PainWeek

ADVANCED EDUCATION

CERTIFICATION SERIES

CANNABINOIDS

The Endocannabinoid System Defined

Theresa Mallick-Searle, MS, PMGT-BC, ANP-BC

Disclosure

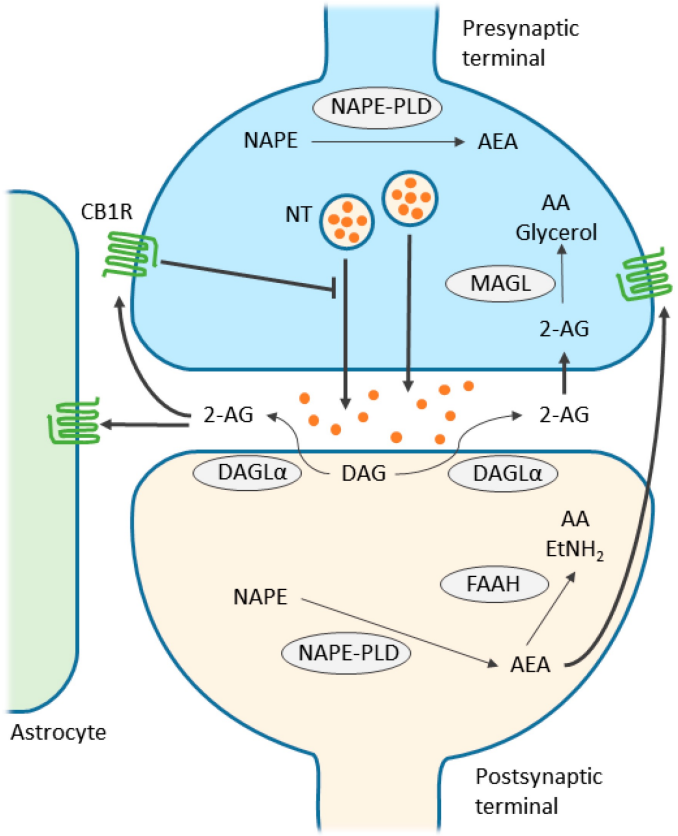
Speakers Bureau: Allergan/AbbVie, Lilly

Learning Objectives

- Define the endocannabinoid system (eCS)
- Explore the role of the eCS in wellness and disease
- Discuss the effects of cannabis on the eCS

Endocannabinoid System

What the Biochemist Sees



(Zou & Kumar, 2018)

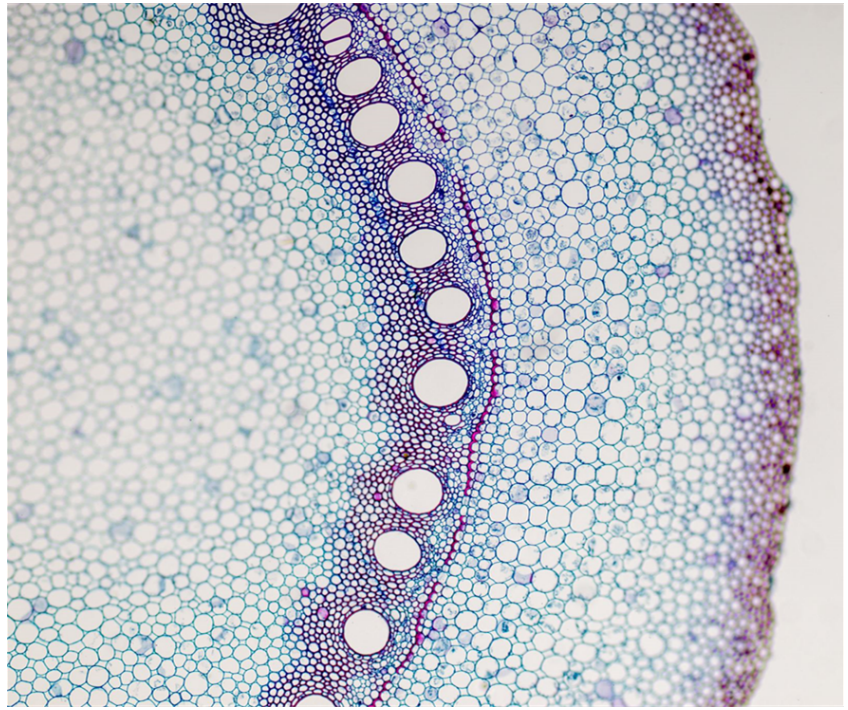
Simplified[2]

- Homeostatic, regulatory system, inherited by all mammals
- Group of ligands/molecules/chemicals – endocannabinoids. #13
  - Anandamide (AEA)
  - 2-arachidonoyglycerol (2-AG)
- Receptor sites #2+
  - CB1 (brain, CNS, adipocytes, hepatocytes, MSK tissues)
  - CB2 (cells governing immune function, CNS)
- Synthesizing and degrading enzymes

Constituents

- **Receptor sites**
  - CB1 and CB2
  - CBx, VR1, GPRs
  - Other G protein-coupled receptors – influenced by endocannabinoids
    - TRPV channels (transient receptor potential vanilloid)
    - PPARs (peroxisome proliferator-activated receptors)
- **Ligands**
  - Anandamide (AEA)
  - 2-arachidonylglycerol (2AG)
  - Nolan ether
  - Virodhamine
  - NADA
- **Synthesizing enzymes**
  - NAPE-PLD (N-acyl phosphatidylethanolamine phospholipase D)
  - DAGLα and DAGLβ (diacylglycerol lipase)
- **Degrading enzymes/system**
  - FAAH1 (fatty-acid amide hydrolase 1)
  - MAGL; ABHD-6; COX2; FAAH1 (monoacylglycerol lipase, abhydrolase domain containing 6, acylglycerol lipase, cyclooxygenase-2)

Biosynthesis and Catabolism Endocannabinoids



NAPE-PLD → AEA → CB1/CB2 → FAAH1

DAGLα & DAGLβ → 2-AG → MAGL; ABHD-6; COX2; FAAH1

AEA & 2-AG work in a homeostatic fashion, thus they are broken down after they activate CB1 or CB2

Two main metabolic pathways have been identified so far: one hydrolytic & the other oxidative

