MICHAEL STEWARD M.D.
Chief Medical Officer & Co-Founder Endourage

- HIV, Palliative and Cannabinoid medicine specialist
- Developed multiple HIV protocols still in use today
- Sat on multiple pharma advisory boards
- Previously Board-Certified in Family Practice
- Previous Medical Director Kings Garden, A+ Home Health Care and Vitas Innovative Hospice Care
- Previous Owner/Operator Apex Family Medicine
- Member of the Society of Cannabis Clinicians, the American Academy of Family Practice and the American Society of Addiction Medicine.

The Endocannabinoid System & Chronic Disease:

Clinical Context & the Long COVID Case Study

RESIDENT SEMINAR SERIES

- TWO 60MIN SEGMENTS WITH 10MIN BREAK -

endourage®

The Endocannabinoid System (ECS) Begins with History

Part 1: Physiology_ECS Components, Mechanisms

Historical Use of Cannabis

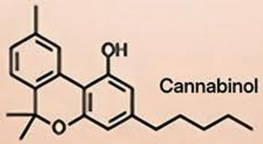
2700 BCE
Earliest recorded use of cannabis for medicinal purpose

Cannabis mentioned as one of five sacred plants in Hindu scripture Atharva Veda
1000 BCE

450 BCE
Cannabis seeds burned at Scythian funerals

Avicenna's Canon on Medicine reports Cannabis use for gout, edema, headache
1000 AD

Cannabis Research

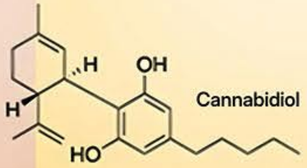


1838-43
O'Shaughnessy investigates medical use of cannabis in India

First isolation of cannabinol from cannabis resin by Wood *et al.*
1899

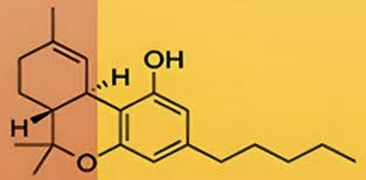
1930-40
Cannabinol structure elucidated, isolated, and synthesized

Cannabinoid Research



Discovery of cannabidiol by Adams *et al.*
1940

1964
THC isolation and structure elucidation by Gaoni & Mechoulam



Discovery of the Cannabinoid (CB)1 receptor by Devane *et al.*
1988

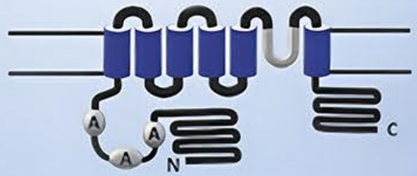
1990
The CB1 receptor is cloned by Matsuda *et al.*

Isolation, structure elucidation (Mechoulam) and pharmacology (Pertwee) of Anandamide
1992

1993
Discovery & cloning of the Cannabinoid (CB)2 receptor by Munro *et al.*

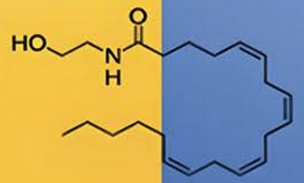
SR-141716A, the first CB1 antagonist is synthesized at Sanofi by Rinaldi-Carmona *et al.*
1994

Endocannabinoid Research



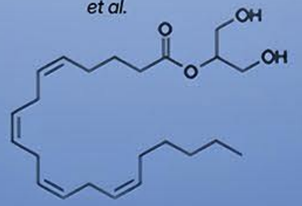
1995
Discovery of 2-Arachidonoylglycerol by Mechoulam *et al.*, & Sugiara *et al.*

Anandamide



Cloning of Fatty Acid Amide Hydrolase by Cravatt *et al.*
1996

1998
First selective CB2 antagonist, SR-144528, synthesized by Rinaldi-Carmona *et al.*



Anandamide activation of Vanilloid receptors Zygmunt *et al.*, Smart *et al.*
1999-2000

2001
Retrograde signaling by endocannabinoids discovered by Wilson & Nicolli

Bisogno *et al.* clones the first endocannabinoid biosynthesizing enzymes
2003

Drugs & Medical Cannabis

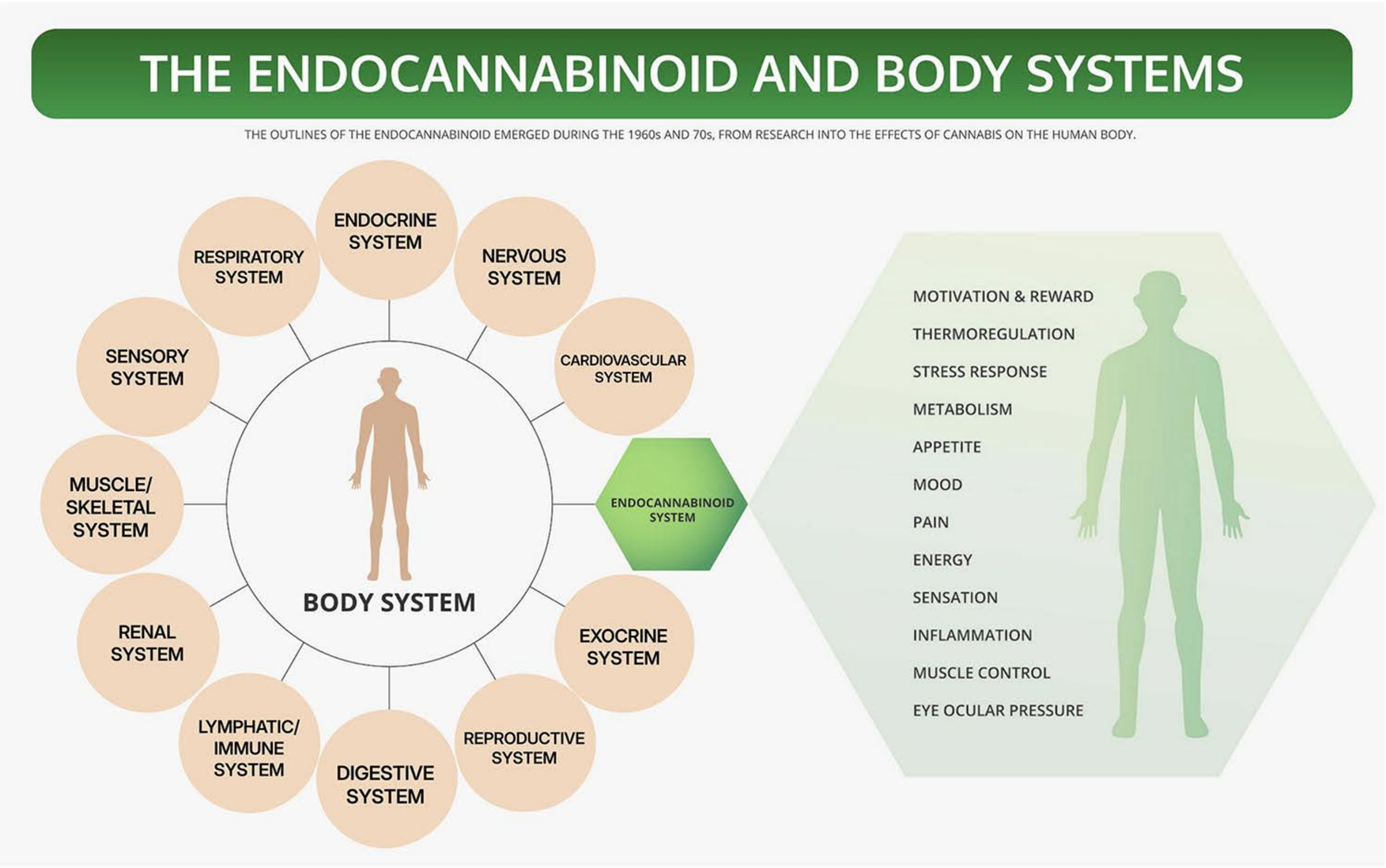
2005
Sativex® is approved for use in Canada

Rimonabant approved for obesity in Europe (withdrawn in 2008)
2006

2018
FDA approval os Epidiolex® for childhood epilepsy

Medical Cannabis available in 33 states, Guam, Puerto Rico, District of Columbia, & US Virgin Islands and 56 countries worldwide
2019

Part 1: The ECS is the Master Regulator in the Body



frontiers in Neuroscience

REVIEW
published: 28 October 2021
doi: 10.3389/fnins.2021.747229

Quality of Life and a Surveillant Endocannabinoid System

Ricardo Augusto de Melo Reis[1], Alinny Rosendo Isaac[1], Hércules Rezende Freitas[2], Mariana Macedo de Almeida[3], Patricia Fernanda Schuck[2], Gustavo Costa Ferreira[2], Belmira Lara da Silveira Andrade-da-Costa[4] and Isis Hara Trevenzoli[3]*

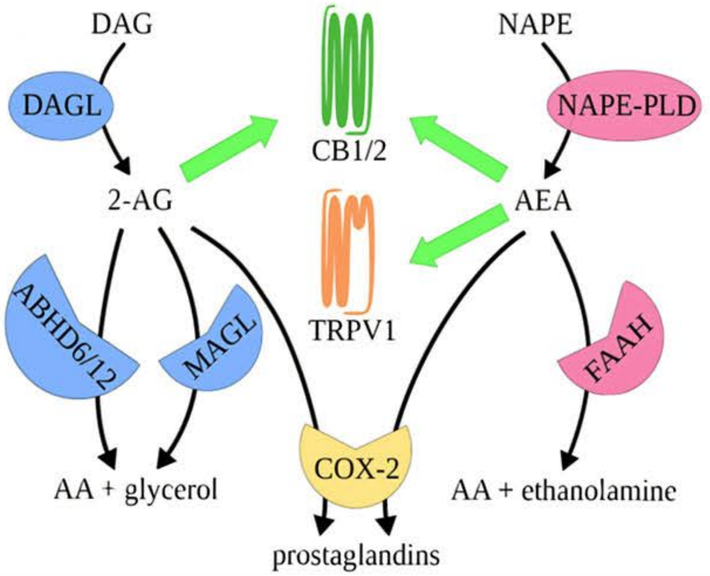
[1] Laboratory of Neurochemistry, Institute of Biophysics Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, [2] Laboratory of Neuroenergetics and Inborn Errors of Metabolism, Institute of Medical Biochemistry Leopoldo de Meis, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, [3] Laboratory of Molecular Endocrinology, Institute of Biophysics Carlos Chagas Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil, [4] Physiology and Pharmacology Department, Center for Biosciences, Universidade Federal de Pernambuco, Recife, Brazil

The endocannabinoid system (ECS) is an important brain modulatory network. ECS regulates brain homeostasis throughout development, from progenitor fate decision to neuro- and gliogenesis, synaptogenesis, brain plasticity and circuit repair, up to learning, memory, fear, protection, and death. It is a major player in the hypothalamic-peripheral system-adipose tissue in the regulation of food intake, energy storage, nutritional status, and adipose tissue mass, consequently affecting obesity. Loss of ECS control might affect mood disorders (anxiety, hyperactivity, psychosis, and depression), lead to drug abuse, and impact neurodegenerative (Alzheimer's, Parkinson, Huntington, Multiple, and Amyotrophic Lateral Sclerosis) and neurodevelopmental (autism spectrum) disorders. Practice of regular physical and/or mind-body mindfulness and meditative activities have been shown to modulate endocannabinoid (eCB) levels, in addition to other players as brain-derived neurotrophic factor (BDNF). ECS is involved in pain, inflammation, metabolic and cardiovascular dysfunctions, general immune responses (asthma, allergy, and arthritis) and tumor expansion, both/either in the brain and/or in the periphery.

