

The Cannabinoids: Looking Back and Ahead

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For the relief of certain kinds of pain, I believe, there is no more useful medicine than Cannabis within our reach.

J. Russell Reynolds, Archives of Medicine, 2, 154, 1859

“...modulating endocannabinoid system activity may have therapeutic potential

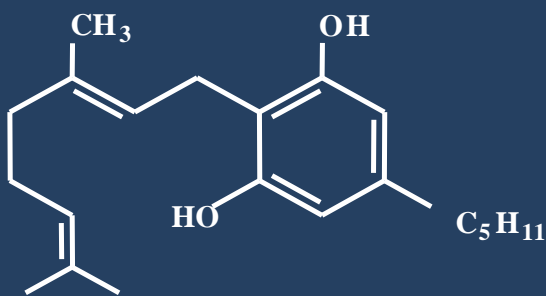
in almost all diseases affecting humans,

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

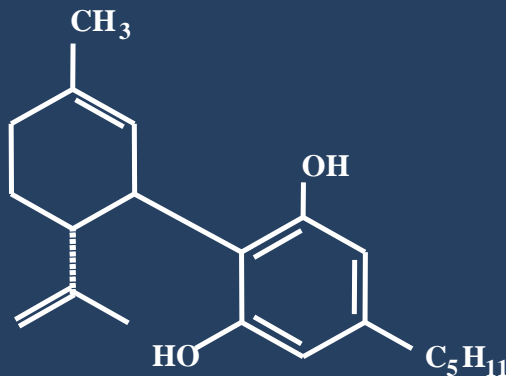
Phases of cannabinoid research

1. Phytocannabinoid Research (THC and CBD)
2. Endocannabinoid (EC) Research (AEA and 2-AG)
3. EC- like Compounds Research

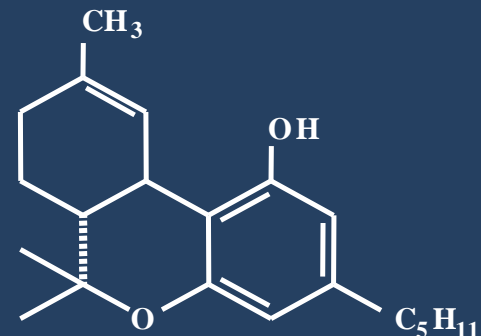
Phytocannabinoids



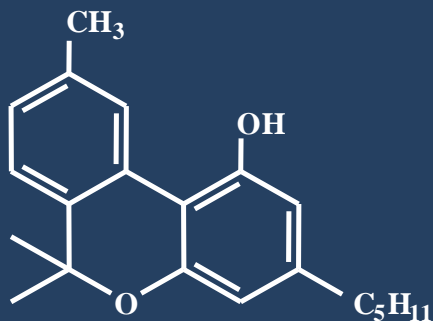
Cannabigerol (CBG)
(Gaoni and Mechoulam, 1964)



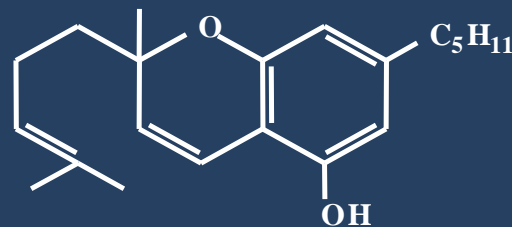
Cannabidiol (CBD)
(Mechoulam and Shvo, 1963)



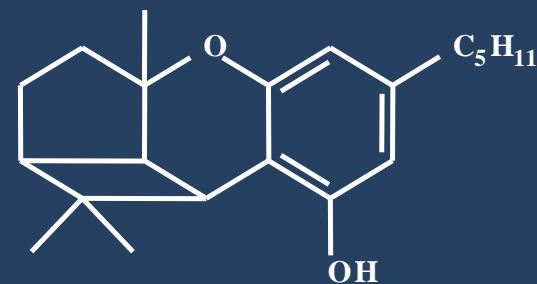
Δ⁹-tetrahydrocannabinol (THC)
(Gaoni and Mechoulam, 1964)



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 (1963)**

Δ^9 -Tetrahydrocannabinol (Δ^9 -THC)