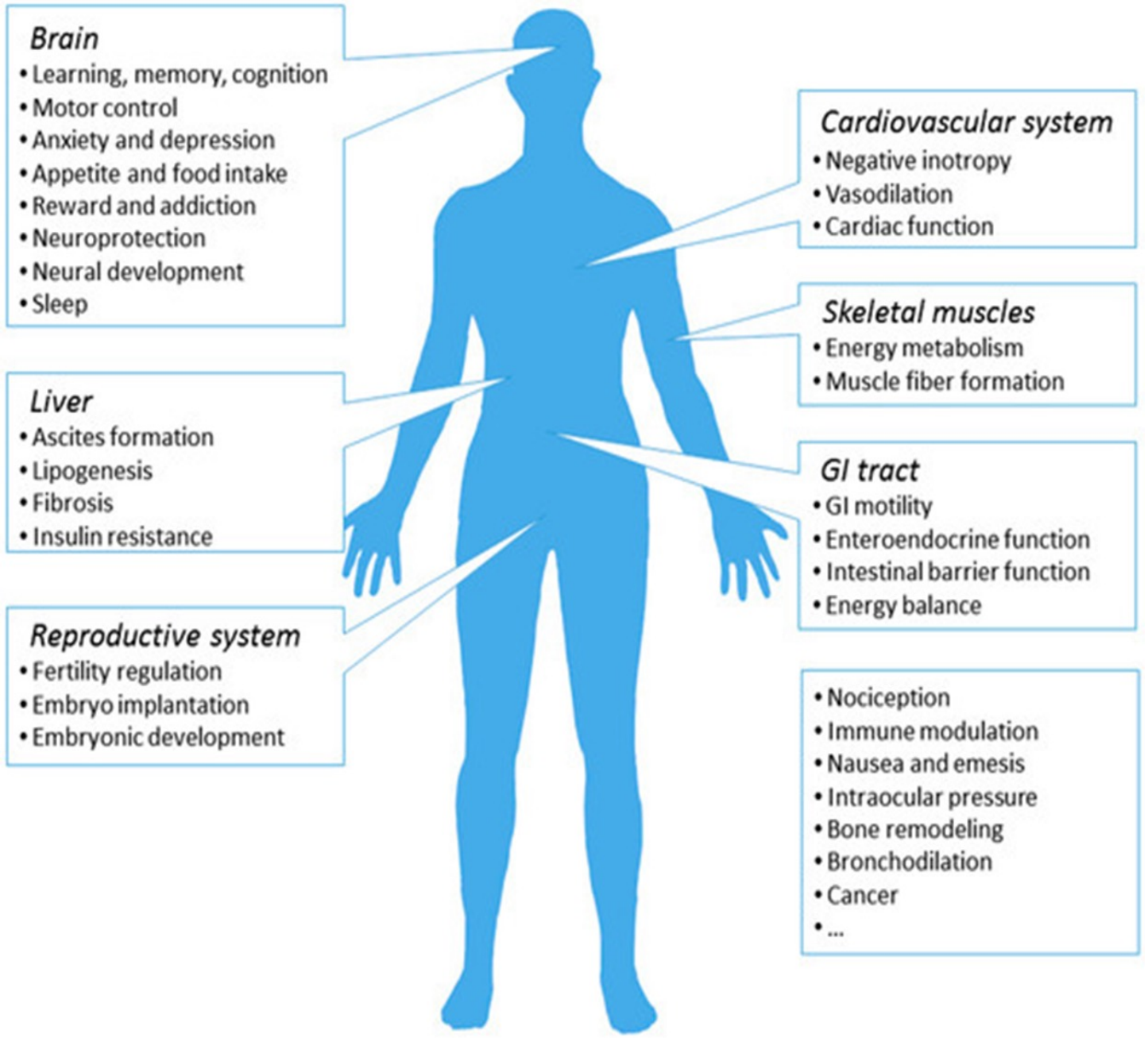
Synthesized on demand (in a Ca2+ - dependent manner in response to physiological stimuli)

AEA can also be stored inside the cell (Oddi et al, 2008)

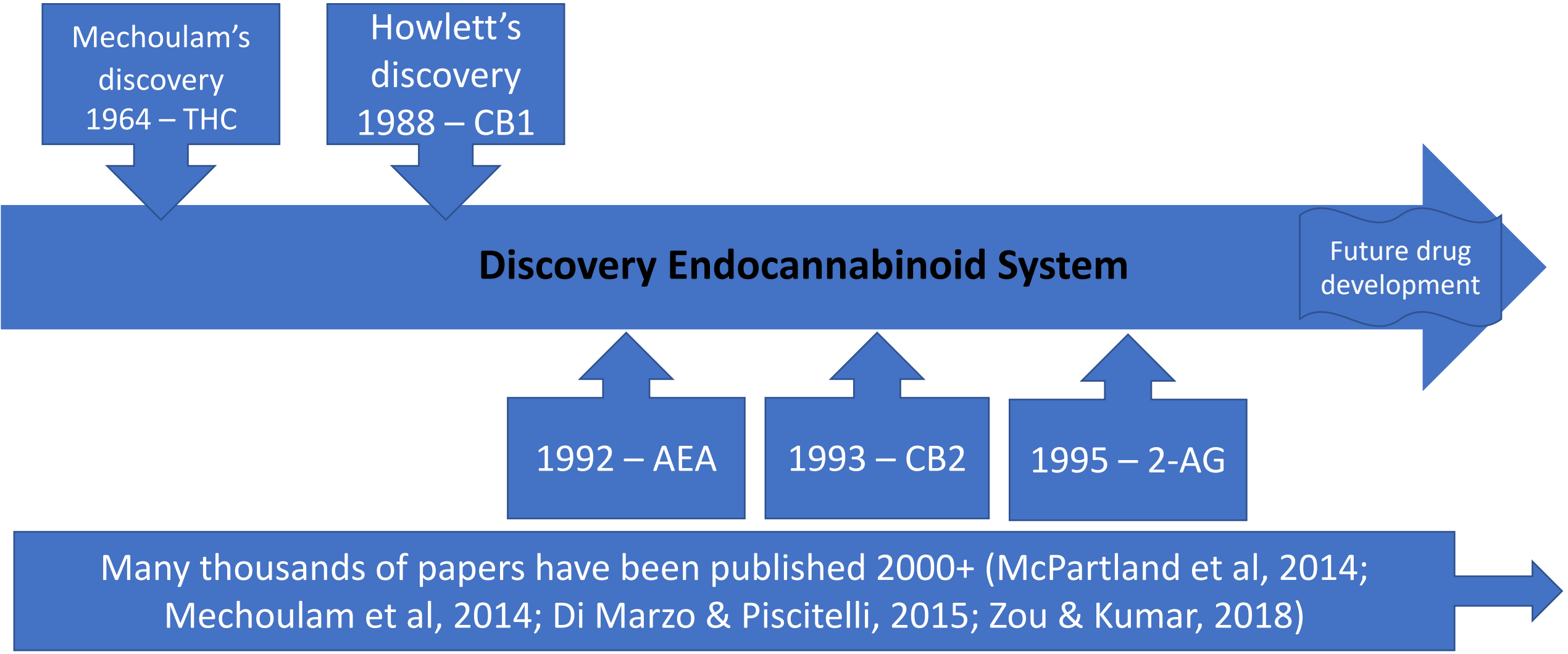
- The eCB system's salient homeostatic roles have been summarized:

  "relax, eat, sleep, forget, and protect"

- Embryological development
- Neural plasticity
- Neuroprotection
- Immunity and inflammation
- Apoptosis and carcinogenesis
- Pain and emotional memory
- Hunger/satiety/metabolism



Background Highlights



Basic Principals – What We Know

- Endocannabinoids are (mostly) made on demand → responding to needs of the individual, to maintain homeostasis:
  - Modulate stress
  - Active autonomic nervous system (fight or flight)
  - Induce sleep
  - Response to exercise
  - Appetite/hunger
- Adaptive
- eCS exists from cradle → grave

- Effected/modulated/influenced by exposure to phytocannabinoids (cannabis)

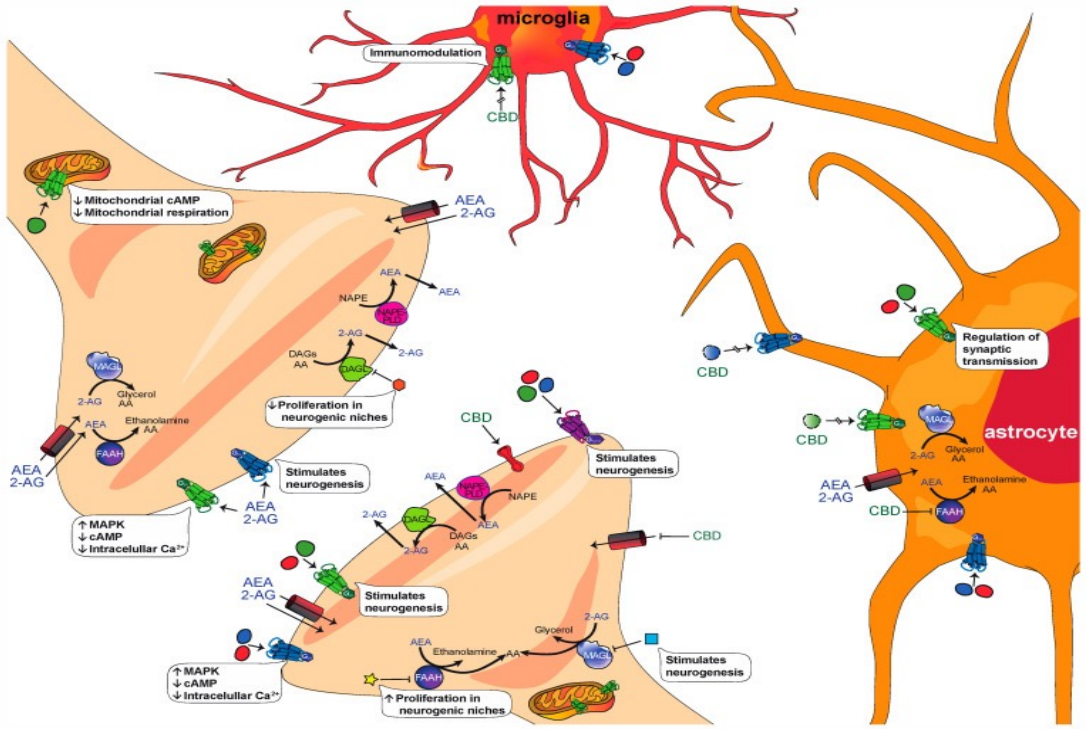
- THC → CB1 ← anandamide

  ↑

- 2AG

- It explains how cannabis works, but cannabis is not why it exists

Is the eCS More Complex Than First Thought?