Part 1: The ECS has Receptors + Endocannabinoids + Enzymes

ECS COMPONENTS

Receptors	Enzymes
CB1, CB2 GPR18, GPR55, GPR119 TRPV1 PPARγ	DAGL, NAPE-PLD MAGL, ABHD6/12 FAAH NAAA
Transport proteins	**Endocannabinoids**
FABPs HSP70s AMT (?)	2-AG AEA PEA OEA



THE ENDOCANNABINOID SYSTEM

HUMAN CANNABINOID RECEPTORS

CB1

Receptors are concentrated in **the brain & the central nervous system** but are also present in some **nerves & organs**

CB2

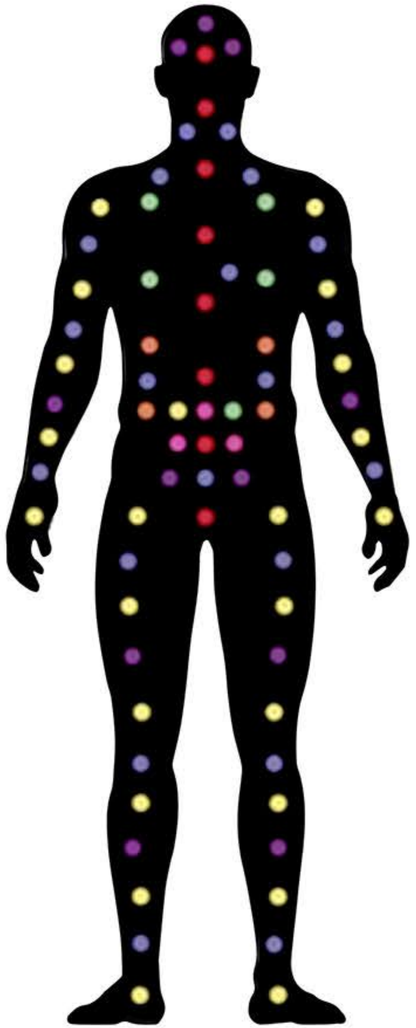
Receptors are mostly in peripheral organs, especially **cells associated with the immune system**

TRPV1

Receptors are concentrated in the **blood, bone marrow, tongue, kidney, liver, stomach, & ovaries**

TRPV2

Receptors are concentrated in the **blood, bone marrow, tongue, kidney, liver, stomach, & ovaries**



GPR 18

Receptors can be found primarily in **bone marrow, the spleen and lymph nodes**, and to a lesser extent **the testes**

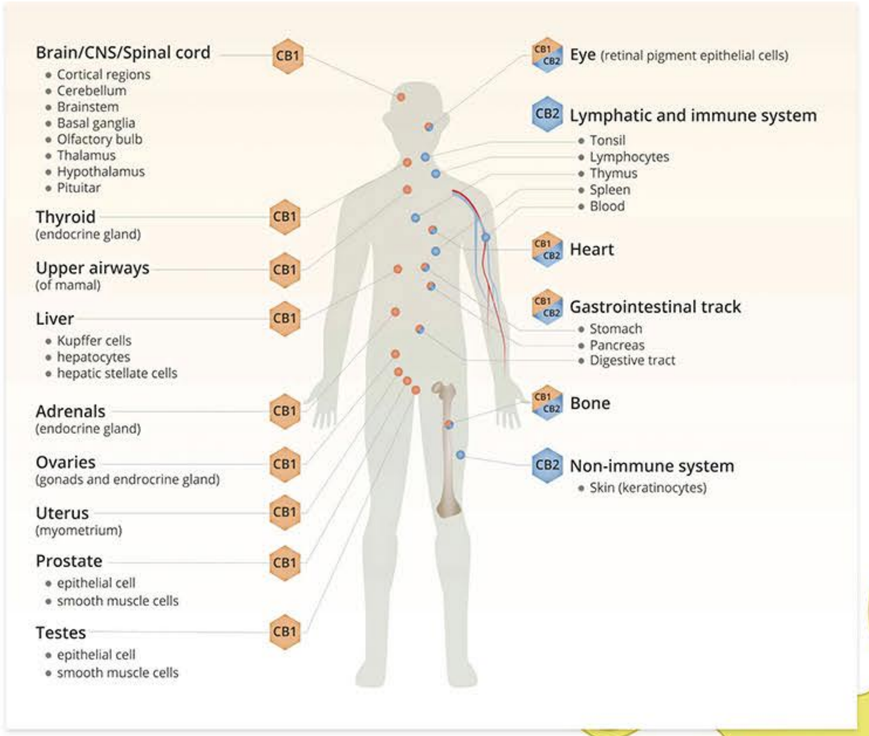
GPR 55

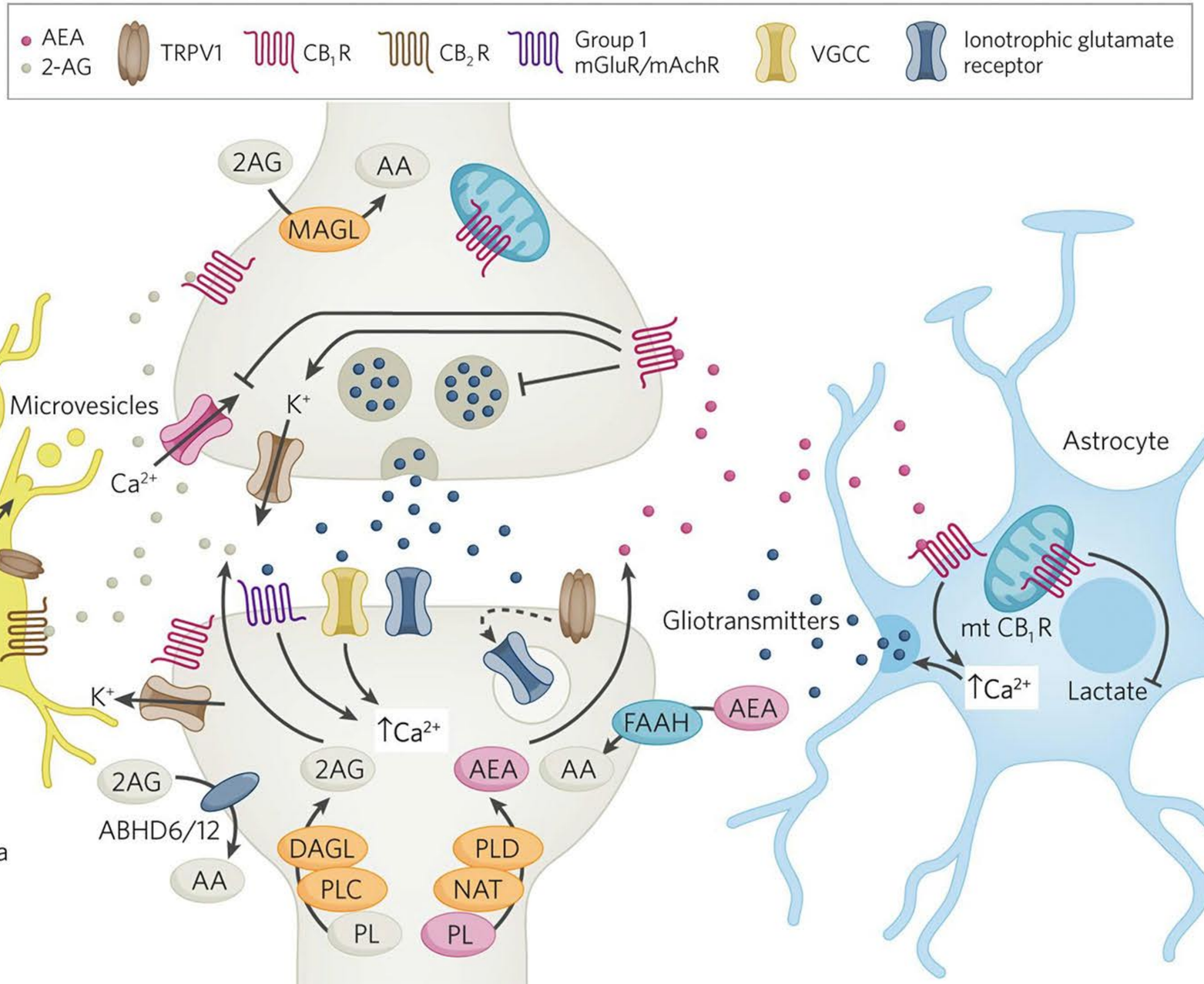
Receptors are found in **bone, the brain (particularly the cerebellum), and the jejunum and ileum**

GPR 119

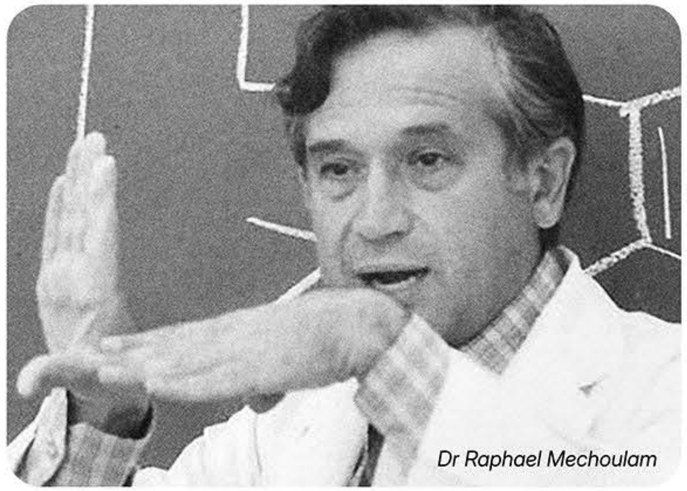
Receptors are found predominantly in the **pancreas and intestinal tract (in small amounts)**