**Gaoni and Mechoulam
J. Am. Chem. Soc. (1964)**

Δ^9 -Tetrahydrocannabinol (Δ^9 -THC)

Dorabinol: Appetite stimulant and Antiemetic

Nabiximols (Sativax): Multiple sclerosis symptoms
(neuropathic pain, spasticity and overactive bladder)

THC: Sleep and Anxiety (depends upon the dose)

May cause psychotic attacks at high doses

Preliminary, Open-Label, Piolet Study of Add-On Oral
 Δ^9 -Tetrahydrocannabinol in Chronic Post-Traumatic
Stress Disorder

Shalev A (2014)

Roitman P, Mechoulam R, Cooper-Kazaz R,

Cannabidiol (CBD)

Epilepsy

Diabetes

Schizophrenia

Cancer

Bone fractures

Inflammation

Anxiety

Graft-versus-host disease (GVHD)

Cognition

Movement disorders

Pain

Many more.....

Epilepsy

Phase 2 study

Drug: CBD in capsules, 200-300 mg/day for 4.5 months

Patients: 15 patients with secondary generalized epilepsy

Results: 4 of the 8 CBD subjects remained almost free of seizures

3 patients had partial improvement

1 patient showed no improvement

Placebo patients: only one showed improvement

Cunha, Carlini, Mechoulam, 1980

2018: FDA approved Epidiolex (CBD) oral solution for the seizures associated with two rare and severe forms of epilepsy, in patients 2 years of age and older

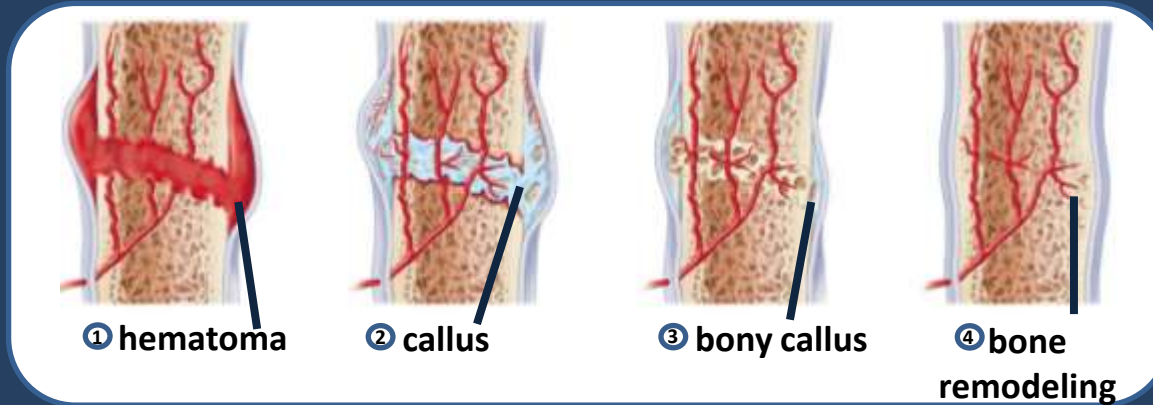
Type 1 Diabetes

CBD reduced the incidence of Type 1 Diabetes in NOD mice from an incidence of 86% in non-treated control mice to an incidence of 30% in CBD-treated mice

Inhibition of the progression to destructive insulinitis

Treatment	No. of scored islets	Intact islets	Percent intact islet
Control	73	6	8
CBD	140	108	77