Symbol	Nomenclature	Symbol	Nomenclature	Symbol	Nomenclature
	CB1 Receptor	→	Agonist		Agonist CB1/CB2
	CB2 Receptor	⊸	Antagonist		Agonist CB1
	GPR55 Receptor	⊣	Inhibitor		Agonist CB2
	TRPV1/TRPV2	↑ ↓	Up / Down		Antagonist / inverse agonist > CB1
	Monoacylglycerol lipase (MAGL)		MAGL inhibitor		Antagonist / inverse agonist > CB2
	Fatty acid binding protein (FABP): reuptake transporter		Diacylglycerol lipase (DAGL)		DAGL Inhibitor
	N-acylphosphatidylethanolamine specific phospholipase D (NAPE-PLD)		Fatty acid amide hydrolase (FAAH)		FAAH Inhibitor

Netzahualcoyotzi. *Int J Mol Sci*. 2021;22:7450.

Other Receptors Influenced by Endocannabinoids

- **GPR55** (G protein-coupled receptor 55, along with GPR119 and GPR18, have been implicated as novel cannabinoid receptors)

- **Ligand-gated ion channels**
  - 5-HT3 receptors
  - Nicotinic acetylcholine receptors
  - Glycine receptors
  - Glutamate NMDA receptors

(Zou 2018)

- Transient receptor potential channels
  - TRPV1, TRPM8

- **Voltage-gated ion channels**
  - T-type calcium
  - Potassium

eCS is much more complex than was thought cross-talk with many other transduction cell signaling pathways → regulating key biological processes → cell proliferation and differentiation, synaptic plasticity

Upregulation/Downregulation of eCS Receptors

Increasing/decreasing the number of receptors

- Compensatory/protective – cells are looking for more endo-cannabinoids/internalization (reduce availability of activation)
- Maladaptive – increase number of circulating endocannabinoids (↑adipocytes)

Animal studies:

- Seizures, nerve pain, sleep deprivation - ↑ CB1R in brain (Karlocai, 2011; Navarro, 2003; Siegling, 2001).
- Crohn's – ↑ CB1R in intestines (Izzo, 2001).

➢ Autistic children - ↑CB2R on white blood cells (Siniscalco, 2013).

➢ Depression/suicidality - ↑ CB1R (Hungund, 2004).

Epigenetics/Genetics and eCS

- Epigenetics – How your behaviors/environment can cause changes that affect the way your genes work. Unlike genetic changes, epigenetic changes are modifiable.
- Epigenetic changes in the eCS have been detected in several disorders such as Alzheimer's disease, glioblastoma, and colorectal cancer

  (Meccariello et al, 2020).
- Evidence eCS undergoes epigenetic modulation by alcohol/diet/stress/smoking/exercise

  (Chen et al, 2018; Lomazzo et al, 2017)
- eCS has been implicated in several dopamine-related disorders, such as schizophrenia, Parkinson disease, Huntington disease, and drug addiction. (Centonze et al, 2008)
- Studies have looked at association between ADHD and a specific polymorphism of the cannabinoid CB1 receptor gene. (Lu et al, 2008)

Epigenetics/Genetics and eCS

Epigenetic cues	Molecular changes	Study model	Results	References
Maternal high-fat diet	↑ histone acetylation rate	Rat hypothalamus	↑ binding of androgen receptor at CNR1 promoter → over expression of CB1	Almeida et al, 2019
Extra-virgin olive oil (EVOO)	↓ DNA methylation of CNR1 promoter	Short and long-term dietary EVOO rats and human colon cancer cells	Increased expression of the CB1 & reduced proliferation of colorectal cancer cells	Di Francesco et al, 2015
Colorectal Cancer (CRC)	↑ DNA methylation of CNR1 & ↑ GPR55 demethylation	Human CRC tissues (n = 566)	GPR55 is highly expressed in CRC patients while CB1 levels are reduced	Hasenoehrl et al, 2018
Δ 9THC	Up-down regulation of several miRNAs	CD4+ T cells, during simian immunodeficiency virus infection	Immunomodulatory role for cannabinoids	Molina et al, 2011

Endocannabinoid Deficiency Syndrome

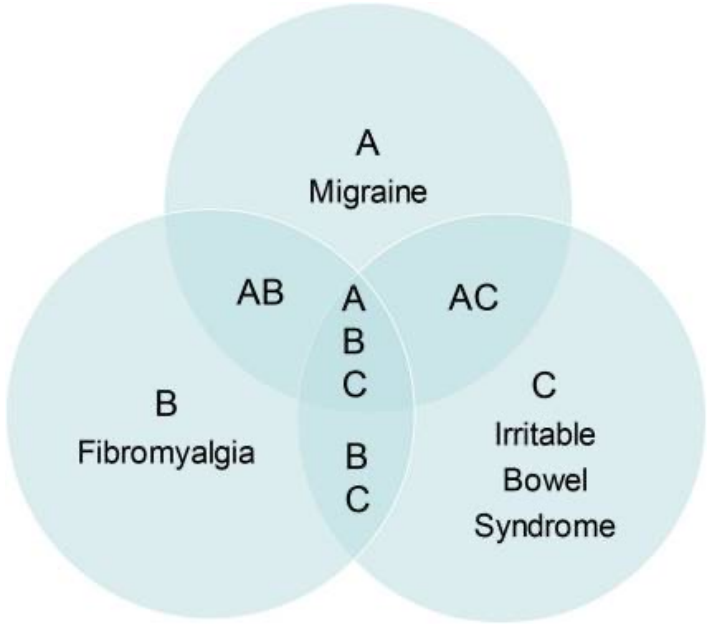
Ethan Russo, MD (2004/2016)

- Theory that in certain conditions (congenital or acquired), endocannabinoid tone becomes deficient → pathophysiological syndromes.
- Deficit in eCS tone → derangements of digestion, mood, sleep, nociception. Universal physiological systems sub served by the endocannabinoid system.
- Based on the concept that many disorders are associated with neurotransmitter deficiencies → acetylcholine (Alzheimer's disease), dopamine (parkinsonian syndromes), serotonin, and norepinephrine (depression).
- Phytocannabinoids (THC, CBD) can bind to the cannabinoid receptor sites (CB1, CB2) and mimic the physiological processes seen with binding of the endocannabinoids.

Russo. *Cannabis Cannabinoid Res*. 2016;1(1):154-155.

Endocannabinoid Deficiency Syndrome

The greatest evidence is present for migraine, fibromyalgia, and irritable bowel syndrome (IBS). A strong case can be advanced for unifying pathophysiological trends in the three conditions.



(Russo, 2016)

Show Me the Evidence!

- ↓circulating endocannabinoid levels in individuals with **post-traumatic stress disorder.** (Hill et al, 2013)
- ↓ endocannabinoids in CSF samples **migraine**, **multiple sclerosis.** (Sarchielli et al, 2007; Di Filippo et al, 2008)
- Plasma and cerebrospinal fluid AEA levels are ↑ in patients with **schizophrenia** than in normal control. (Zou et al, 2019)
- Circulating plasma levels of eCBs are ↓ in patients with mild **depression** and chronic **post-traumatic stress.** (Coccaro et al, 2018)
- Variants of cannabinoid receptor gene (CNR1) risk factor for **ADHD and post-traumatic stress disorder.** (Lu et al, 2008)
- Tonic activity at the lumbar spinal CB1R maintains thermal nociceptive thresholds. (Richardson et al, 1998)

Endocannabinoid Overactivity

- Dysregulation can also occur with “too much of a good thing”

- Examples are seen:
  - Regulation appetite
  - Digestion
  - Energy metabolism
  - Obesity
  - ADHD

Show Me the Evidence!