Part 1: Endocannabinoids Employ Retrograde Synaptic Messaging





Part 1: Phytocannabinoids are Chemical Proxies for Endocannabinoids



Hexanoyl-CoA ← Fatty Acid

POLYKETIDE PATHWAY

3 × Malonyl-CoA

Olivetolic Acid (OLA)

CBGA

Pyruvate — Acetyl-CoA

IPP

Plastidial DOXP/MEP PATHWAY

Cytoplasmic MVA PATHWAY

DAMPP (C_5)

IPP (C_5)

GPP (C_{10}) → FPP (C_{15}) → Squalene (C_{30})

CBDA

CBCA

THCA

β-Myrcene

β-Caryophyllene

Friedelin

β-Sitosterol

Phenylalanine

PHENYLPROPANOID PATHWAY

p-Coumaroyl-CoA

3 × Malonyl-CoA

Naringenin

Apigenin

Cannabinoids | Monoterpenoids | Sesquiterpenoids | Triterpenoids | Sterols | Flavonoids

Three Categories:

- Cannabinoids
- Terpenes
- Flavonoids

Entourage Effect:

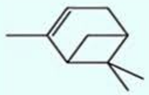
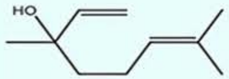
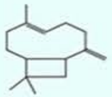
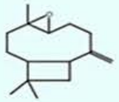
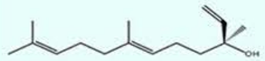
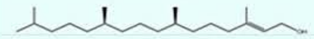
- Single v. Multi-Molecule Discussion

Historical Research v. Future Research Comps:

- Pre 2018 @ USA / incinerated, isolates, high concentrations, high frequencies
- 2023 @ USA / most funded R&D isolates & in-vivo/vitro
- Patent System Effect re: Isolate R&D Disappointment
- Future Phytocannabinoid R&D multi-molecule/ synergistic/selective modalities
- Terpenes not trivial

Part 1: Terpenes Appear to Matter

- Safe
- Abundant in Nature, not in Lab
- Cannabis Proxies not Interchangeable
- Don't Play Well with Artificial Flavors
- Highly Unstable - Degrades in Pressure, Heat, & Light
- Synergistic with Endo & Phyto Cannabinoids
- Clinician Modality is Key
  - -Topical, Sublingual Preferences

Terpenoid	Structure	Commonly Encountered In	Pharmacological Activity (reference)	Synergistic Cannabinoid
Limonene		 Lemon	**Potent AD/immunostimulant** via inhalation (Komori *et al.*, 1995)	CBD
			Anxiolytic (Carvalho-Freitas & Costa, 2002; Pultrini Ade *et al.*, 2006) via 5-HT$_{1A}$ (Komiya et al.,2006)	CBD
			Apoptosis of breast cancer cells (Vigushin *et al.*, 1998)	CBD, CBG
			Active against acne bacteria (Kim *et al.*, 2008)	CBD
			Dermatophytes (Sanguinetti *et al.*, 2007; Singh *et al.*, 2010)	CBG
			Gastro-esophogeal reflux (Harris, 2010)	THC
α-Pinene		 Pine	**Anti-inflammatory** via PGE-1 (Gil *et al.*, 1990)	CBD
			Bronchodilatory in humans (Falk et al., 1990)	THC
			Acetylcholinesterase inhibitor, aiding memory (Perry *et al.*, 2000)	THC?, CBD
β-Myrcene		 Hops	**Blocks inflammation** via PGE-2 (Lorenzetti *et al.*, 1991)	CBD
			Analgesic, antagonized by naloxone (Rao *et al.*, 1990)	CBD, THC
			Sedating, muscle relaxant, hypnotic (do Vale *et al.*, 2002)	THC
			Blocks hepatic carcinogens by aflatoxin (de Oliveira *et al.*, 1997)	CBD, CBG
Linalool		 Lavender	**Anti anxiety** (Russo, 2001)	CBD, CBG
			Sedative on inhalation in mice (Buchbauer *et al.*, 1993)	THC
			Local anesthetic (Re *et al.*, 2000)	THC
			Analgesic via adenosine, A$_{2A}$ (Peana *et al.*, 2006)	CBD
			Anticonvulsant/anti-glutamate (Elisabetsky *et al.*, 1995)	CBD, THCV, CBDV
β-Caryophyllene		 Pepper	**Potent anti-leishmanial** (do Soccer *et al.*, 2003)	?
			AI via PGE-1 comparable phenylbutazone (Basile *et al.*, 1988)	CBD
			Gastro cytoprotective (Tambe *et al.*, 1996)	THC
			Anti-malarial (Campbell *et al.*, 1997)	?
			Selective CB2 agonist (100nM) (Gertsch *et al.*, 2008)	THC
			Treatment of pruritus? (Karsak *et al.*, 2007)	THC
			Treatment of addiction? (Xi *et al.*, 2010)	CBD
Caryophyllene Oxide		 Lemon Balm	**Decreases platelet aggregation** (Lin *et al.*, 2003)	THC
			Antifungal in onychomycosis comparable to ciclopiroxolamine & sulconazole (Yang *et al.*, 1999)	CBC, CBG
			Insecticidal/anti-feedant (Bettering *et al.*, 1993)	THCA, CBGA
Nerolidol		 Orange	**Sedative** (Binet *et al.*, 1972)	THC, CBN
			Skin penetrant (Cornwell & Barry, 1994)	-
			Potent antimalarial (Lopes *et al.*, 1999, Rodrigues Goulart *et al.*, 2004)	?
			Anti-leishmanial activity Arruda *et al.*, 2005)	?
Phytol			**Breakdown product of chlorophyll**	-

Part 1: Physiology - ECS Components & Mechanisms

- Key Endocannabinoid Clinical Foundational Findings

- ECS Master Regulator vs. Tangential Signaling System (driver, not rider)
- ECS is a 911 Neurotransmitter (onsite support in real time)
- Dysfunctional ECS Hypothesis & Chronic Disease (broken battery, broken car)
- The ECS is Driven by Entourage Effect (synergistic), not Patent Effect (isolates)

- Developments & Research_Early Inclinations

2018 Farm Bill_R&D Emancipation

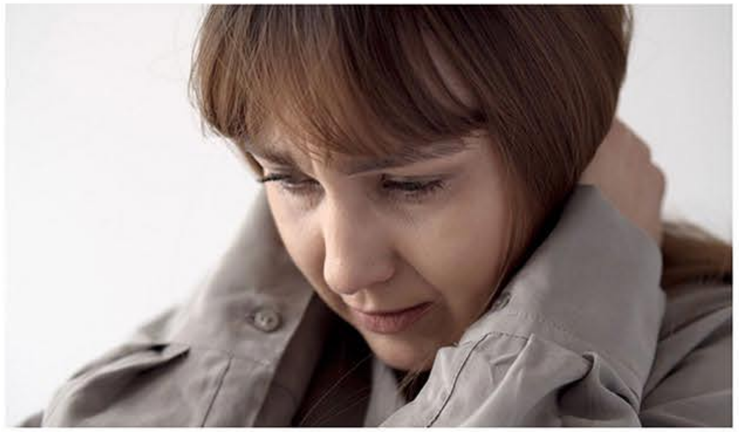
- These are early days – ~400 phytocannabinoids...lots to learn...tech expedites
- Multi-molecule + Dosing + Modality central to R&D of efficacy moving forward

R&D Muscle Memory Dillemma_Funding v. Finding Paradox

- Isolates attract funding, but Multi-molecule research produces findings

KEY TERMS:

- **Receptors** (GBPCG's: CB1, CB2, TRPV1[5-TH1A], TRPV2, GPR18, GPR55, GPR119)
- **Endocannabinoids** (Ligands)
  - **Anandamide** (AEA "bliss molecule"
  - **2-arachidonoyl glycerol** (2AG)
  - **Noladin Ether**
  - **N-Arachidonoyl**
  - **Virodhamine**
  - **Docosatetraenoy lethanol-amide**
  - **Lysophosphatidylinositol**
  - **Oleoylethanolamide**
- **Enzymes** (FAAH>AEA; MAGL>2AG)
- **Phytocannabinoids** (cannabinoids, flavonoids, terpenes)



What Happens when the ECS breaks?

- Discussion of Stressors & Indications

- ECS impacted by chronic stress, traumatic stress
- ECS dysfunction manifested by chronic disease

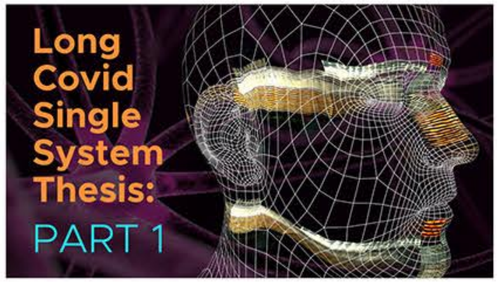
- Discussion of Phytocannabinoid Therapy

- Regulatory Basics
  - Hemp is 100% legal because it contains < .3% THC
  - Marijuana is regulated because it contains > .3% THC
- Is Hemp Medicine? Nutrient?...depends on dosing...aka Vitamin C...low dose = nutrient
- Isolates (patent driven R&D) v. Multi-Molecule (synergistic – patient driven R&D)
  - The "Entourage Effect": nature's use of a multi-molecule design that must be complete and natural to be optimal
- Transparency - labels
  - Ingredients - allergies (MCT, Aloe, etc)
  - Testing: full array (6) & status v. Quantified results
- Synthetic – always isolates & side effects; incompatible with Entourage Effect; strongly discouraged
- Modalities – must be measurable for clinical use
- Dosing – physiological variability/naivete, BMI q's, upregulation window
- Risk Discussion
  - Brain stem
  - Chemovar profile
  - Modality &frequency
  - Pediatrics
  - Nursing Mothers
  - Vocational testing (military, federal jobs, etc.)
  - Accessibility (insurance not common but FSA, HSA more common)
- Red flags – artificial molecules, synthetics, proxies, flavors, labeling tricks, test disclosures

Part 2: Case Study - ECS Hypothesis Tested with Long COVID

- Endourage studied Long COVID... but truly initiated study of ECS Dysfunction in context of Chronic Disease

ECS Clinical Training_Video_Part 1:
https://vimeo.com/952391107/a8287c6d1f



ECS Clinical Training_Video_Part 2:
https://vimeo.com/952392218/cf2c1ce6ca

List of Published Research with Citations:

Inflammopharmacology (2023) 31:2807–2817
https://doi.org/10.1007/s10787-023-01204-1

Inflammopharmacology

ORIGINAL ARTICLE

Check for updates

Long COVID and possible preventive options

Szilvia Sebők[1] · Klara Gyires[2]

Received: 17 March 2023 / Accepted: 22 March 2023 / Published online: 21 June 2023

International Journal of *Molecular Sciences*

MDPI

Review

Possible Role of Cannabis in the Management of Neuroinflammation in Patients with Post-COVID Condition

Noemi Cárdenas-Rodríguez [1,†], Iván Ignacio-Mejía [2,†], Jose Correa-Basurto [3], Humberto Carrasco-Vargas [4], Marco Antonio Vargas-Hernández [5], Exal Manuel Albores-Méndez [5], Rodolfo David Mayen-Quinto [6], Reynita De La Paz-Valente [7] and Cindy Bandala [7,*]

Exploration of Medicine

Open Exploration

Open Access Review

Check for updates

Cannabis-based medicinal products (CBMPs) for the treatment of Long COVID symptoms: current and potential applications

Hannah Thurgur[1*], Anne Katrin Schlag[1], Elizabeth Iveson[2], Adele Hosseini[3], Michael Lynskey[1], David J. Nutt[1,4]

Clinical Science (2023) **137** 633–643
https://doi.org/10.1042/CS20220193

PORTLAND PRESS

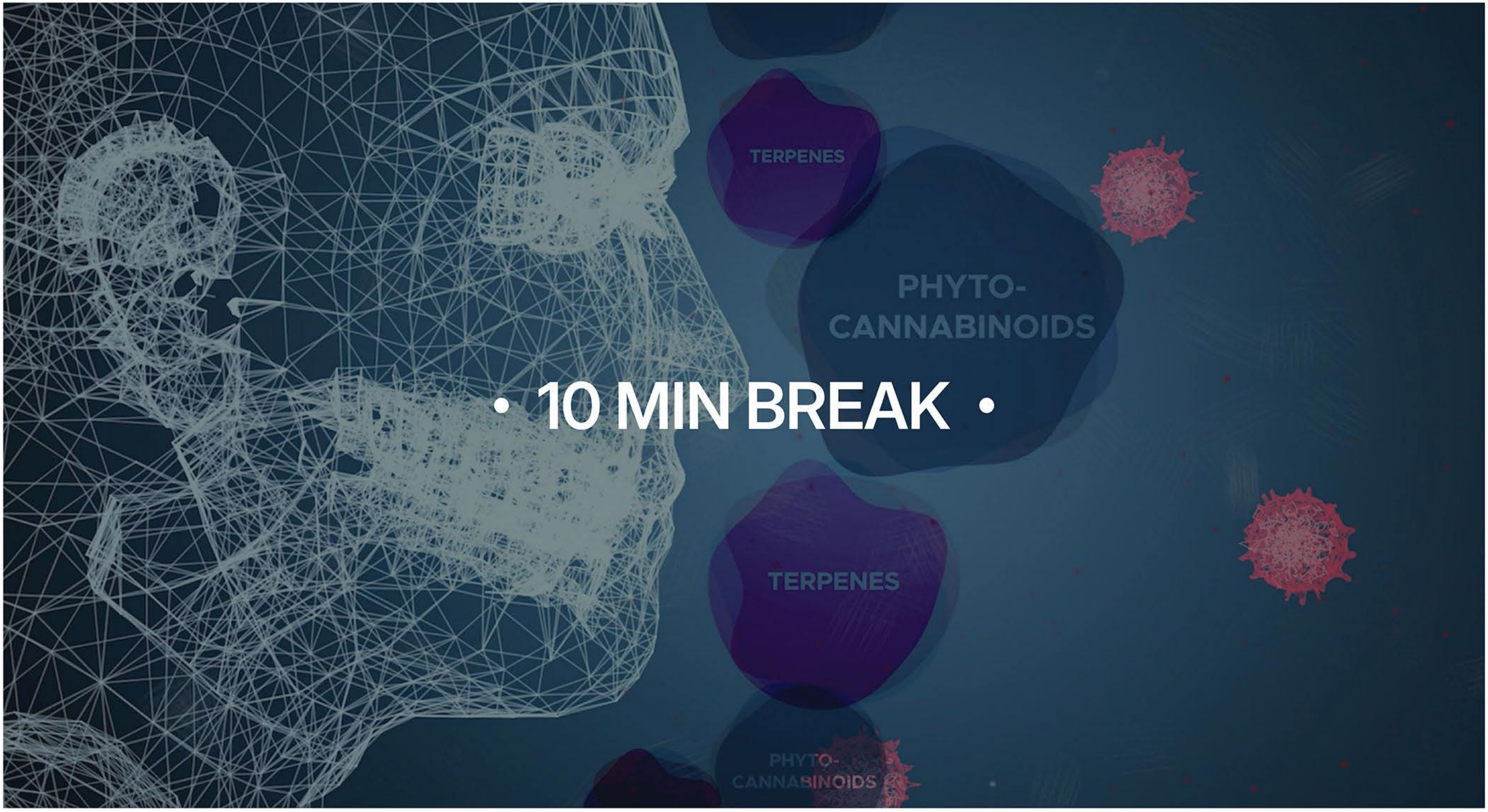
Review Article

Antiviral activities of hemp cannabinoids

Richard B. van Breemen and Daniel Simchuk

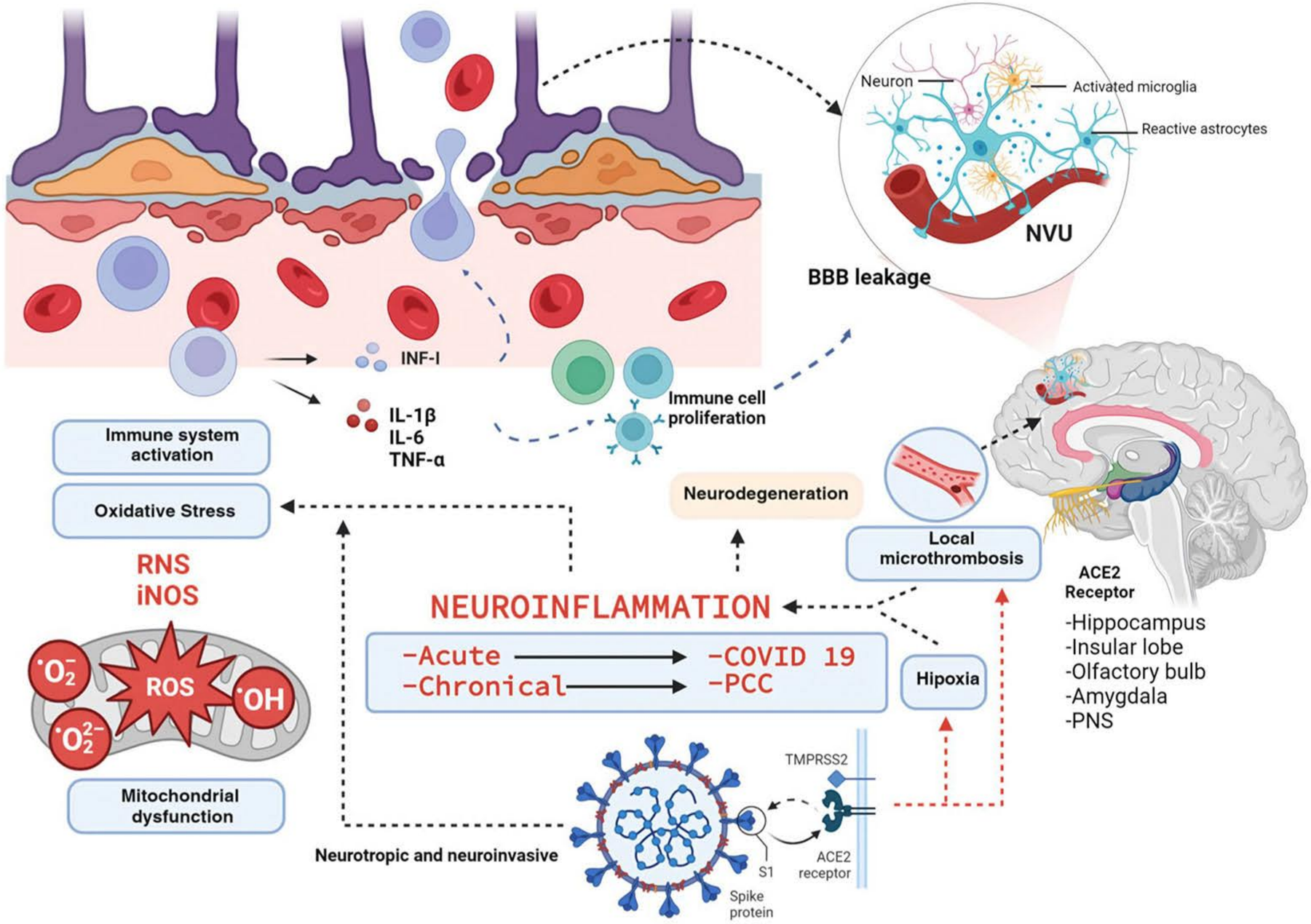
Department of Pharmaceutical Sciences, College of Pharmacy, Linus Pauling Institute, Global Hemp Innovation Center, Oregon State University, 2900 SW Campus Drive, Corvallis, OR 97331, U.S.A.