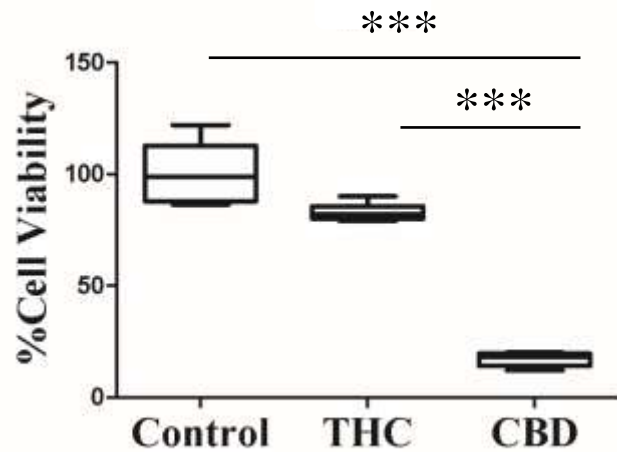
Bone Fractures



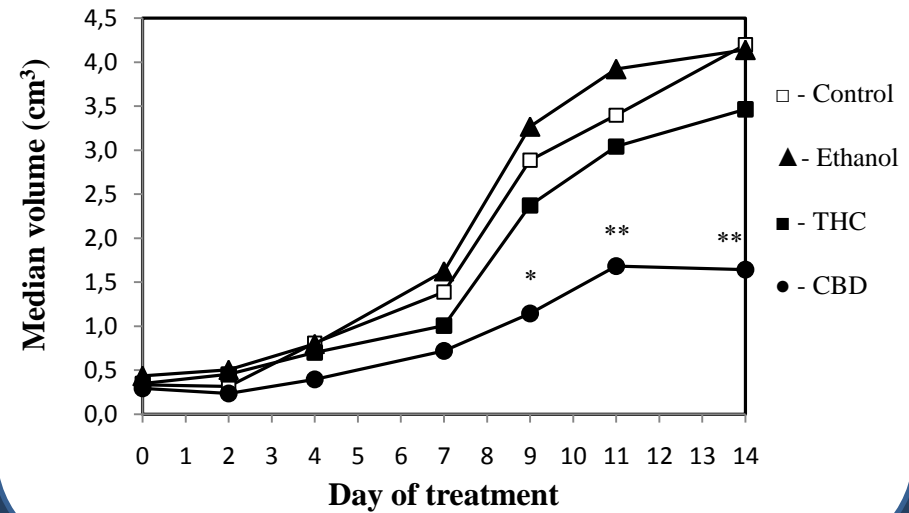
CBD induced enhancement of the callus strength and toughness likely through an effect on osteoblastic bone formation, and it increased collagen crosslinking

Neuroblastoma

Neuroblastoma cell viability



Tumor growth in animals



CBD reduced the viability and invasiveness of treated tumor cells *in vitro* and impeded the growth of tumor xenografts *in vivo*

Endocannabinoids

The endocannabinoid system



Endocannabinoids

Anandamide (AEA)

Devane et al., 1992

2-Arachidonoyl glycerol (2-AG)