- **Endocannabinoids are present in adipocytes → under the negative control of insulin.**

- Chronic treatment of adipocytes with insulin is accompanied by permanently ↑ endocannabinoid signaling.

- CB1R stimulation ↑ lipid droplets and ↓adiponectin expression in adipocytes → intracellular calcium & insulin release in β-cells kept in high glucose.

- CB1R blockade reduces these metabolic parameters in obese individuals independently not only from inhibition of food intake and body weight loss.

(Matias et al, 2006)

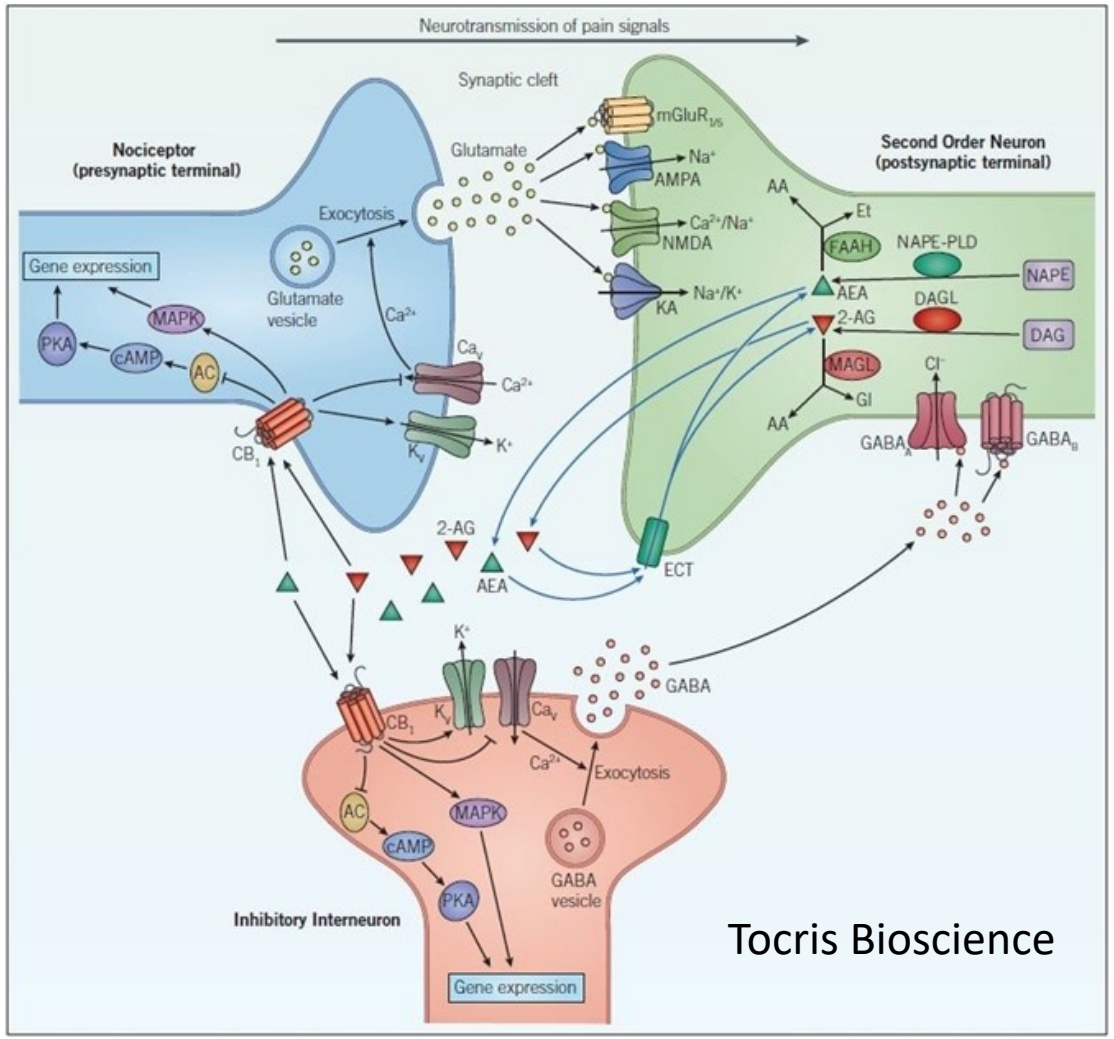
More Evidence

- ↓ FAAH → sustained release of AEA & 2-AG → ongoing activation CB1R → maintained cycle of adipogenesis & lipogenesis. (Di Marzo, 2008; Gruden et al, 2016)

- Altered anandamide degradation in attention-deficit/hyperactivity disorder.
  - An inhibition of FAAH activity - ↑AEA in (ADHD) (Centonze et al, 2009)

Other Chronic Pain

- There is evidence that AEA can act through a CB1 receptor independent mechanism to ↑ activation of glutamate N-methyl-D-aspartate (NMDA) receptors.
- AEA can target T-type calcium channels.
- There is good evidence that certain delayed K+ channels can be blocked by AEA & 2-AG.



Tocris Bioscience

commons.wikimedia.org/wiki/File:Sodium-potassium_pump_and_diffusion.png.

Modulating the Neuromodulators: Dopamine, Serotonin, and the eCS

- The interaction between the dopaminergic, serotonergic, and endocannabinoid systems in anatomically defined circuits underlies complex aspects of reward-guided behavior.

- Dopamine, serotonin, and endocannabinoids are key neuromodulators involved in many aspects of motivated behavior, including reward processing, reinforcement learning, and behavioral flexibility.

- eCS is uniquely placed to influence dopaminergic and serotonergic neurotransmission.

(Peters et al 2021)

What is Cannabis Sativa (aka Marijuana)?

It's a plant with over 400 different chemicals/components:

- >80 types of cannabinoids (chemically active)
  - Delta-9-tetrahydrocannabinol (THC)
  - Cannabidiol (CBD)
  - Cannabinol (CBN)
  - Cannabichromene (CBC)
  - Cannabigerol (CBG)
  - Tetrahydrocannabivarin (THCV)

- Flavonoids, terpenes, terpenoids

Cannabis and the eCS

- Endocannabinoid system was discovered → path of THC.
- Much of the supposition about endocannabinoid deficiency syndrome – observations of symptom improvement with phytocannabinoids.
- Interference in eCS signaling following phytocannabinoid abuse or the impairment of the system may represent a threat for the maintenance of health/homeostasis.
  - Up/down regulation of receptors
  - Competition with endocannabinoids
  - Anxiety
  - Psychosis
  - Obesity
  - Cognitive impairment
  - Addiction

Maroon. *Surg Neurol Int*. 2018;9:91.
Meccariello. *Int J Mol Sci*. 2020;21:1113.

How Does THC Effect the eCS?

THC binds to CB1 & CB2 as a weak partial agonist.

“compound promiscuity” – many other biological targets:

- Allosteric modulator of mu and delta opioid receptors → alter the way endorphins and opioids attach to these receptors.
- Binds to glycine receptors - ↓ pain signaling.
- Action at the PPARs receptors – shown to exert anticancer effects.
- Effects at a subset of serotonin receptors, transient receptor potential channels (TRP) and G protein-coupled receptors (GPR-18, 55).

Proposed medicinal effects:

- Anticancer
- Anti-inflammatory
- Antioxidant
- Neuroprotective
- Antiemetic
- Reduces intraocular pressure
- Antispasmodic
- Antinociceptive
- Appetite stimulant

How Does CBD Effect the eCS?