Correspondence: Richard B. van Breemen (richard.vanbreemen@oregonstate.edu)


TERPENES
PHYTO-
CANNABINOIDS
• 10 MIN BREAK •
TERPENES
PHYTO-
CANNABINOIDS

Part 3: Chronic Disease - Presentations of ECS Dysfunction

- **PACS Triggered Inflammation & the ECS:** Implications



Part 3: Chronic Disease - Presentations of ECS Dysfunction

- **PACS Triggered Inflammation & the ECS:** Implications

NEUROINFLAMMATION

Post COVID Condition

CANNABIS COMPOUNDS

Improve neurological symptoms

CBD

Antiviral (COVID-19)

↓ ACE2
↓ TMPRSS2
↓ IL-6

Neuroinflammation

↓ Apoptosis
-BIM
-Caspase 12

↑ Synaptic plasticity

↓ TNFα
↓ IL-1β
↓ IL-6
↓ IL-8
↓ IL-17
↓ IFNγ
↓ MPO
↓ iNOS
↓ NO_2
↓ Lipid peroxides
↓ PGE2
↓ ROS
↓ TRPM3/8

↑ IL-4
↑ IL-10
↑ MDSCs
↑ GRP78
↑ MANF

CBG+CBD

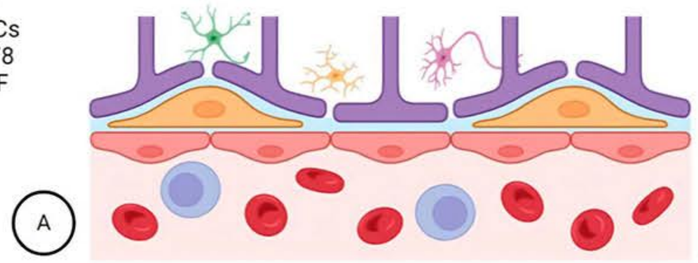
↓ COX
↓ NO
↓ TNFα
↓ IL-1β
↓ IL-6
↓ IL-8
↓ IFNγ
↓ MPO
↓ iNOS
↓ ROS

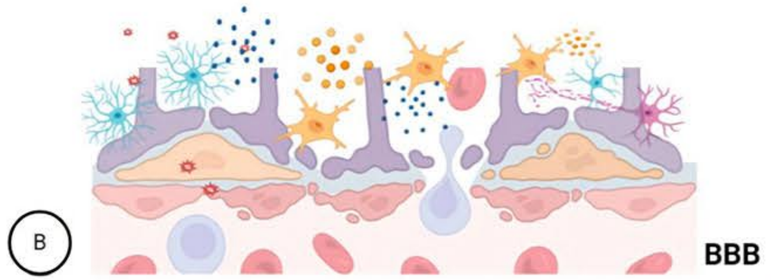
↑ IL-10
↑ Nrf-2

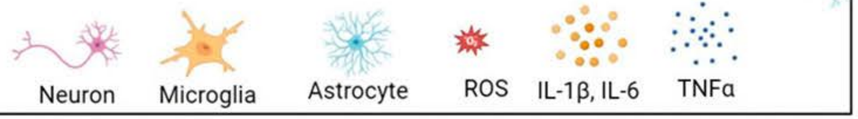
THC+CBD

↓ IL-17
↓ TNFα

↑ IL-10
↑ BDNF

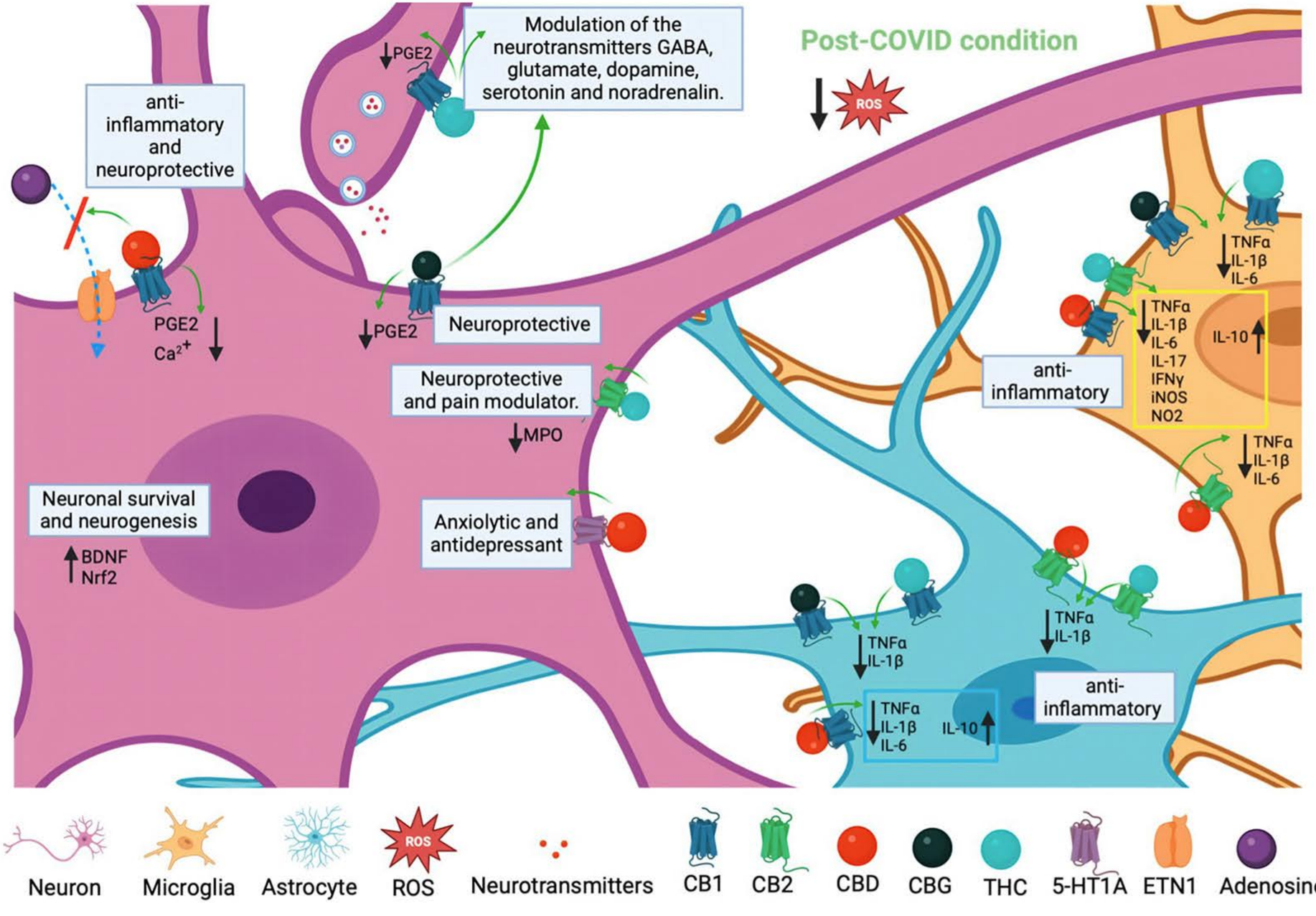






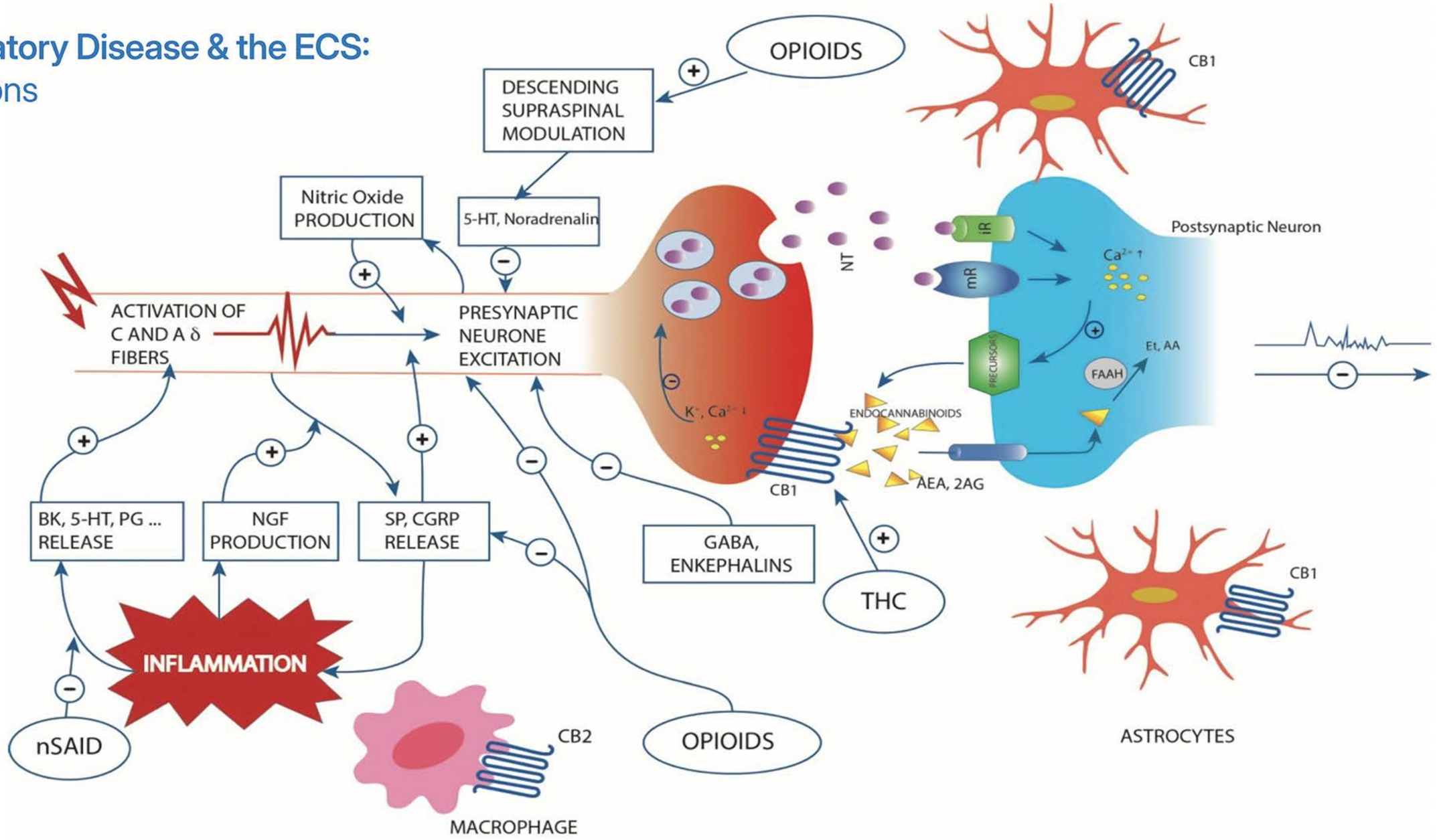
Part 3: Chronic Disease - Presentations of ECS Dysfunction