Mechoulam et al., 1995

N-arachidonoyl dopamine

Virodhamine

Noladin ether



Receptors

CB₁R

CB₂R

GPR55

GPR18

GPR119

GPR35

PPAR

Ion channels



Enzymes Transporters

FAAH

MAGL

PLC

DAGL

ABHDx

HSP

Serum albumin

FLAT

Cholesterol

Ceramide

exosomes

Endocannabinoid research

Anxiety

Appetite/feeding

Blood pressure

Bone formation

Cerebral blood flow

Digestive system

Emesis and nausea

Immune system

Inflammation

Memory

Mood

Movement

Neuroprotection

Pain

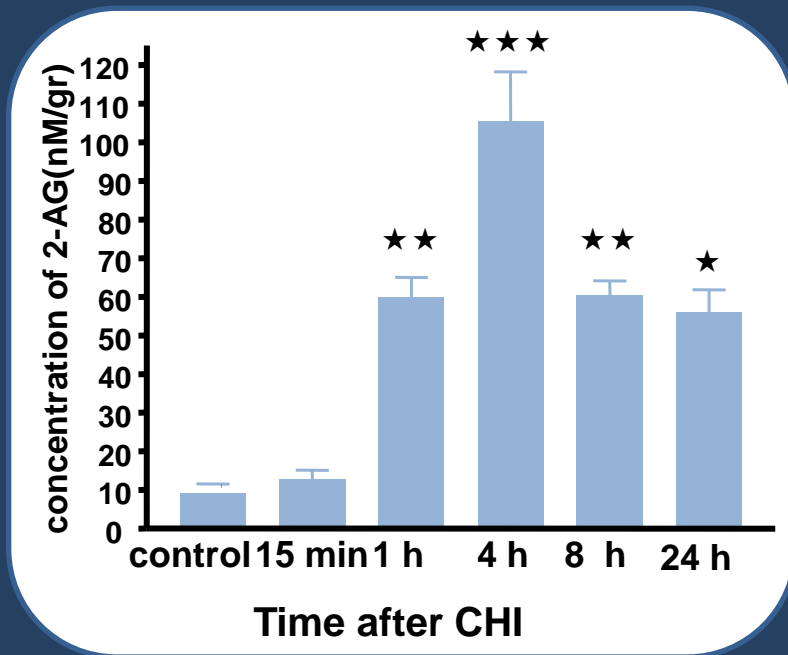
Stress

Reproduction

Traumatic Brain Injury

2-AG

Levels of 2-AG in mouse brain after Closed Head Injury (CHI)



Infarct volume 24 h after CHI

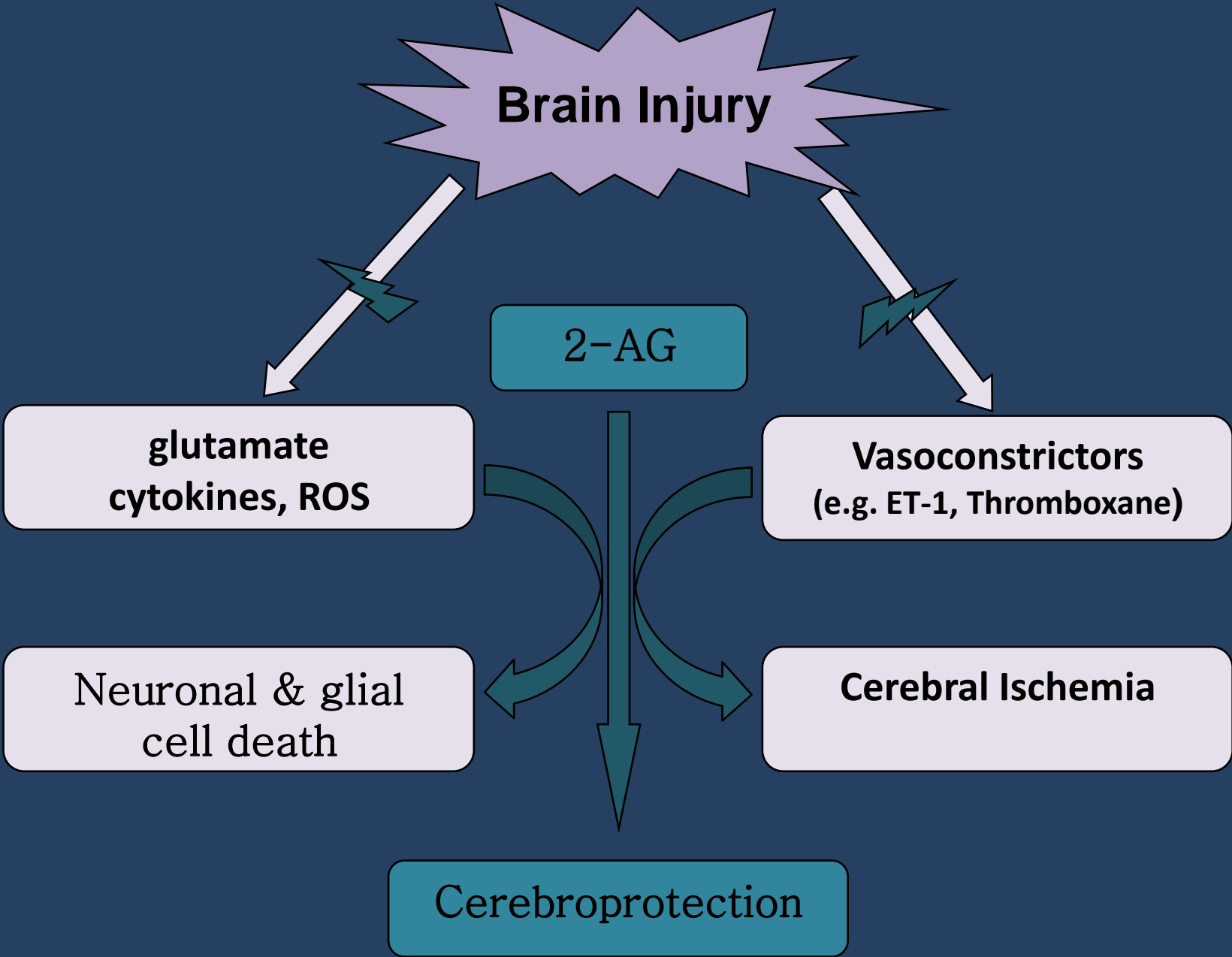
control



2-AG



2-AG attenuated neurological deficits, edema formation, infarct volume, blood-brain barrier permeability, neuronal cell loss and neuroinflammation



