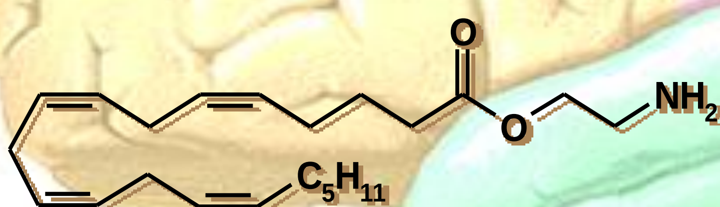
Endogenous cannabinoids



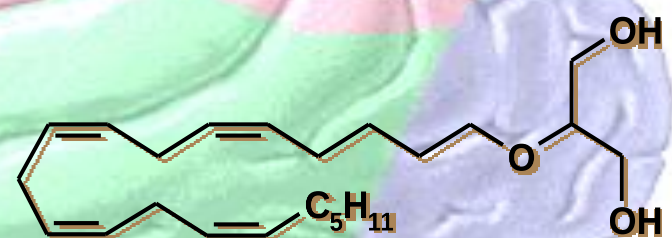
anandamid



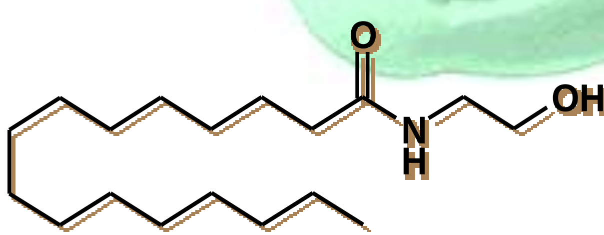
2-arachidonoil-glycerol (2-AG)