- **PACS Triggered Inflammation & the ECS:** Implications



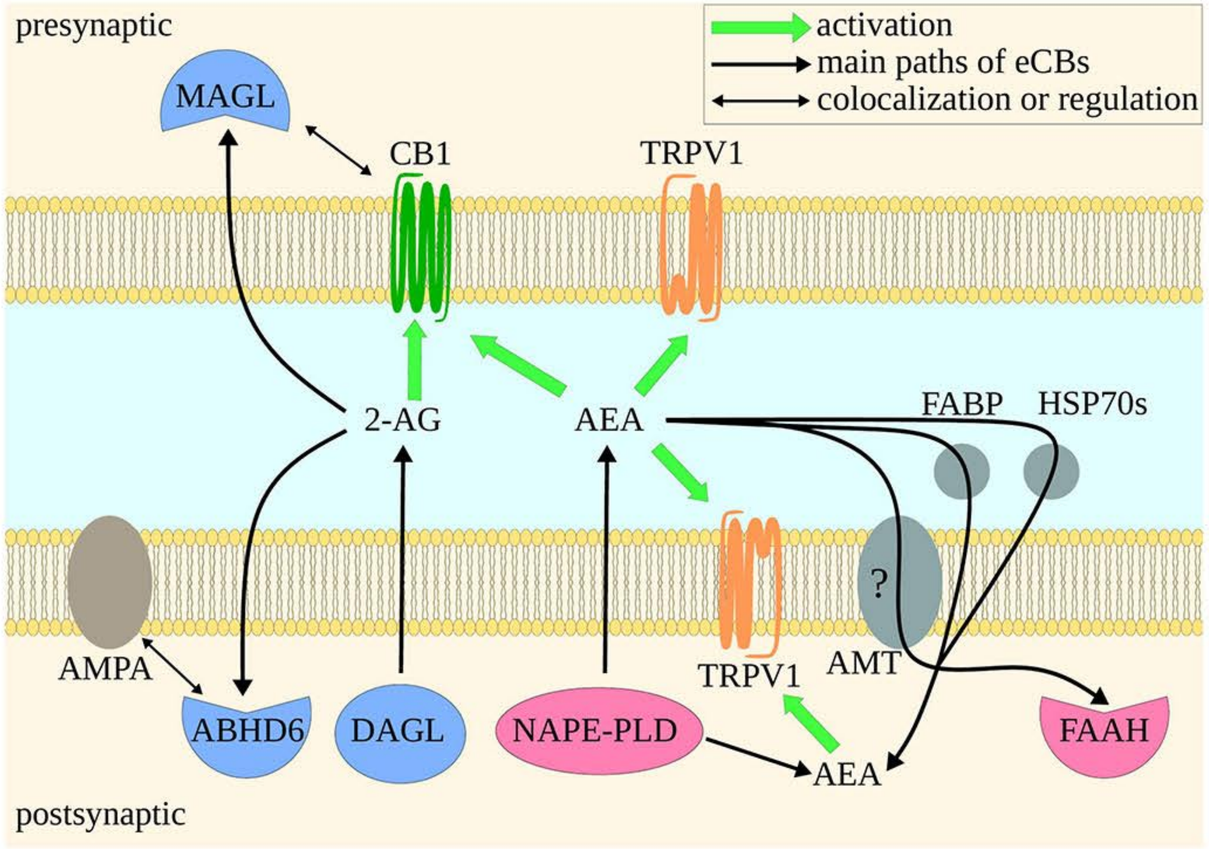
Part 3: Chronic Disease - Presentations of ECS Dysfunction

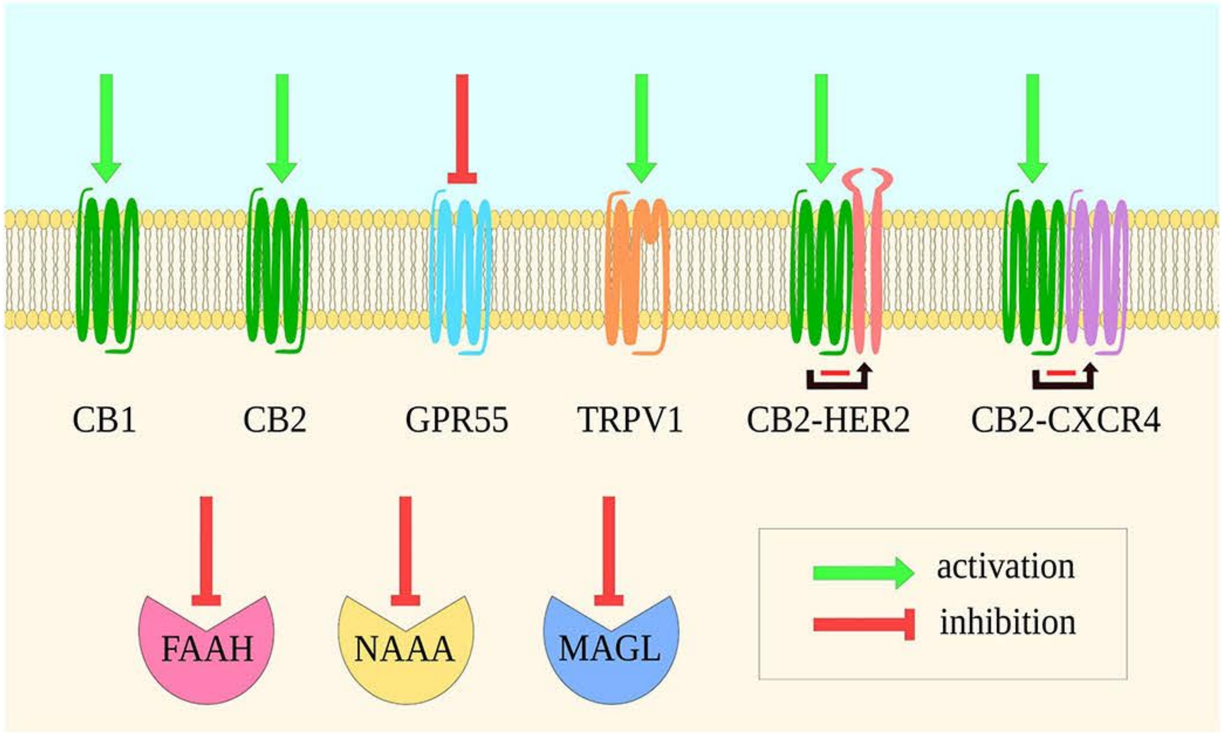
- **Inflammatory Disease & the ECS:**
  Implications



Part 3: Chronic Disease - Presentations of ECS Dysfunction

- **Cancer Disease & the ECS: Implications**

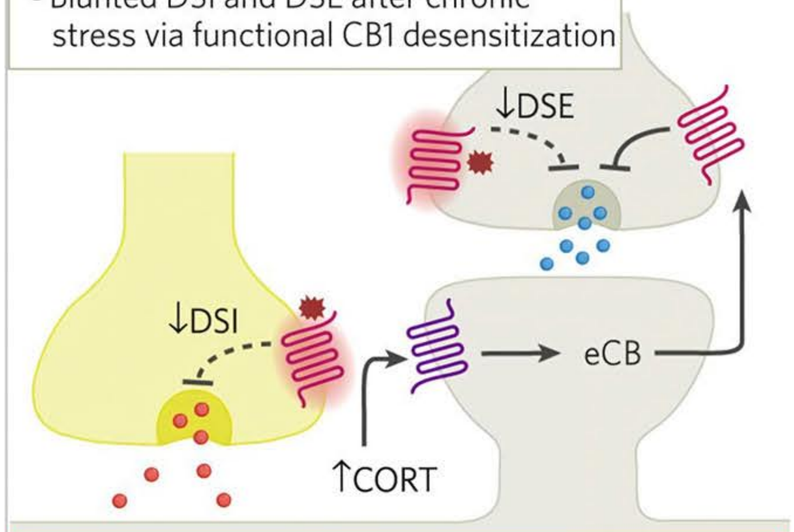


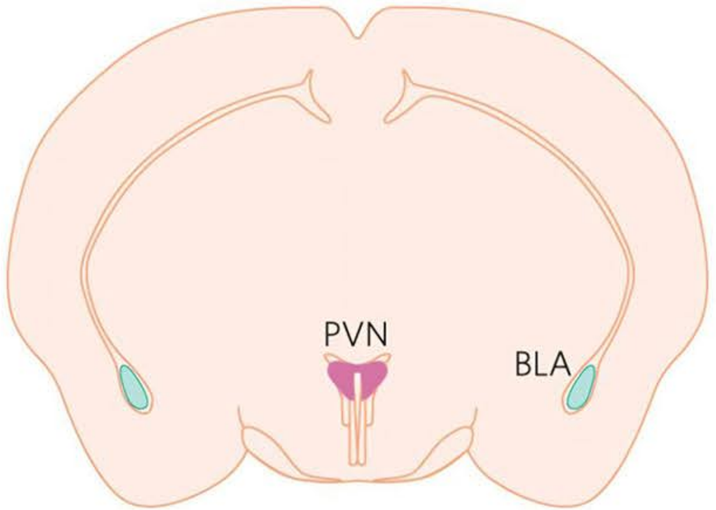


Part 3: Chronic Disease - Presentations of ECS Dysfunction

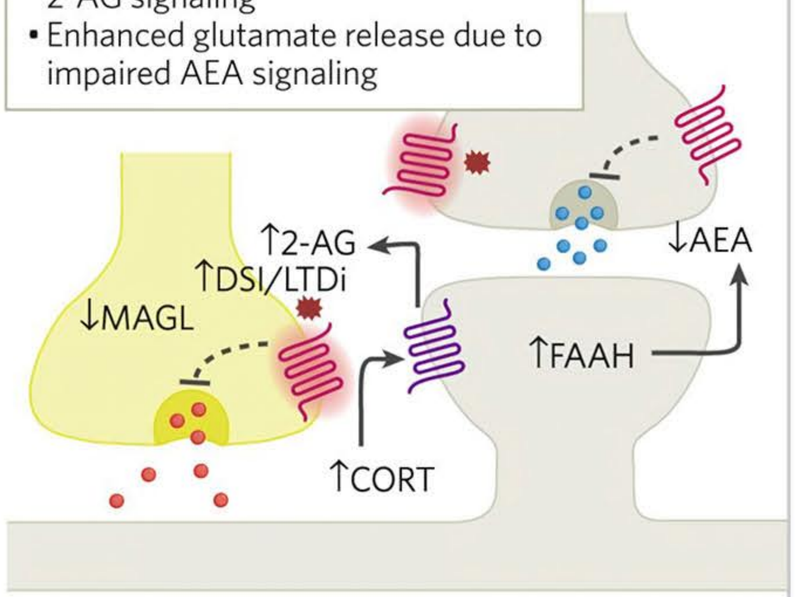
- **Stress & the ECS:** Implications

The stressed PVN:
- CORT mediated eCB synthesis inhibits glutamate release
- Fast feedback inhibition of HPA axis by CORT is CB1R dependent
- Blunted DSI and DSE after chronic stress via functional CB1 desensitization