Endocannabinoid-like Compounds



Anandamide (AEA)



2-arachidonoyl glycerol, 2-AG

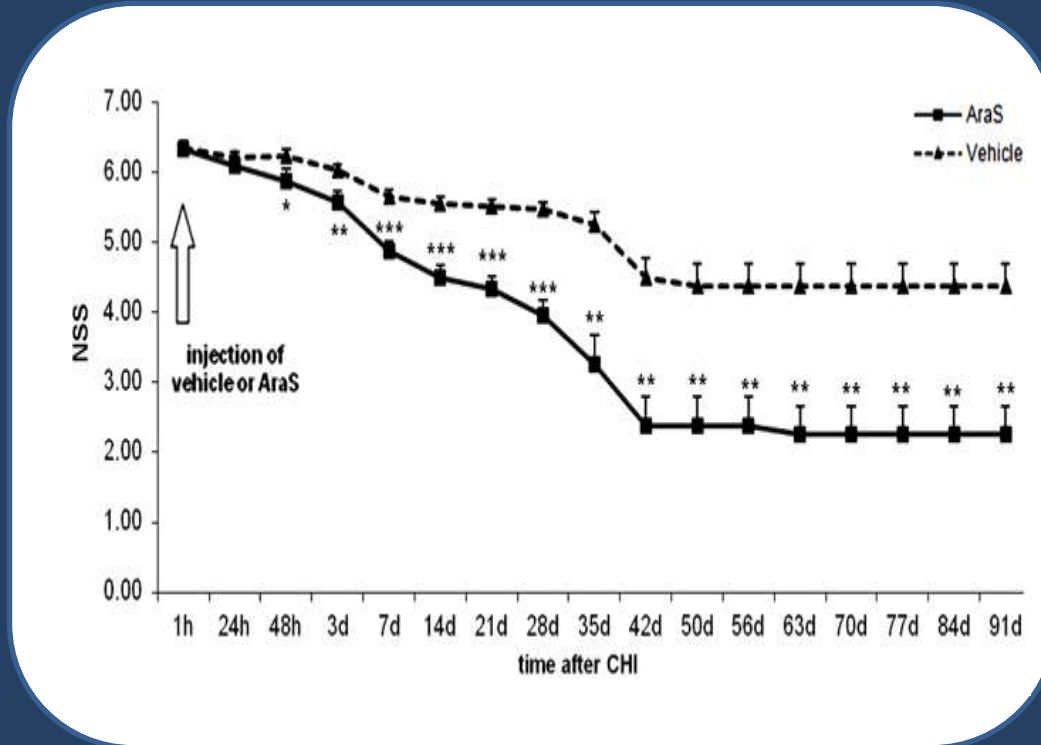


Arachidonoyl serine

Traumatic Brain Injury

AraS

Functional outcome after Traumatic Brain Injury (CHI)

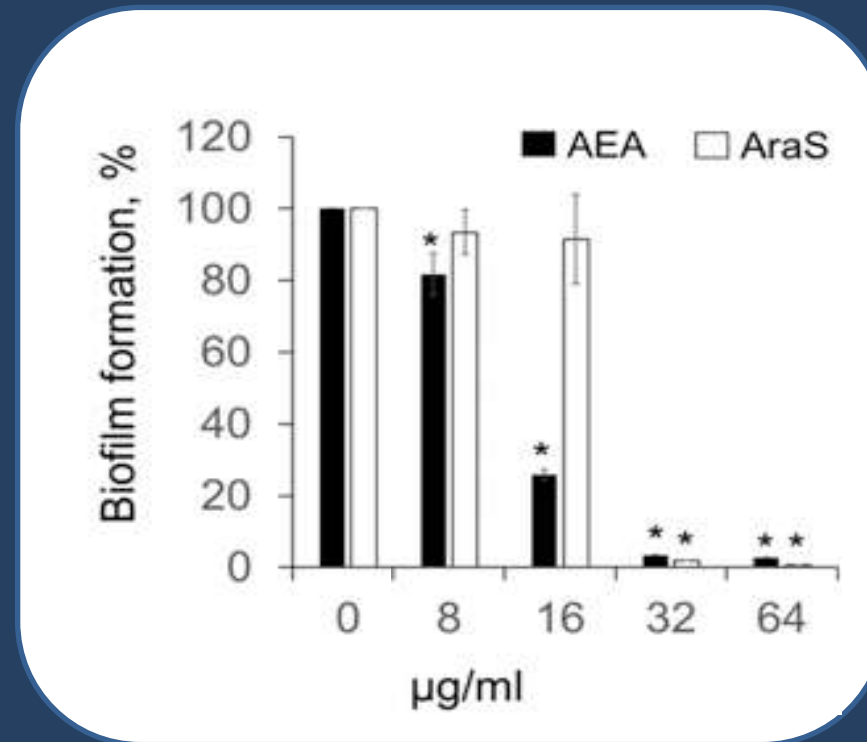


AraS improved functional outcome CHI and reduced the volume of the lesioned tissue