virodhamin



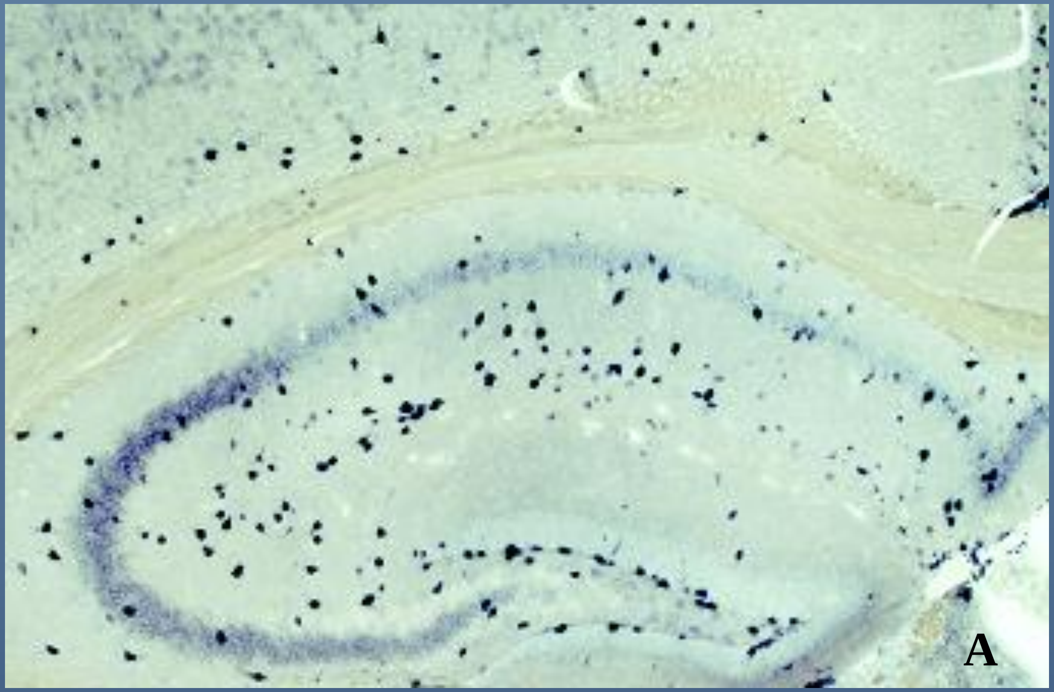
noladin ether



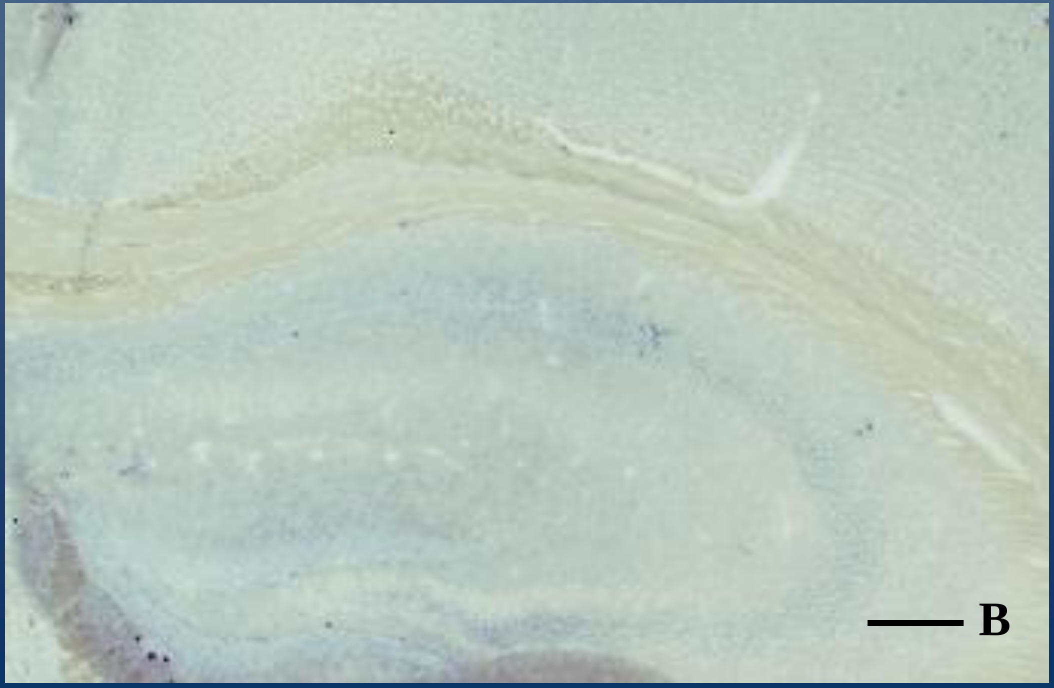
N-palmitoil-etanolamin

Devane, Mechulam and coworkers (1992; 1995), Sugiura et al. (1995)