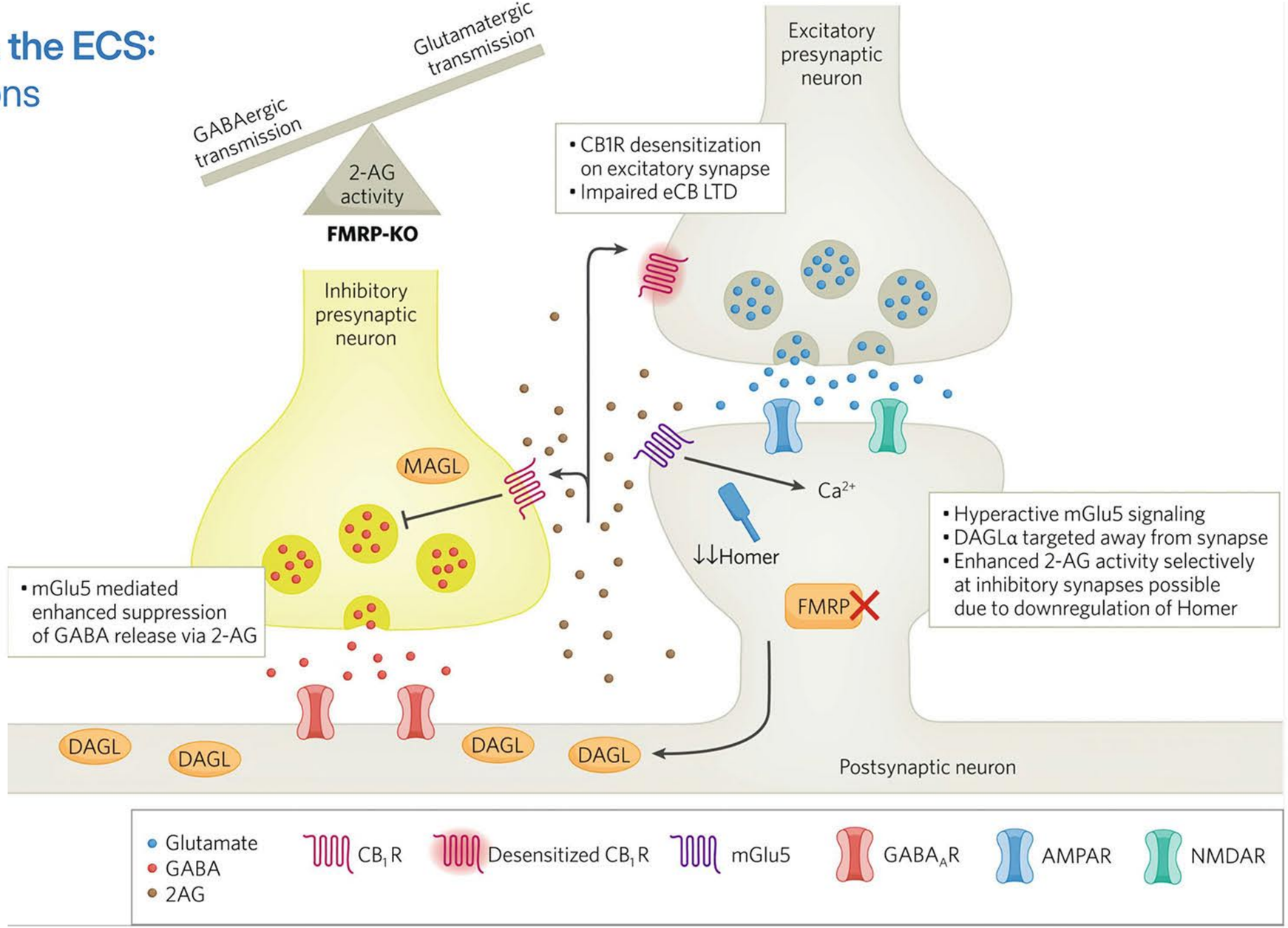
The stressed BLA:
- Enhanced DSI and iLTD and CB1 desensitization after chronic stress
- CORT-mediated supression of GABA release via sustained activation of 2-AG signaling
- Enhanced glutamate release due to impaired AEA signaling



PVN - Paraventricular Nucleus of the Hypothalamus
BLA - Basolateral Amygdala; a key brain reward region that also regulates stress responses
CORT - Corticosterone
DSE - Depolarization-Induced Suppression of Excitation
DS1 - Depolarization-Induced Suppression of Inhibition

Part 3: Chronic Disease - Presentations of ECS Dysfunction

- **Autism & the ECS:** Implications

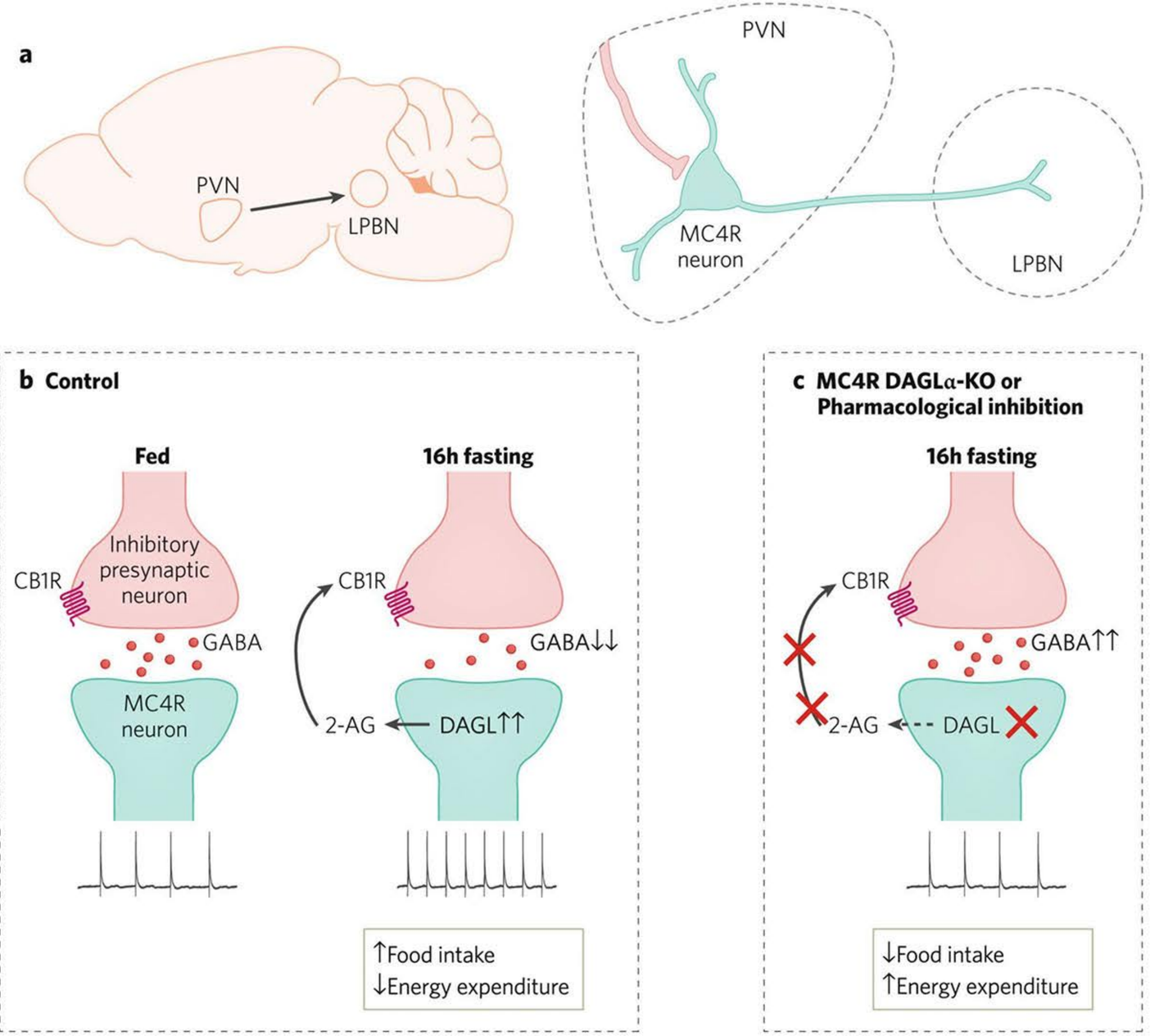


Part 3: Chronic Disease - Presentations of ECS Dysfunction

- **Obesity & the ECS:** Implications

  Discussion of brain circuits impacted by ECS
  - HPA Axis
  - Etc.

  Discussion of Correlated Gut dysfunction symptoms (e.g. serotonin modulation).
  - IBS
  - Etc.



Part 3: Chronic Disease - Presentations of ECS Dysfunction

- **Pain & the ECS:** Implications

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> Pain. 2024 May 2. doi: 10.1097/j.pain.0000000000003265. Online ahead of print.

Terpenes from Cannabis sativa induce antinociception in a mouse model of chronic neuropathic pain via activation of adenosine A2A receptors

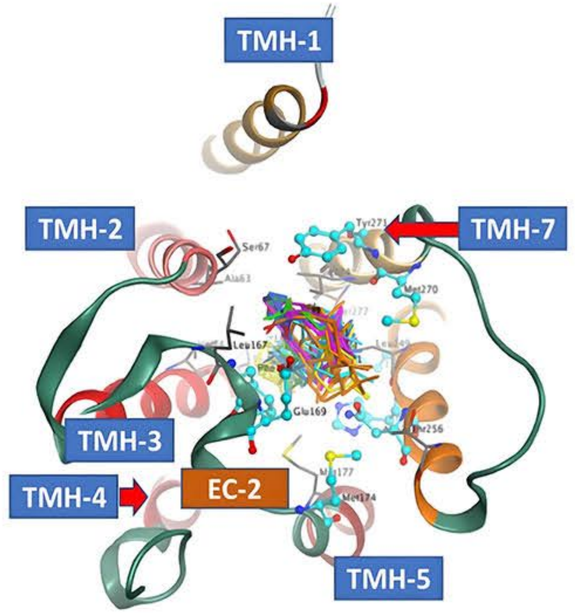
Abigail M Schwarz [1], Attila Keresztes [1], Thai Bui [1], Ryan Hecksel [1], Adrian Peña [1], Brianna Lent [1], Zhan-Guo Gao [2], Martín Gamez-Rivera [1], Caleb A Seekins [1], Kerry Chou [1], Taylor L Appel [1], Kenneth A Jacobson [2], Fahad A Al-Obeidi [1], John M Streicher [1 3]