Antimicrobial potential

AEA & AraS

Biofilm formation

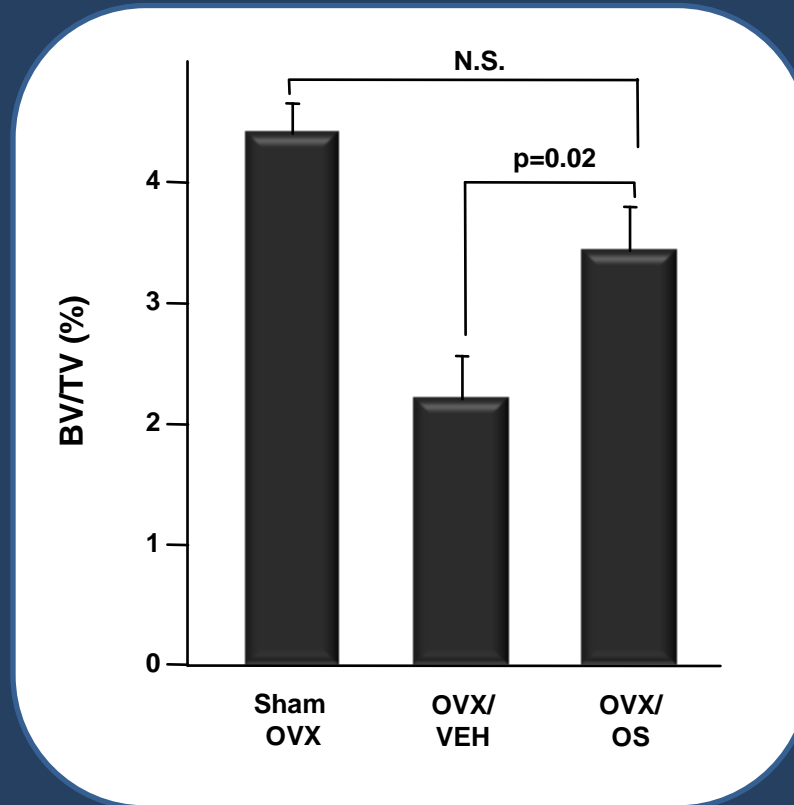


AEA and AraS inhibited biofilm formation, colony spread and bacterial aggregates

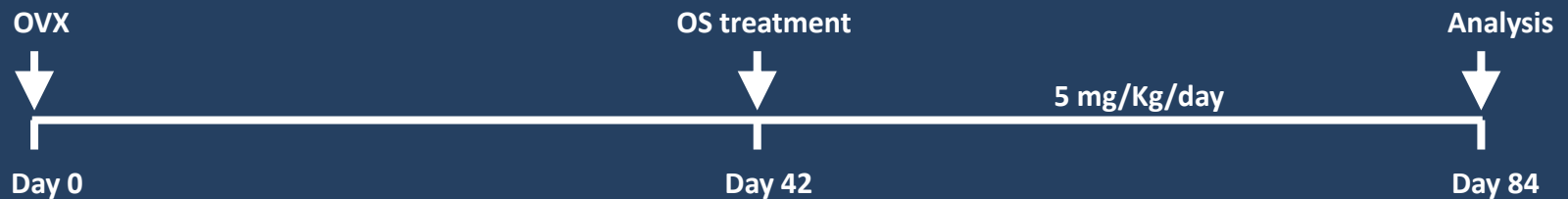
Osteoporosis

OS

Bone volume density



OS rescues OVX-induced trabecular bone loss



CB₂ Receptor

CB₂ is expressed in the immune system. Selective modulation of CB₂ has therapeutic potential in inflammatory, fibrotic & neurodegenerative diseases

e.g. Myocardial infarction, Heart failure, Atherosclerosis, Stroke, Spinal cord injury, Hepatic ischemia-reperfusion injury, Liver fibrosis, Pancreatitis, Inflammatory bowel disease, Colitis, Rheumatoid arthritis, Nephropathy, Neurodegenerative disorders, Psychiatric disorders, Colitis, Pain, Osteoporosis, Cancer, etc.....

Potent selective CB₂ agonists

HU-308 (+ enantiomer)

HU-433 (- enantiomer)

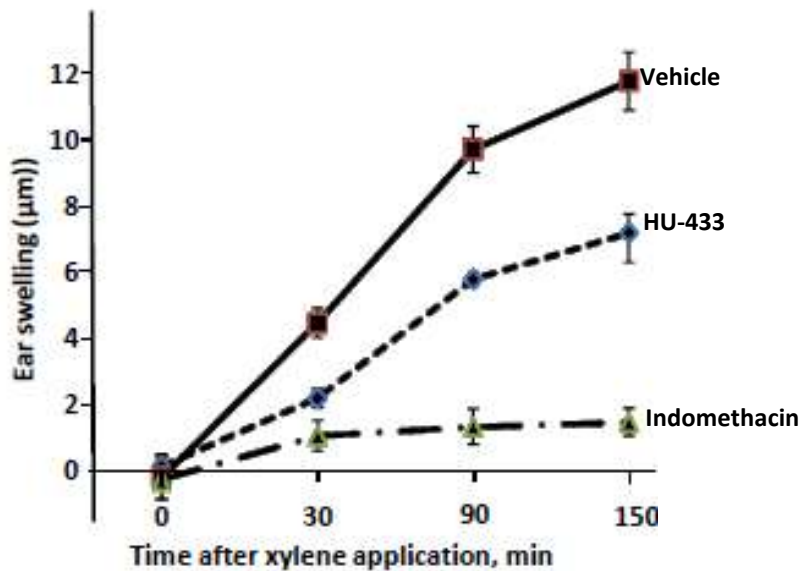
HU-910

HU-914

Inflammation

HU-433

Xylene induced ear swelling

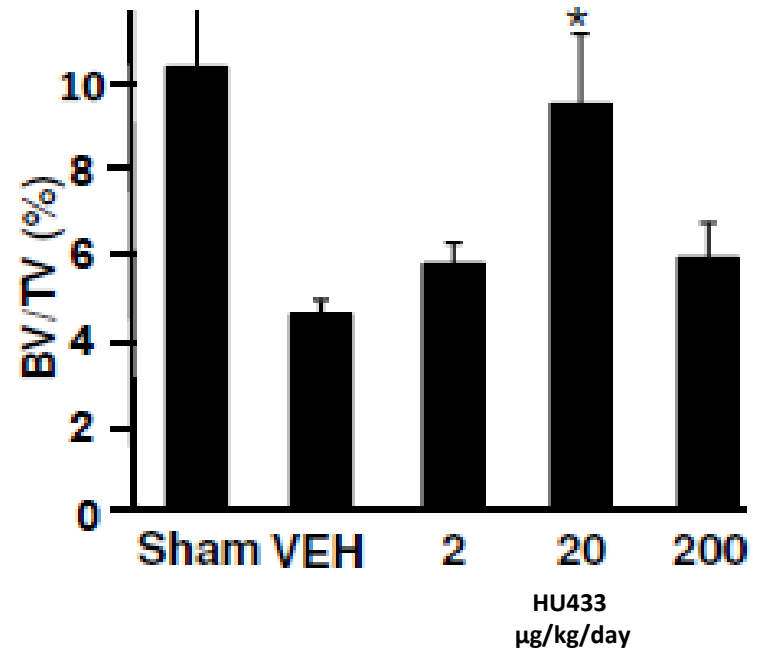


WT mice

HU-433 attenuated xylene induced ear swelling in mice

Osteoporosis

Bone volume density

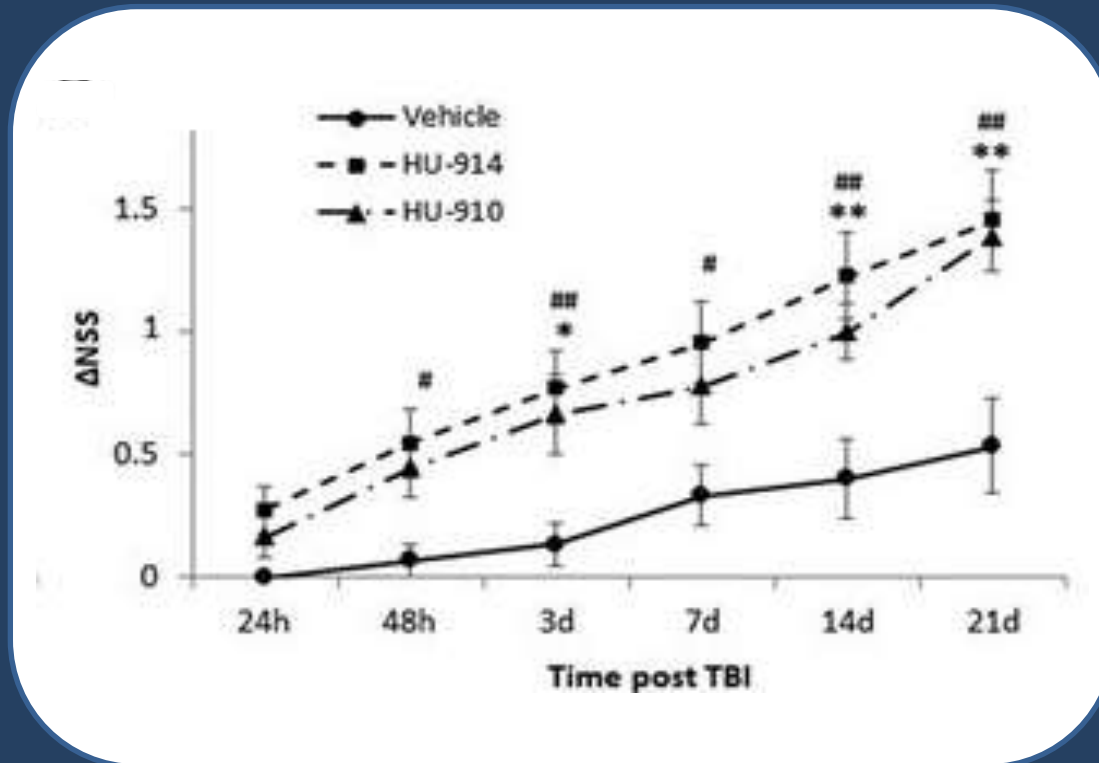


HU-433 rescues ovariectomy-induced bone loss

Traumatic Brain Injury

HU-910 & HU-914

Functional recovery TBI



Novel CB₂ agonists enhanced neurobehavioral recovery, inhibition of tumor necrosis factor α production, increased synaptogenesis, and partial recovery of the cortical spinal tract *Magid et al. J Neurotrauma 2019*

SUMMARY

1. Endocannabinoids are involved in a large number of physiological processes. THC – a plant cannabinoid – mimics their actions
2. CBD derivatives – may lead to a wide spectrum of novel drugs
3. Fatty acids – amino acids (FAAA) and derivatives may lead to better understanding of biological processes as well as to novel drugs
4. CB₂ specific agonists – may lead to a wide spectrum of novel drugs. May be part of a general protective system

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Thank You