CBD has low affinity for CB1 and CB2; “negative allosteric modulation”

- “positive allosteric modulation”
  - Glycerin receptors - ↓ inflammation ↓neuropathic pain.
  - GABA receptors – antianxiety & anticonvulsant
- Binds to serotonin, PPARs, adenosine receptors.
- Receptor antagonist GPR55, weak antagonist GPR18
- Interacts with TRP ion channels, and numerous enzymes: FAAH, COX, AANAT

Proposed medicinal effects:

- Antibacterial
- Anticancer
- Anticonvulsant
- Anti-inflammatory
- Neuroprotective
- Promotes bone growth
- Anxiolytic
- Antiemetic
- Antispasmodic
- Antinociceptive
- Appetite stimulant

What About Pharmaceutical Grade Cannabis?

Nabiximols is an herbal preparation containing standardized extract of tetrahydrocannabinol (THC), cannabidiol (CBD), other minor cannabinoids, flavonoids, and terpenes.

- Moderate to severe spasticity due to multiple sclerosis.
- Binding to CB1R and CB2R - ↓ excitatory neurotransmitter release ↓spasticity.

(Keating 2017; Syed et al, 2014; Vermersch et al, 2016)

Cannabidiol is an herbal preparation containing standardized extract of cannabidiol (CBD).

- Seizures associated with Lennox Gastaut syndrome, Dravet syndrome, or tuberous sclerosis complex (TSC) in patients 1 year of age and older.
- The precise mechanisms by which it exerts its anticonvulsant effect in humans are unknown. Cannabidiol does not appear to exert its anticonvulsant effects through interaction with cannabinoid receptors.

(Devinsky et al, 2017; Thiele et al, 2018; Yang et al, 2019)

The eCS and Its Modulation by Phytocannabinoids

- Cannabinoids (similar to AEA) interact with the TrpV1 receptor and ↓ sensation of thermal pain.

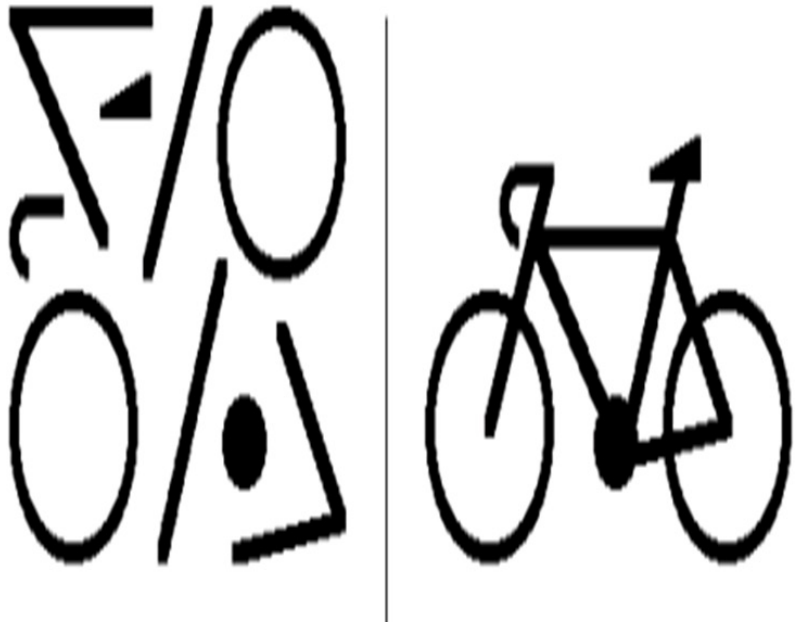
- Cannabinoids inhibit the cellular reuptake of anandamide, and CBD is also a moderate inhibitor of anandamide hydrolysis by FAAH.

- CBD (which has low affinity for CB1R and CB2R) can indirectly inhibit CB1 activity, particularly in the central nervous system.

(Di Marzo & Piscitelli, 2015)

Entourage Effect: “Sum of the Parts”

- A proposed mechanism by which cannabis compounds act synergistically to modulate the overall physiological effects of the plant.
- Example: CBD + THC = possibly mitigating some of the psychosis-like effects of THC.
- Cannabis is a multimodal treatment. It can be used to treat multiple symptoms and conditions concurrently, which can therefore help to reduce polypharmacy burden.

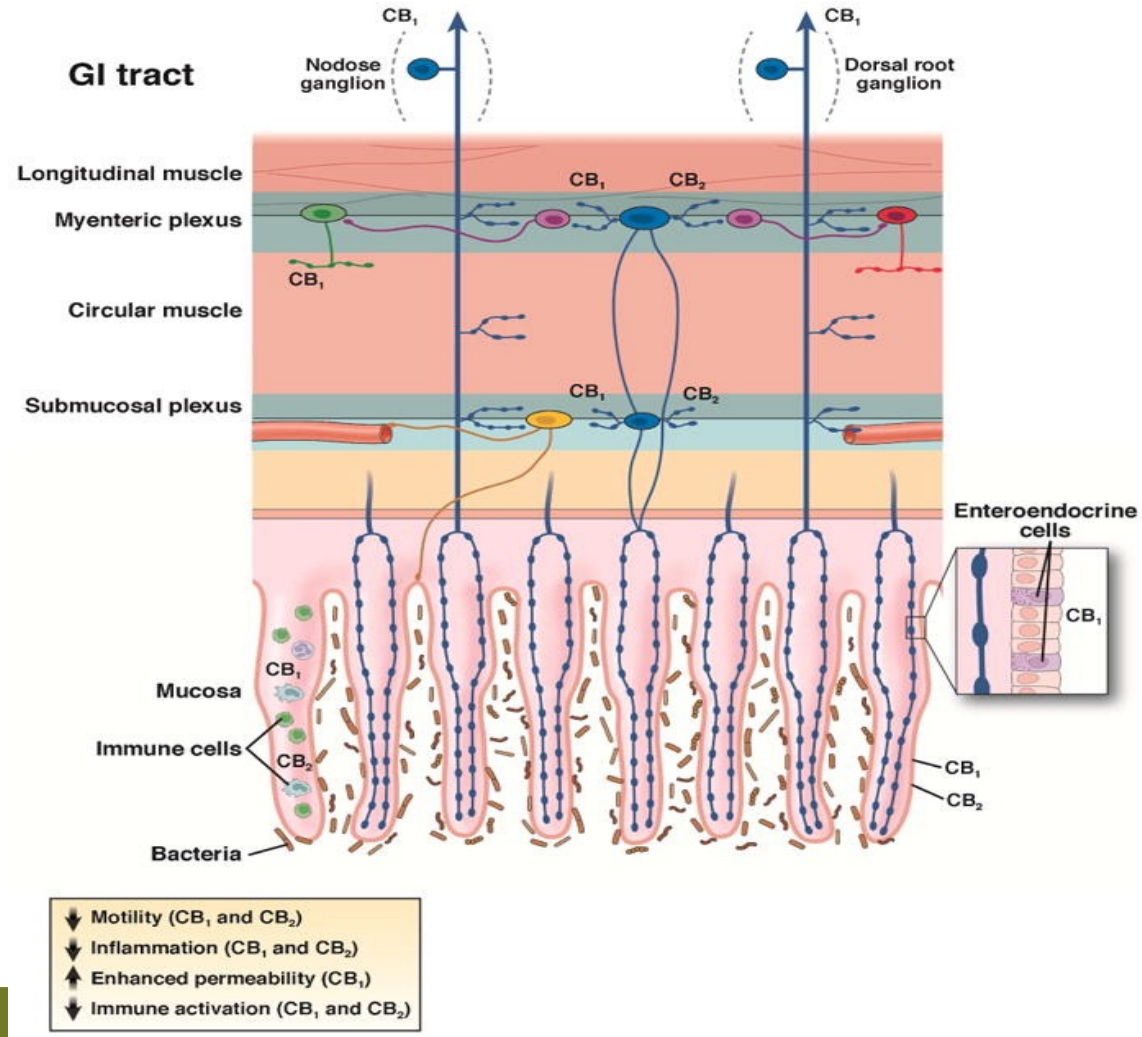


(Russo, 2016; Goldstein, 2020; Ferber et al, 2020)