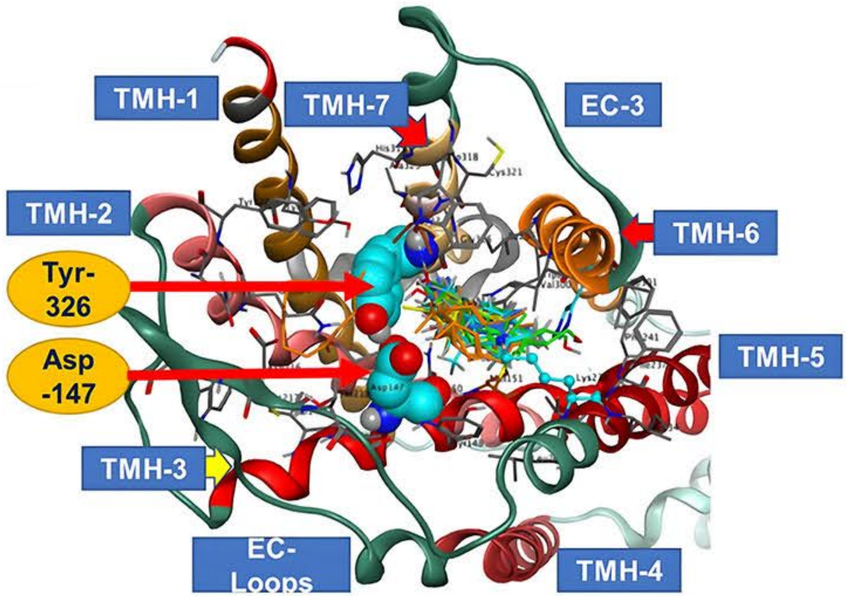
Affiliations + expand

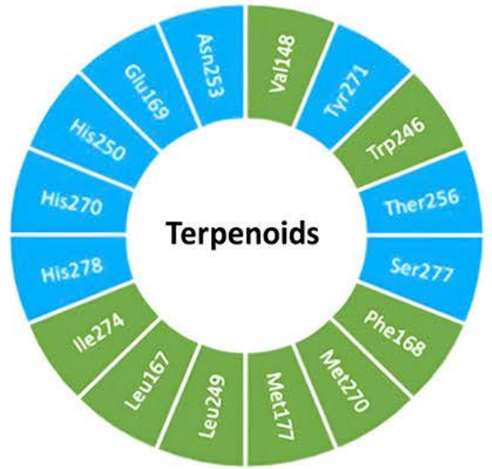
PMID: 38709489 DOI: 10.1097/j.pain.0000000000003265

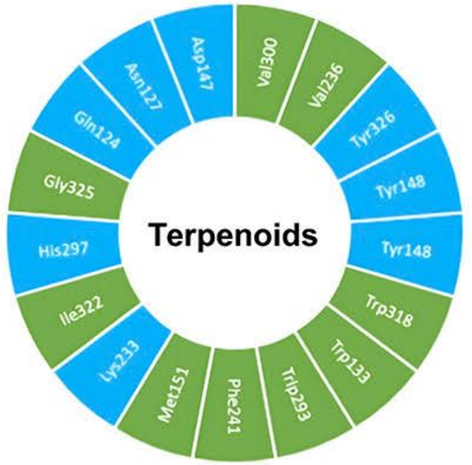
Results:

- Relieved Neuropathic Pain
- Relieved Inflammatory Pain
- Enhanced Morphine Antinociception in CIPN
- Comparable Antinociceptive Tolerance to Morphine in CIPN
- Limited Bioavailablity via Oral & Inhaled Modalities
- Terpenes are Adenosine A2A Receptor Agonists
- Terpenes May Have Anti-Inflammatory MoA's





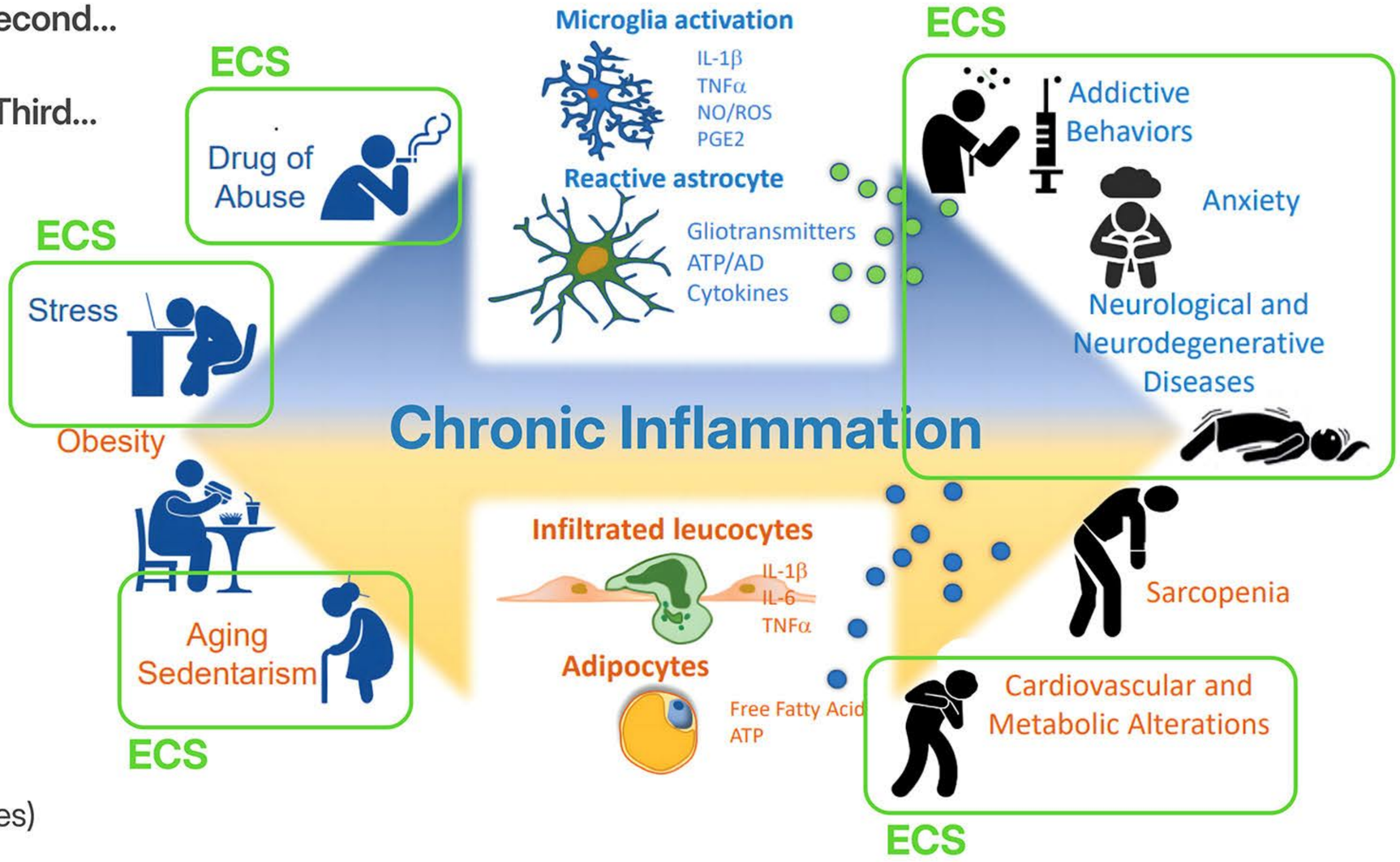




Part 4: Clinical Observations - Anecdotal & Adjuvant Implications

- **Starting with ECS Dysfunction First...**
- **Targeting Chronic Inflammation Second...**
- **May Attenuate These Conditions Third...**

  - Headaches
  - Diabetes
  - ME/CFS
  - PTSD
  - Inflammatory Disease
    - Arthritis
    - Rheumatoid Arthritis (RA)
    - Inflammatory Bowel Disease (IBS)
  - Alzheimer's Disease
  - Huntington's Disease
  - Multiple Sclerosis
  - Parkinson's Disease
  - Traumatic Brain Injuries (THC studies)
  - Others...



Improved telomerase activity with positive psychological change

(Jacobs et al., 2011)

Analgesic effect through endogenous opioid pathways

(Sharon et al., 2016)

Improved motor function & mobility in PD patients

(Kwok et al., 2019)

Meditation-induced anandamide, 2-AG, 1-AG, DEA, & BDNF release

(Sadhasivam et al., 2020)


TERPENES
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CANNABINOIDS
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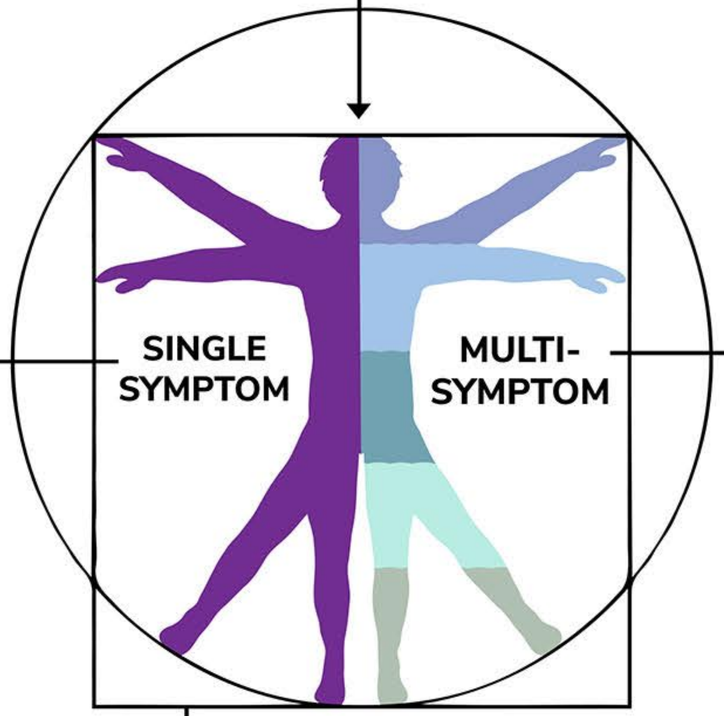
CLIENT PRESENTS SINGLE OR MULTIPLE SYMPTOMS?

- DEPRESSION
- ANXIETY
- SLEEP PROBLEMS
- MYALGIC ENCEPHALOMYELITIS
- ADHD
- ADDICTION SEEKING BEHAVIOR
  - OPIOID MANAGEMENT → 

  - ADDICTION BEHAVIOR → 



PAIN (TOPICAL) → 

TRAINING LINKS

VERASOME:

FORMULA C: