The Cannabinoids: 
Looking Back and Ahead 

Raphael Mechoulam 

Pueblo, 2017
I live my life in widening circles
that reach out across the world
I may not complete the last one
but I give myself to it

Rainer Maria Rilke
Book of Hours
"…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
Phases of cannabinoid research

1. Phytocannabinoid research

2. Endocannabinoid research (anandamide and 2-AG)

3. Endogenous, anandamide-like compounds
Gan-zi-gun-nu – the drug that takes away the mind
Azallu – hand of ghost, poison of all limbs
(nervous diseases?)
Qunnabu – used in religious rites
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, Vol 2, 154, 1859
Representative natural cannabinoids

cannabigerol (CBG) (Gaoni and Mechoulam, 1964)
cannabidiol (CBD) (Mechoulam and Shvo, 1963)
$\Delta^9$-tetrahydrocannabinol ($\Delta^9$-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)
cannabidiolic acid (CBDA)  \(\Delta^9\)-tetrahydrocannabinolic acid A (\(\Delta^9\)-THCA A)

\(\Delta^9\)-tetrahydrocannabinolic acid B (\(\Delta^9\)-THCA B)
cannabidiol (CBD)

Mechoulam and Shvo: Tetrahedron 19, 2073 (1963)

Δ⁹-tetrahydrocannabinol (Δ⁹-THC)

Gaoni and Mechoulam: J.Amer.Chem.Soc. 86, 1646 (1964)
Prevention of side effects of cancer chemotherapy
THC – CB1
Appetite and feeding
Physical growth during treatment with Δ⁹-THC and CB₁ antagonist (SR141716A)

12 (out of 13) pups dead

Day of Age
Body Weight (g)

Control
THC
SR141716A
THC + SR141716A

all pups died
Cannabidiol (CBD)
Zahir-ad-din, the epileptic son of the Chamberlain of the Caliphate Council in Baghdad, was given hashish as medication. It cured him completely but he could not be without the drug ever after.

Ibn al Badri, 1464
(manuscript in Paris found by Rosenthal)
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
Diabetes type 1
Histological analysis of pancreas tissue from mice treated with CBD, vehicle and untreated.

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. of scored islets</th>
<th>Intact islets</th>
<th>Total ruined islets</th>
<th>Full infiltrated islets</th>
<th>Partial infiltrated islets</th>
<th>Percent intact islets</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>73</td>
<td>6</td>
<td>29</td>
<td>28</td>
<td>5</td>
<td>8</td>
</tr>
<tr>
<td>Vehicle</td>
<td>94</td>
<td>12</td>
<td>30</td>
<td>43</td>
<td>7</td>
<td>13</td>
</tr>
<tr>
<td>CBD</td>
<td>140</td>
<td>108</td>
<td>-</td>
<td>12</td>
<td>15</td>
<td>77</td>
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</table>
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)

<table>
<thead>
<tr>
<th></th>
<th>101 patients control</th>
<th>46 patients (with CBD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2-4 grade</td>
<td>46%</td>
<td>12%</td>
</tr>
<tr>
<td>3-4 grade</td>
<td>10%</td>
<td>5%</td>
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</tbody>
</table>
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).
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.
(−)-Δ⁹-THC (natural)

(+)-Δ⁹-THC
Brain regions in which cannabinoid receptors are abundant

Basal ganglia
  Substantia nigra pars reticulata
Enteropeduncular nucleus
Globus pallidus
Putamen
Cerebellum
Hippocampus
Cerebral cortex, especially cingulate, frontal, and parietal regions
Intrabulbar anterior commissure
Nucleus accumbens

Movement control
Body-movement coordination
Learning and memory, stress
Higher cognitive function
Link between cerebral hemispheres
Reward pathway
$\text{CH}_2\text{OH}$

$\text{OH}$

$\text{HU-210}$

$\text{H}_2$ $\rightarrow^* \text{H}_2$

$\text{CH}_2\text{OH}$

$\text{OH}$

$\text{HU-243}$

$K_d = 45 \text{ pM}$

$^* = \text{tris(triphenylphosphine)rhodium}$
Δ⁹-tetrahydrocannabinol
(Δ⁹-THC)
anandamide
2-arachidonoyl glycerol
(2-AG)
The endocannabinoid system

CB1 and CB2 receptors

Anandamide; 2-arachidonoyl glycerol (2-AG)

N-acyl-aminoacids (or N-acyl-ethanolamides)

Enzymes: synthesis of endocannabinoids
hydrolysis of endocannabinoids

THC and Cannabidiol (CBD)
What do endocannabinoids do?

“Relax, eat, sleep, forget and protect”

Di Marzo, 1998
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
Inflammation
Inhibition of TNFα production by 2-AG

In vitro

Inhibition of TNFα production by 2-AG in mice

In vivo

<table>
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<tr>
<th>Condition</th>
<th>TNFα in serum (S50 units)</th>
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<tbody>
<tr>
<td>LPS</td>
<td>1750 ± 50</td>
</tr>
<tr>
<td>LPS + 2-AG</td>
<td>450 ± 50</td>
</tr>
<tr>
<td>LPS + 2-AG + 2-LG + 2-PG</td>
<td>50 ± 50</td>
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Brain Trauma
Levels of 2-AG in mouse brain after CHI

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

- $\star\star\star P<0.001$ vs. control
- $\star\star P<0.01$ vs. control
- $\star P<0.05$ vs. control

Nature 413, 527 (2001)
2-AG Reduces Infarct Volume 24 h After CHI

2-AG

control

![Infarct volume comparison](image)

- Infarct volume (%)
  - control (n=9)
  - 2-AG (5 mg/kg) (n=7)

Unpaired t-test, P=0.03
Actions through CB₂ receptor
We believe that the CB$_2$ receptor is part of general protective system and its stimulation leads mostly to sequences of activities of a protective nature.

This receptor works in conjunction with the immune system and with various other physiological systems.
### The Most Interesting Compounds

<table>
<thead>
<tr>
<th>Compound</th>
<th>CB$_2$R Binding Ki (nM)</th>
<th>CB$_1$R Binding Ki (nM)</th>
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<tbody>
<tr>
<td>HU-308</td>
<td>14</td>
<td>&gt;10,000</td>
</tr>
<tr>
<td>HU-910</td>
<td>6</td>
<td>1410</td>
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Role of CB2 receptor signaling in disease

Myocardial infarction
Atherosclerosis
Stroke
Liver fibrosis
Pancreatitis
Rheumatoid arthritis
Colitis
Neurodegenerative diseases
Pain
Osteoporosis
Brain injury

2-AG

- glutamate, cytokines, ROS
- neuronal & glial cell death
- cerebral ischemia

Vasoconstrictors (e.g. ET-1, Thromboxane)
Regulation of vasodilation
Corticosteroids
Androgens
Estrogens
Aldosterone
Costicosteroids
Progesteron
Digitalis
Androgens
Estrogens
anandamide

2-arachidonoyl glycerol (2-AG)

arachidonoyl serine
ΔNSS of mice 91 days post CHI

- 2-AG
- AraS
- Vehicle

Time post CHI (days):

0  4  7  15  21  28  35  42  50  56  63  70  77  84  91

ΔNSS:

0  1  2  3  4  5
Antagonism of Ara-S-induced vasorelaxation in aortic rings by SR-144528 (CB₂ antagonist)

Ara-S [μM]

% initial tension

Control (n=6)
4 μM SR-144528 (n=3)
Fatty Acids – Amino Acids (FAAA)

Arachidonoyl glycine --- antinociceptive
Arachidonoyl serine --- vasodilator; neuroprotective
Arachidonoyl dopamine --- affects neurotransmission in dopaminergic neurons
Oleoyl serine --- anti-osteoporotic (also found in brain)
Palmitoyl serine --- neuroprotective
Fatty Acids – Ethanol Amides

Arachidonoyl ethanolamide (anandamide)
Palmitoyl ethanolamide --- anti-inflammatory
Stearoyl ethanolamide --- causes apoptosis
Oleoyl ethanolamide --- regulates feeding
Bone Remodeling
oleoyl serine (HU-639)
Oleoyl Serine Stimulates Osteoblast Number

MC3T3 E1 osteoblasts

Primary newborn calvarial osteoblasts
Oleoyl Serine Rescues Ovariectomy-induced Bone Loss

Day 0  Day 42  Day 84

OVX  OS treatment  Analysis

Sham OVX  OVX/VEH  OVX/OS

BV/TV (%)

p = 0.065

p = 0.017

5 mg/Kg/day
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. May act through DNA methylation.
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
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
<table>
<thead>
<tr>
<th>Location</th>
<th>Collaborators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aberdeen</td>
<td>R. Pertwee</td>
</tr>
<tr>
<td>Bonn</td>
<td>M. Karsak A. Zimmer</td>
</tr>
<tr>
<td>Brno</td>
<td>A. Šulcová</td>
</tr>
<tr>
<td>Greece</td>
<td>C. Simeonidou</td>
</tr>
<tr>
<td>Richmond</td>
<td>B. Martin A. H. Lichtman</td>
</tr>
<tr>
<td>Canada</td>
<td>L. A. Parker</td>
</tr>
<tr>
<td>Bethesda</td>
<td>G. Kunos M. Spatz</td>
</tr>
<tr>
<td>Napoli</td>
<td>V. Di Marzo</td>
</tr>
<tr>
<td>Rome</td>
<td>M. Maccarrone</td>
</tr>
<tr>
<td>Siberia</td>
<td>L. Maslov</td>
</tr>
<tr>
<td>London</td>
<td>M. Feldmann A. M. Malfait P. F. Sumariwalla</td>
</tr>
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