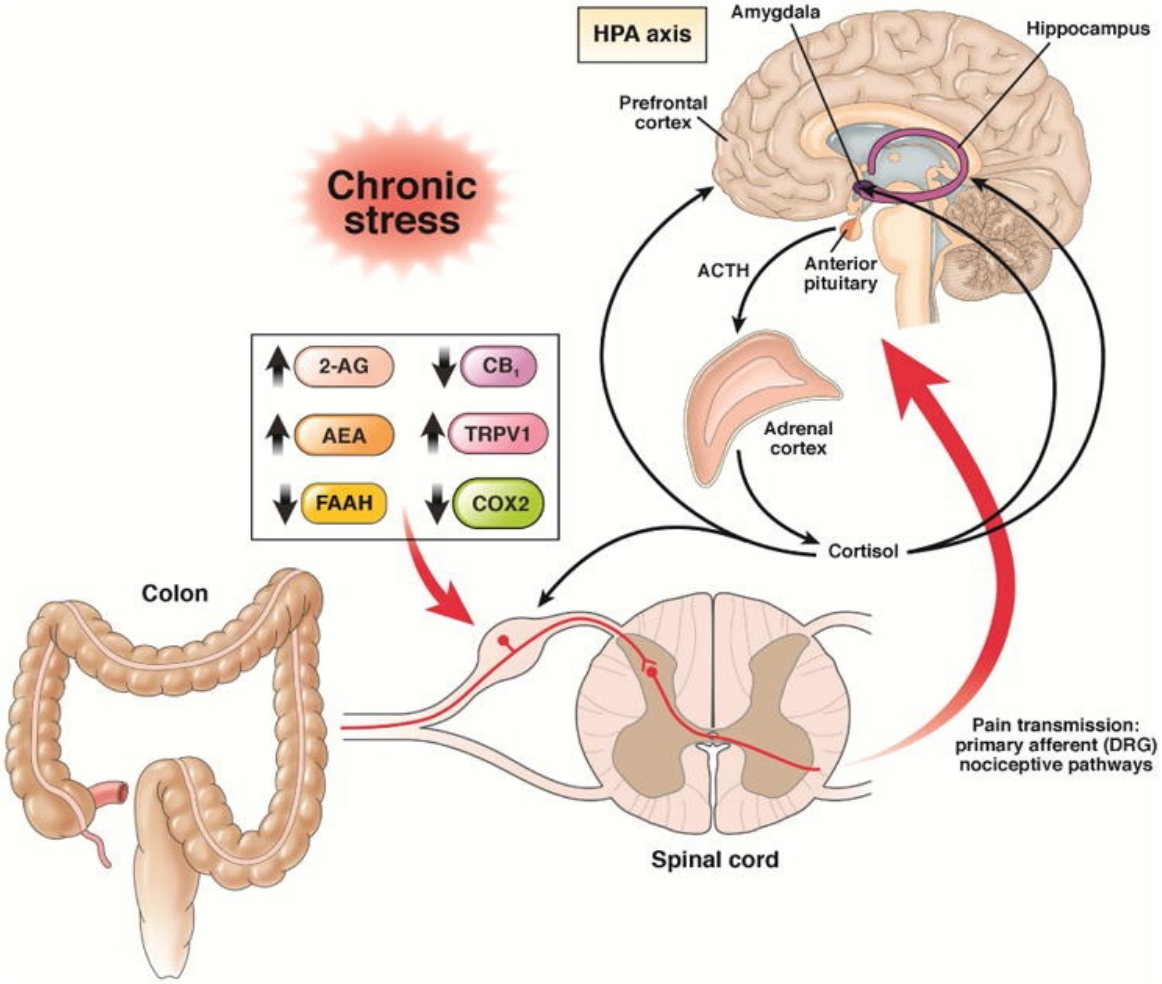
Gut-Brain Axis – Microbiome – eCS

- eCS an important physiologic regulator of gastrointestinal motility.
- Polymorphisms in the gene encoding CB1R have been associated with some forms of irritable bowel syndrome.
- The ECS is involved in the control of nausea/vomiting and visceral sensation.
- The homeostatic role of the eCS also extends to the control of intestinal inflammation.

(Sharkey & Wiley, 2016)



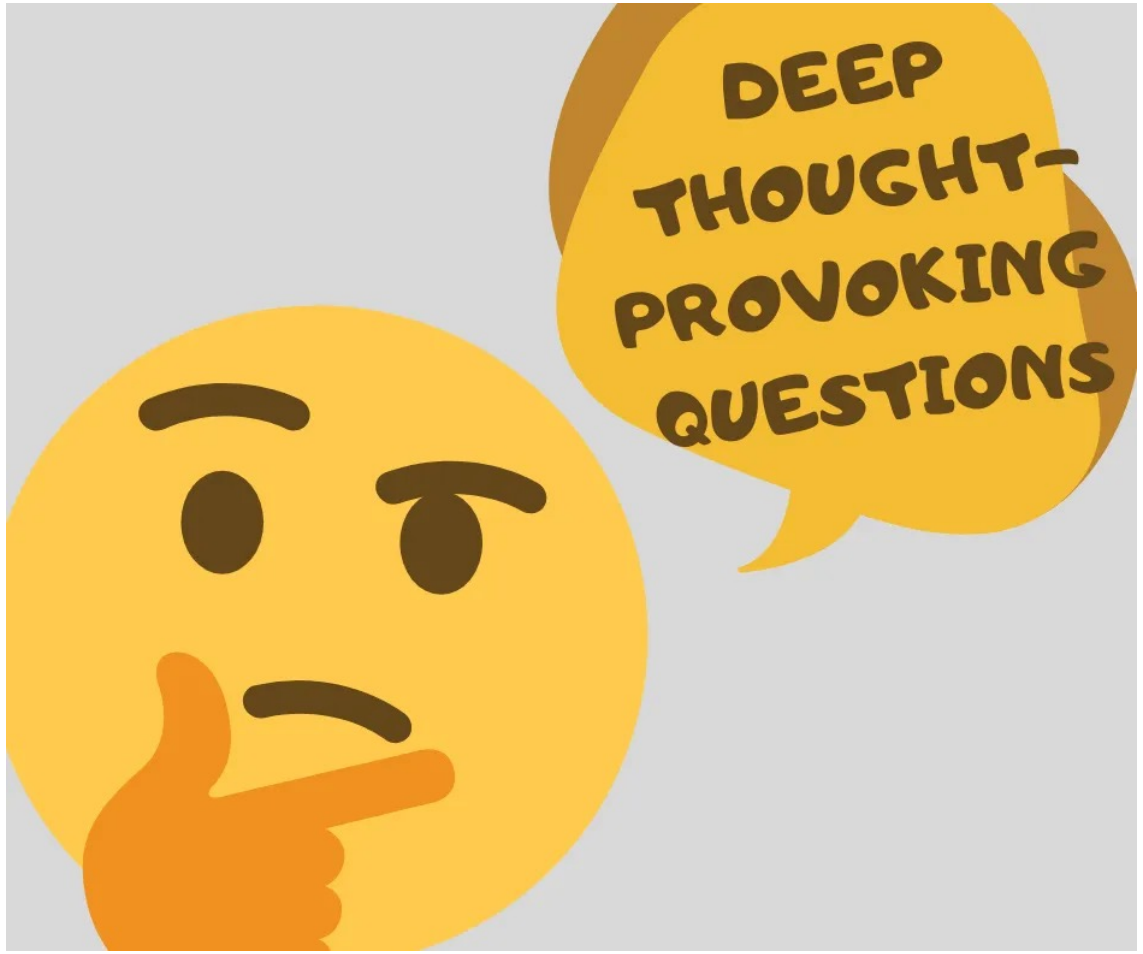
Gut-Brain Axis – Microbiome – eCS



- Many patients with chronic visceral pain find that it is exacerbated by stress.
- There is increasing evidence that the eCS modulates chronic stress-associated increases in abdominal pain (visceral hyperalgesia).
- Under conditions of chronic stress, levels of 2-AG and AEA ↑ and endocannabinoid degradation enzymes COX-2 & FAAH are ↓ in nociceptive DRG neurons that innervate the colon and pelvis.
- Levels of CB1 are ↓ and there is an ↑ in TRPV1 expression and phosphorylation in nociceptive primary afferent neurons.
- These effects are mediated by corticosteroids from the HPA pathway.

(Sharkey & Wiley, 2016)

Thought Provoking Questions



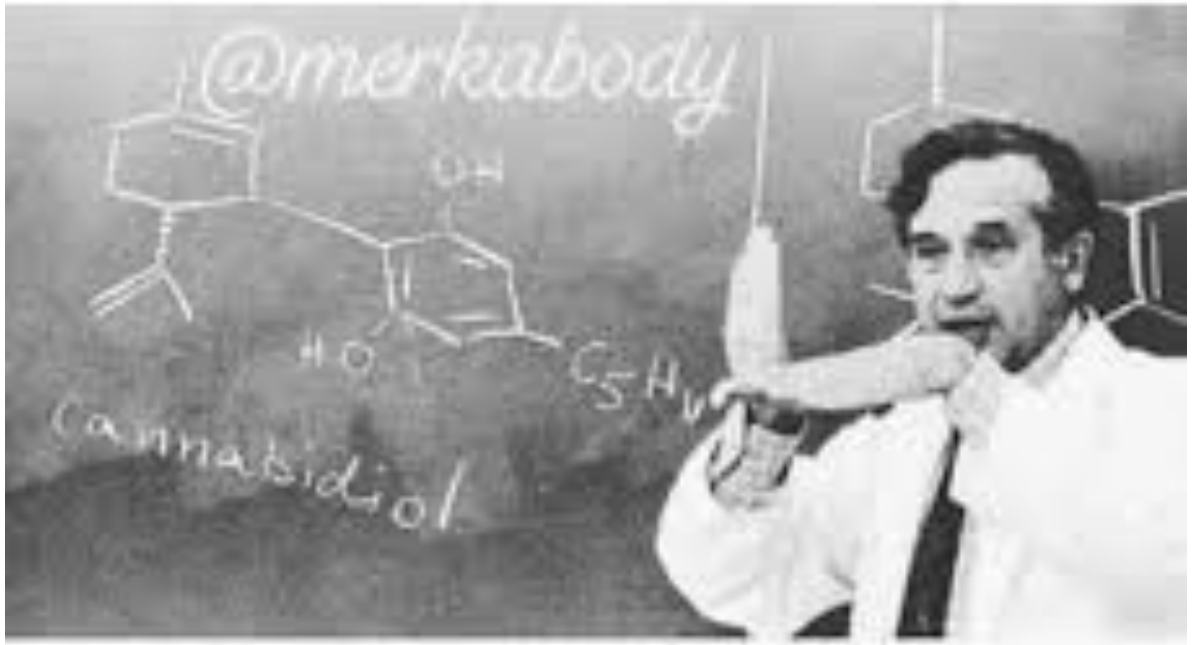
Should more focus be placed on correcting from within: health and wellbeing of the endocannabinoid system and the microbiome?

Medication use as PRN versus daily? Reemergence of controversy, what about cannabis?

Final Take Home

- eCS is “our birth right,” functions to maintain homeostasis.
- Most importantly it helps us to: “relax, eat, sleep, forget, and protect”
- Influenced by intrinsic and external factors → susceptible to dysregulation.
- Dysregulation/dysfunction → disease
- Possibility of modulation/correction/further dysregulation with cannabis.
- Further research (in humans) is needed.

I believe that the most important future steps in the endocannabinoid area are to advance cannabinoid-based clinical trials in many disease states where strong anecdotal evidence already exists.



Raphael Mechoulam
Jerusalem, Israel

"The endocannabinoid system is very important. Almost all illnesses we have are linked to it in some way or another. And that is very strange."

- Raphael Mechoulam

Resources

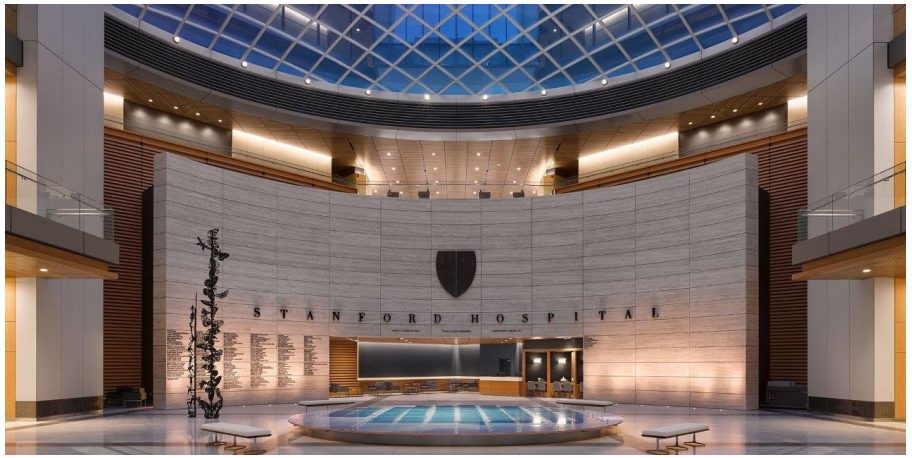
- Canadian Consortium for the Investigation of Cannabinoids (CCIC): www.ccic.net
  - Accredited cannabinoid education (ACE) programs
  - Informed by needs assessments, expert faculty
- International Cannabinoid Research Society (ICRS): https://icrs.co/
- International Association for Cannabinoid Medicine (IACM): www.cannabis-med.org
- University of Washington & Alcohol and Drug Abuse Institute (ADAI)
- http://adai.uw.edu/mcacp/index.htm
- Society of Cannabis Clinicians: www.cannabisclinicians.org

Thank You

Tmallick@stanfordhealthcare.org

@tmallic

https://www.linkedin.com/in/theresa-mallick-searle



Selected References

1. Almeida MM, Dias-Rocha CP, Reis-Gomes CF, et al. Maternal high-fat diet impairs leptin signaling and up-regulates type-1 cannabinoid receptor with sex-specific epigenetic changes in the hypothalamus of newborn rats. *Psychoneuroendocrinology* . 2019;103:306–315.
2. Centonze D, Bari M, Di Michele B, et al. Altered anandamide degradation in attention-deficit/hyperactivity disorder. Neurology. 2009 Apr 28;72(17):1526-7
3. Centonze D, Battistini L, Maccarrone M. The endocannabinoid system in peripheral lymphocytes as a mirror of neuroinflammatory diseases. *Curr Pharm Des.* 2008;14:2370–2382.
4. Chen J, Hutchison KE, Bryan AD, et al. Opposite Epigenetic Associations With Alcohol Use and Exercise *Intervention. Front*. Psychiatry 2018;9:594
5. Coccaro EF, Hill MN, Robinson L, et al. Circulating endocannabinoids and affect regulation in human subjects. Psychoneuroendocrinology. 92: 2018; 66–71
6. Devinsky O, Cross JH, Laux L, et al; Cannabidiol in Dravet Syndrome Study Group. Trial of cannabidiol for drug-resistant seizures in the dravet syndrome. N Engl J Med. 2017;376(21):2011-2020.
7. Di Filippo M, Pini LA, Pelliccioli GP, et al. Abnormalities in the cerebrospinal fluid levels of endocannabinoids in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2008 Nov;79(11):1224-9.
8. Di Francesco A, Falconi A, Di Germanio C, et al. Extravirgin olive oil up-regulates CB1 Tumor suppressor gene in human colon cancer cells and in rat colon via epigenetic mechanisms. J. Nutr. Biochem. 2015;26:250–258.
9. Di Marzo V. The endocannabinoid system in obesity and type 2 diabetes. Diabetologia. 2008 Aug;51(8):1356-67.
10. Di Marzo V, Piscitelli, F. Gut feelings about the endocannabinoid system. *Neurogastroenterol Motil.* 2011;23:391–398.
11. Di Marzo V, Piscitelli F. The Endocannabinoid System and its Modulation by Phytocannabinoids. *Neurotherapeutics.* 2015;12**:**692–698.