Expression of CB1 cannabinoid receptor mRNA

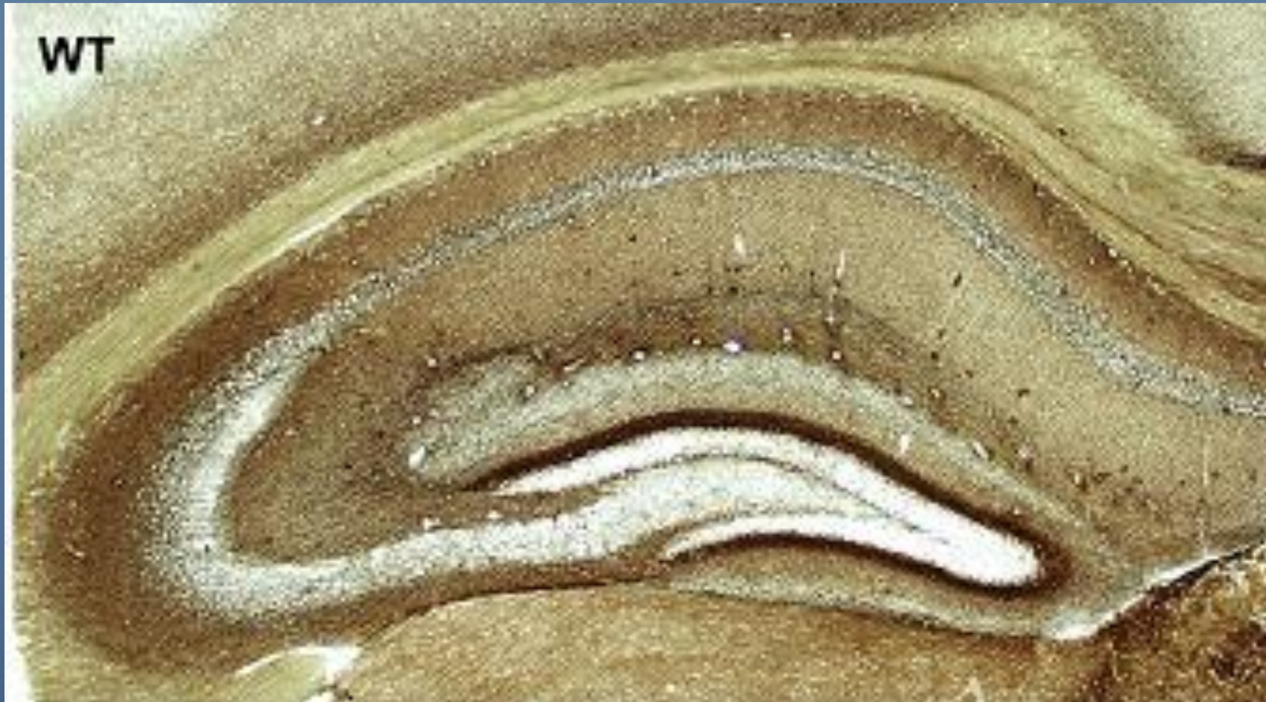


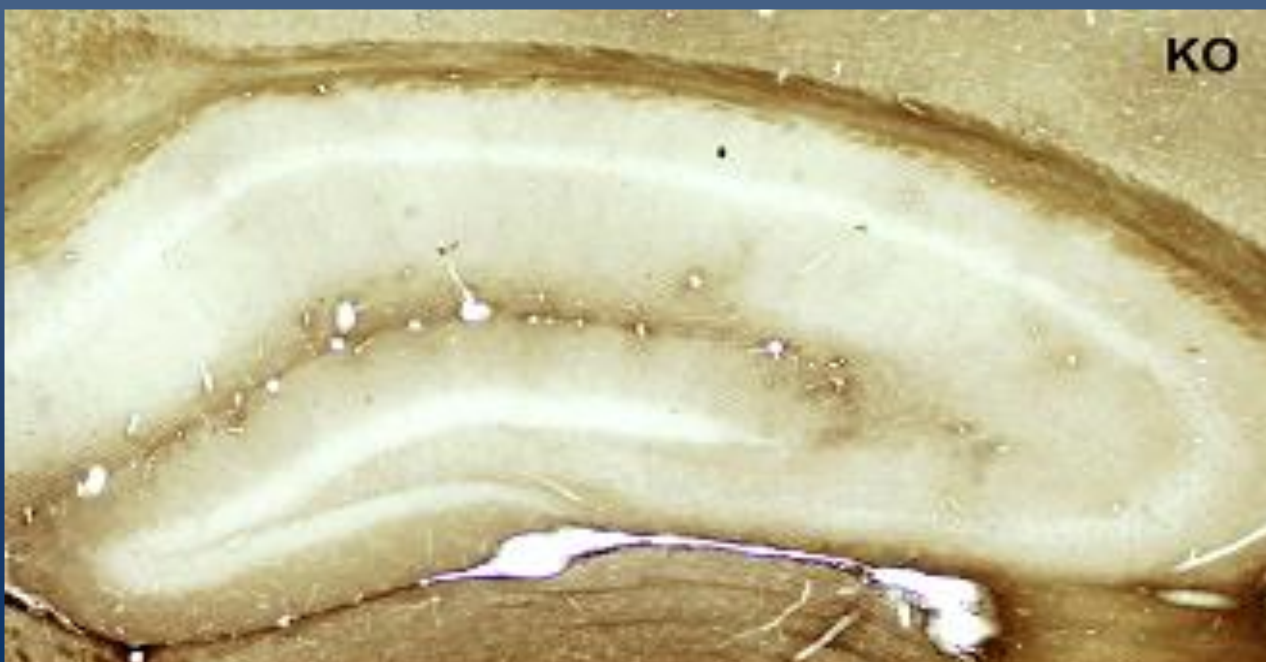
Antisense probe

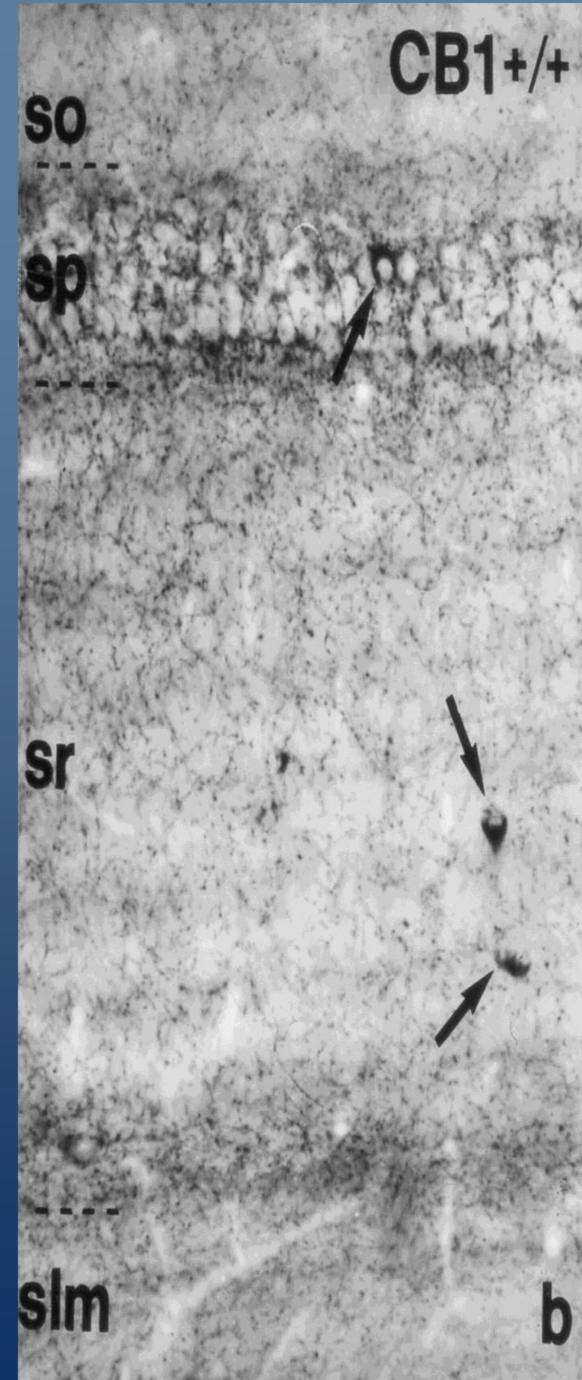


Sense probe

Katona et al., J.Neurosci. 2006







Katona et al., J.Neurosci. 2006