The Cannabinoids: Looking Back and Ahead

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"….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
Representative natural cannabinoids

cannabigerol (CBG) (Gaoni and Mechoulam, 1964)
cannabidiol (CBD) (Mechoulam and Shvo, 1963)
Δ⁹-tetrahydrocannabinol (Δ⁹-THC) (Gaoni and Mechoulam, 1964)
cannabinol (CBN) (Adams et al., 1940)
cannabinol (CBG) (Gaoni and Mechoulam, 1964)
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)

\[ \text{cannabinoid structures} \]

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

Mechoulam and Shvo: Tetrahedron \textbf{19}, 2073 (1963)

\[ \Delta^9\text{-tetrhydrocannabinol (}\Delta^9\text{-THC}) \]

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.
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)

<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>
</tr>
</tbody>
</table>
Schizophrenia
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>
</tr>
</tbody>
</table>
CBD $\xrightarrow{1\text{-fluoropyridinium triflate}}$ HU-474
Brain regions in which cannabinoid receptors are abundant

<table>
<thead>
<tr>
<th>Region</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal ganglia</td>
<td>Movement control</td>
</tr>
<tr>
<td>Substantia nigra pars reticulata</td>
<td></td>
</tr>
<tr>
<td>Enteropeduncular nucleus</td>
<td></td>
</tr>
<tr>
<td>Globus pallidus</td>
<td></td>
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<tr>
<td>Putamen</td>
<td></td>
</tr>
<tr>
<td>Cerebellum</td>
<td>Body-movement coordination</td>
</tr>
<tr>
<td>Hippocampus</td>
<td>Learning and memory, stress</td>
</tr>
<tr>
<td>Cerebral cortex, especially cingulate,</td>
<td>Higher cognitive function</td>
</tr>
<tr>
<td>frontal, and parietal regions</td>
<td></td>
</tr>
<tr>
<td>Intrabulbar anterior commissure</td>
<td>Link between cerebral hemispheres</td>
</tr>
<tr>
<td>Nucleus accumbens</td>
<td>Reward pathway</td>
</tr>
</tbody>
</table>
Δ⁹-tetrahydrocannabinol
(Δ⁹-THC)

anandamide

2-arachidonoyl glycerol
(2-AG)

The endocannabinoid system

CB1 and CB2 receptors

Anandamide; 2-arachidonoyl glycerol (2-AG)

Enzymes: synthesis of endocannabinoids
hydrolysis of endocannabinoids

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

<table>
<thead>
<tr>
<th>Anxiety</th>
<th>Inflammation</th>
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<tbody>
<tr>
<td>Appetite/feeding</td>
<td>Memory</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Mood</td>
</tr>
<tr>
<td>Bone formation</td>
<td>Movement</td>
</tr>
<tr>
<td>Cerebral blood flow</td>
<td>Neuroprotection</td>
</tr>
<tr>
<td>Digestive system</td>
<td>Pain</td>
</tr>
<tr>
<td>Emesis and nausea</td>
<td>Reproduction</td>
</tr>
<tr>
<td>Immune system</td>
<td>Stress</td>
</tr>
</tbody>
</table>
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

2-AG

control

unpaired t-test, P=0.03
Role of CB2 receptor signaling in disease

Myocardial infarction

Atherosclerosis

Stroke

Liver fibrosis

Rheumatoid arthritis

Neurodegenerative diseases

Pain
Brain injury

- Glutamate, cytokines, ROS
- Neuronal & glial cell death
- Cerebroprotection
- 2-AG
- Vasoconstrictors (e.g. ET-1, Thromboxane)
- Cerebral ischemia
Regulation of vasodilation
anandamide

2-arachidonoyle glycerol (2-AG)

arachidonoyle serine
Bone Remodeling
arachidonoyl ethanolamide (anandamide)

oleoyl serine (HU-639)

PNAS, 2010
Oleoyl Serine Rescues Ovariectomy-induced Bone Loss

![Graph showing BV/TV (%)]

- Sham OVX: p = 0.065
- OVX/VEH: p = 0.017

Timeline:
- O VX: Day 0
- OS treatment: Day 42
- Analysis: Day 84
- OS treatment: 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.

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
<table>
<thead>
<tr>
<th>Location</th>
<th>Collaborators</th>
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<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>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>
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Fatty Acids – Ethanol Amides

Arachidonoyl ethanolamide (anandamide)
Palmitoyl ethanolamide --- anti-inflammatory
Stearoyl ethanolamide --- causes apoptosis
Oleoyl ethanolamide --- regulates feeding
ΔNSS of mice 91 days post CHI

Time post CHI (days)

ΔNSS

2-AG
AraS
Vehicle

* * *
PalmS does not exert neurobehavioral improvement in CB₂ KO mice

PalmS- mechanism of action

Time post CHI

dNSS

- WT +palm.- 1mg/kg
- WT - veh
- CB2-Ko +palm.- 1mg/kg
- CB2 ko - veh

* p=0.01
** p=0.06
*** p=0.03
vs. CB2-Ko PalmS
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)
CBD (5 mg/kg/day) i.p. to female 14 week old NOD mice with latent diabetes. Administered for 4 weeks/5 days a week. Observed until 24 weeks of age. End point: glucosuria.
Oleoyl Serine Stimulates Osteoblast Number

**MC3T3 E1 osteoblasts**

**Primary newborn calvarial osteoblasts**
$$(-)-\Delta^9-\text{THC (natural)}$$

$$ (+)-\Delta^9-\text{THC}$$
Antagonism of Ara-S-induced vasorelaxation in aortic rings by SR-144528 (CB$_2$ antagonist)