Selected References

12. Di Marzo V, Stella N, Zimmer A. Endocannabinoid signaling and the deteriorating brain. *Nat Rev Neurosci.* 2015;16:30–42.
13. Di Marzo V, Wang J (eds). The Endocannabinoidome. Academic Press, London, 2015.
14. Ferber SG, Namdar D, Hen-Shoval D, et al. The "Entourage Effect": Terpenes Coupled with Cannabinoids for the Treatment of Mood Disorders and Anxiety Disorders. Curr Neuropharmacol. 2020;18(2):87-96.
15. Goldstein B. Cannabis is Medicine. Hachette Book Group, New York, NY, 2020.
16. Gruden G, Barutta F, Kunos G, Pacher P. Role of the endocannabinoid system in diabetes and diabetic complications. Br J Pharmacol. 2016 Apr;173(7):1116-27.
17. Hasenoehrl C, Feuersinger D, Sturm EM, et al. G protein-coupled receptor GPR55 promotes colorectal cancer and has opposing effects to cannabinoid receptor 1. *Int. J. Cancer.* 2018;142:121–132.
18. Hill MN, Bierer LM, Makotkine I, et al. Reductions in circulating endocannabinoid levels in individuals with post-traumatic stress disorder following exposure to the World Trade Center attacks. Psychoneuroendocrinology. 2013 Dec;38(12):2952-61.
19. Hungund BL, Vinod KY, Kassir SA, et al. Upregulation of CB1 receptors and agonist-stimulated [35S]GTPgammaS binding in the prefrontal cortex of depressed suicide victims. Mol Psychiatry. 2004 Feb;9(2):184-90.
20. Izzo AA, Fezza F, Capasso R, et al. Cannabinoid CB1-receptor mediated regulation of gastrointestinal motility in mice in a model of intestinal inflammation. Br J Pharmacol. 2001 Oct;134(3):563-70.
21. Karlócai MR, Tóth K, Watanabe M, et al. Redistribution of CB1 cannabinoid receptors in the acute and chronic phases of pilocarpine-induced epilepsy. PLoS One. 2011;6(11):e27196.
22. Keating GM. Delta-9-Tetrahydrocannabinol/Cannabidiol Oromucosal Spray (Sativex®): A Review in Multiple Sclerosis-Related Spasticity. Drugs. 2017 Apr;77(5):563-574.

Selected References

23. Lomazzo E, König F, Abassi L, et al. Chronic stress leads to epigenetic dysregulation in the neuropeptide-Y and cannabinoid CB1 receptor genes in the mouse cingulate cortex. Neuropharmacology 2017;113 Pt A, 301–313.

24. Lu AT, Ogdie MN, Järvelin MR, et al. Association of the cannabinoid receptor gene (CNR1) with ADHD and post-traumatic stress disorder. Am J Med Genet B Neuropsychiatr Genet 2008;147:1488–1494.

25. Maccarrone M, Guzma´n M, Mackie K, Doherty P, Harkany T. Programming of neural cells by (endo)cannabinoids: from physiological rules to emerging therapies. Nat Rev Neurosci. 2014;15:786–801.

26. Meccariello R, Santoro A, D'Angelo S, Morrone R, Fasano S, Viggiano A, Pierantoni R. The Epigenetics of the Endocannabinoid System. Int J Mol Sci. 2020 Feb 7;21(3):1113.

27. Mechoulam R, Hanusˇ LO, Pertwee R, Howlett AC. Early phytocannabinoid chemistry to endocannabinoids and beyond. Nat Rev Neurosci. 2014;15:757–764.

28. Matias I, Gonthier MP, Orlando P, et al. Regulation, function, and dysregulation of endocannabinoids in models of adipose and beta-pancreatic cells and in obesity and hyperglycemia. J Clin Endocrinol Metab. 2006 Aug;91(8):3171-80.

29. McPartland JM, Guy GW, Di Marzo V (2014) Care and Feeding of the Endocannabinoid System: A Systematic Review of Potential Clinical Interventions that Upregulate the Endocannabinoid System. PLoS ONE 9(3): e89566.

30. Mlost J, Wąsik A, Starowicz K. Role of endocannabinoid system in dopamine signaling within the reward circuits affected by chronic pain. *Pharmacol Res.* 2019 May;143:40-47.

31. Molina PE, Amedee A, LeCapitaine NJ, et al. Cannabinoid neuroimmune modulation of SIV disease. *J. Neuroimmune Pharmacol.* 2011;6:516–527.

32. Navarro L, Martínez-vargas M, Murillo-rodríguez E, et al. Potential role of the cannabinoid receptor CB1 in rapid eye movement sleep rebound. Neuroscience. 2003;120(3):855-9.

33. Netzahualcoyotzi C, Rodríguez-Serrano LM, Chávez-Hernández ME, Buenrostro-Jáuregui MH. Early Consumption of Cannabinoids: From Adult Neurogenesis to Behavior. Int. J. Mol. Sci. 2021, 22, 7450.

Selected References

34. Pertwee RG (ed). Endocannabinoids. In: The Handbook of Experimental Pharmacology. Vol 231. Switzerland: Springer International Publishing, 2015.
35. Peters KZ, Cheer JF, Tonini R. Modulating the Neuromodulators: Dopamine, Serotonin, and the Endocannabinoid System. Trends Neurosci. 2021 Mar 3:S0166-2236(21)00022-9
36. Richardson JD, Aanonsen L, Hargreaves KM. Hypoactivity of the spinal cannabinoid system results in NMDA-dependent hyperalgesia. J Neurosci. 1998 Jan 1;18(1):451-7.
37. Russo EB. Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes. *Cannabis Cannabinoid Res*. 2016;1(1):154-165.
38. Sarchielli P, Pini LA, Coppola F, et al. Endocannabinoids in chronic migraine: CSF findings suggest a system failure. Neuropsychopharmacology. 2007 Jun;32(6):1384-90.
39. Sharkey KA, Wiley JW. The Role of the Endocannabinoid System in the Brain-Gut Axis. Gastroenterology. 2016 Aug;151(2):252-66.
40. Siegling A, Hofmann HA, Denzer D, et al. Cannabinoid CB(1) receptor upregulation in a rat model of chronic neuropathic pain. Eur J Pharmacol. 2001 Mar 9;415(1):R5-7.
41. Siniscalco D, Sapone A, Giordano C, et al. Cannabinoid receptor type 2, but not type 1, is up-regulated in peripheral blood mononuclear cells of children affected by autistic disorders. J Autism Dev Disord. 2013 Nov;43(11):2686-95.
42. Syed YY, McKeage K, Scott LJ. Delta-9-tetrahydrocannabinol/cannabidiol (Sativex®): a review of its use in patients with moderate to severe spasticity due to multiple sclerosis. Drugs. 2014 Apr;74(5):563-78.
43. Thiele EA, Marsh ED, French JA, et al; GWPCARE4 Study Group. Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): a randomized, double-blind, placebo-controlled phase 3 trial. Lancet. 2018;391(10125):1085-1096.
44. Tocris Bioscience. (2020, May 28). Ion Channels Involved in Pain. News-Medical. Retrieved on July 31, 2021 from https://www.news-medical.net/whitepaper/20190817/Ion-Channels-Involved-in-Pain.aspx

Selected References

45. Vermersch P, Trojano M. Tetrahydrocannabinol:Cannabidiol Oromucosal Spray for Multiple Sclerosis-Related Resistant Spasticity in Daily Practice. Eur Neurol. 2016;76(5-6):216-226.

46. Yang YT, Szaflarski JP. The US Food and Drug Administration's Authorization of the First Cannabis-Derived Pharmaceutical: Are We Out of the Haze? JAMA Neurol. 2019 Feb 1;76(2):135-136.

47. Zou S, Kumar U. Cannabinoid Receptors and the Endocannabinoid System: Signaling and Function in the Central Nervous System. International Journal of Molecular Sciences. 2018; 19(3):833.

48. Zou M, Li D, Li L, Wu L, Sun C. Role of the endocannabinoid system in neurological disorders. Int J Dev Neurosci. 2019 Aug;76:95-102.

PainWeek

ADVANCED EDUCATION

CERTIFICATION SERIES

CANNABINOIDS

The Endocannabinoid System Defined

Theresa Mallick-Searle, MS, PMGT-BC, ANP-BC