

Non-Pharmacological Influences on the Endocannabinoid System

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The 15th National Clinical Conference on
Cannabis Therapeutics

Disclosure

- Healer: equity owner and employee
 - patient education, cannabis and hemp products, industry training, consulting, extraction/formulation
- Forian: former paid scientific advisor
- Society of Cannabis Clinicians: unpaid member of board of directors
- Author of “Handbook of Cannabis for Clinicians: Principles and Practice” published by Norton Professional

Overview

- Stress
- Social Interaction
- Exercise
- Diet
- Manual therapy
- Cold
- Fasting

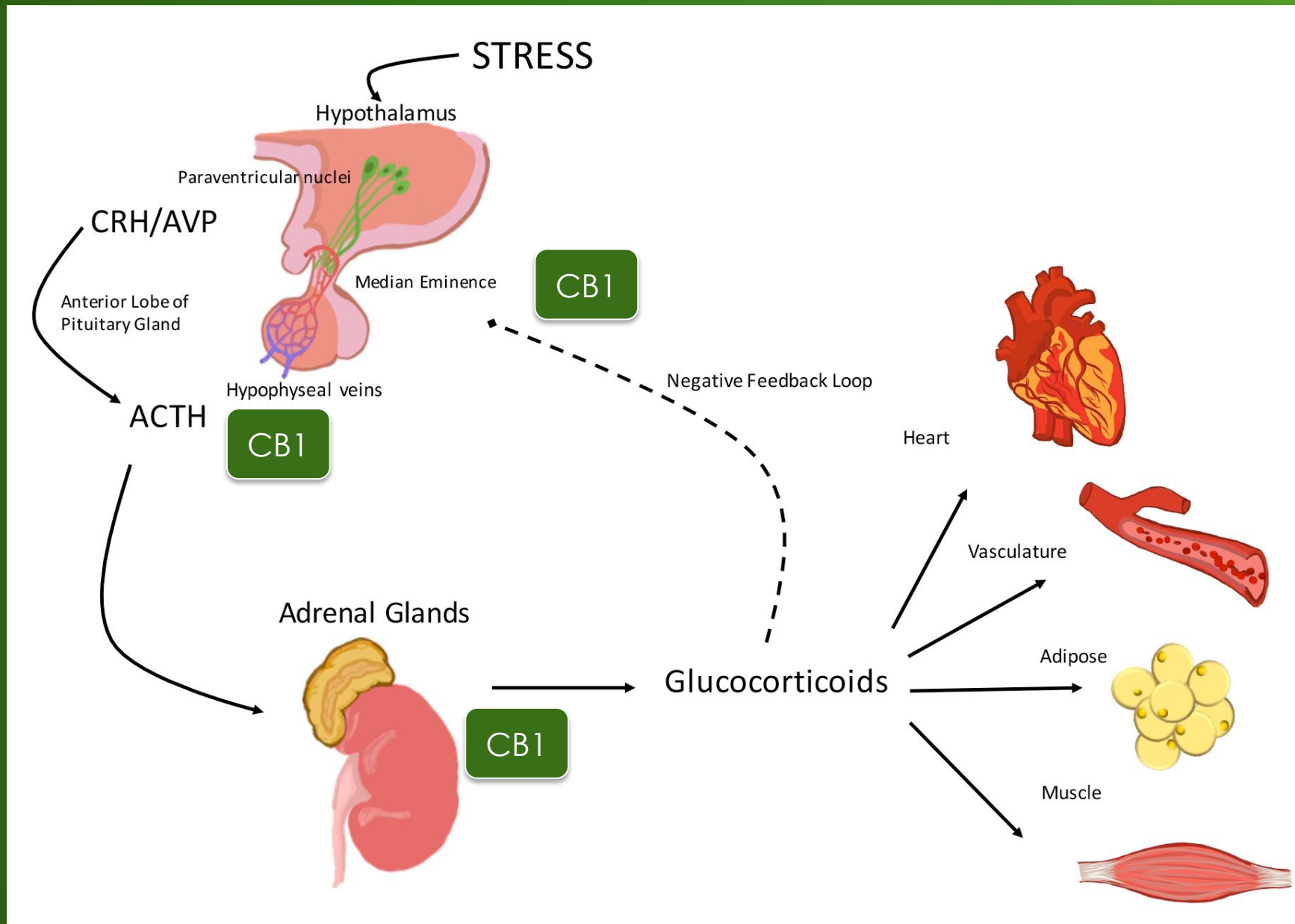
Is Increased ECS Activity
Always Good?

Stress and the HPA Axis

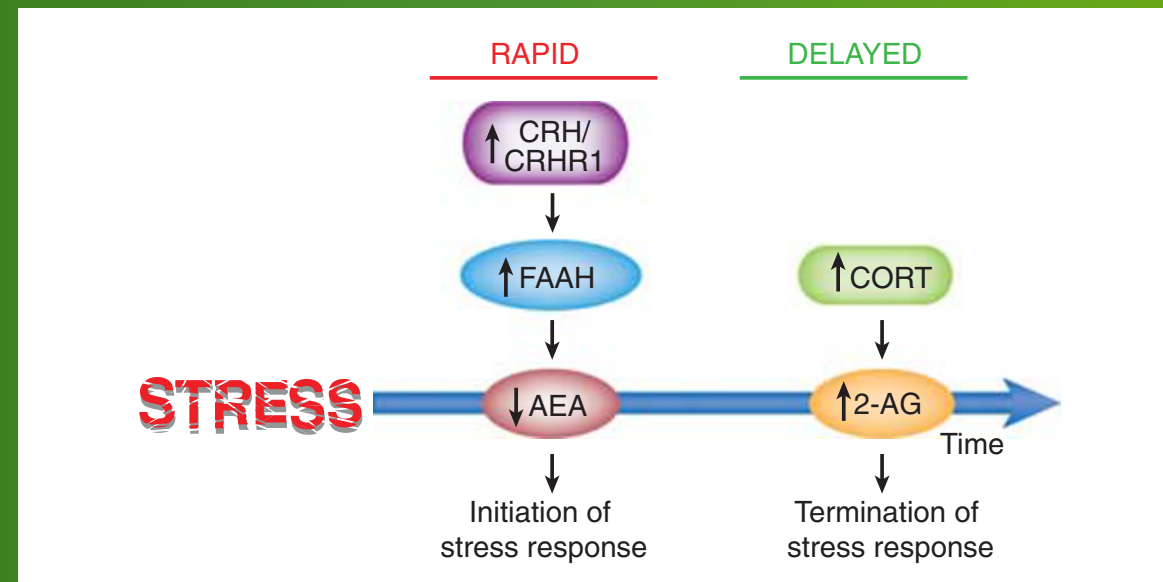
- Physiological stressors (e.g. pain, inflammation)
 - Mid-hindbrain
- Psychological stressors
 - Limbic brain
- Both converge in paraventricular nucleus of hypothalamus and elicit a similar stress responses, including activation of the hypothalamic–pituitary–adrenocortical (HPA) axis
 - Releases cortisol from the adrenal cortex
 - Leads to release of epinephrine from the adrenal medulla and norepinephrine from the sympathetic nerve terminals

ECS Regulates HPA Axis

- Under both basal and stress-related condition
 - Micalle & Drago, 2018
- Via CB1 receptors:
 - limbic brain regions involved in HPA axis regulation, involved in glucocorticoid-mediated feedback of the HPA axis
 - intermediate and anterior lobes of the pituitary, where they likely contribute additional modulatory effects on the HPA axis
 - human adrenal cortex, where their activity inhibits the production of cortisol and aldosterone
 - Ziegler et al., 2010



Anandamide and 2-AG



- Stress exposure reduces AEA levels
 - Increased FAAH activity
 - Contributes to the manifestation of the stress response
- Stress exposure increases 2-AG levels
- These effects become amplified following chronic exposure to the same stressor

– Morena et al., 2016

CB1 and Chronic Stress

- In almost every brain region examined, exposure to chronic stress reliably causes a downregulation or loss of CB1 receptors
- The mPFC is one region in the brain where chronic stressors have reliably been found to increase the expression of the CB1 receptor
 - mPFC is important in human social cognition and behavior; increased plasticity needed for social experience

Stress: Helpful or Harmful?

- **Distress**
 - leads to feelings of being overwhelmed, anxiety, depression, and decreased performance.
 - Occurs more often when one perceives the challenging aspects of an event or situation without simultaneously perceiving the supportive aspects.
- **Eustress**
 - A form of stress having a beneficial effect on health, motivation, performance, and emotional well-being
 - Occurs when we embrace both the challenging and supportive aspects of an event or situation.

Perception

- Determines whether we experience distress or eustress
- We all have the power to transform distress into eustress, though sometimes our rigid perception limits our capacity to do so.



Evidence in Humans

- When exposed to stress, individuals who exhibit an increase in circulating levels of 2-AG exhibit minor changes in HPA axis function
- Those who exhibit no change in 2-AG levels possess massive increases in cortisol,

– Chouker et al, 2010

Rimonobant Trials

- Anxiety and depression significantly increased following sustained rimonabant treatment
- Sustained disruption of eCB signaling can result in anxiety and depression by rendering the individual more vulnerable to the adverse effects of stress

Rimonobant (Preclinical)

- Directly potentiate stress-induced anxiety
 - Bergamaschi et al, 2014
- Promote negative memory bias
 - Horder et al, 2012
- Suppress positive memory recall
 - Horder et al, 2009
- Dampen activation of reward circuits in the brain in response to pleasurable stimuli
 - Horder et al, 2010

ECS and Stress Summary

- ECS is essential in modulating our stress response
- Perception changes our relationship with stress
- Chronic stress can impair ECS function
- ECS dysfunction increases our susceptibility to distress

Social Behavior and Play

- Social play in rats increases CB1 phosphorylation (a marker of CB1 activation) in the amygdala & enhanced AEA levels in the amygdala and nucleus accumbens
 - McPartland, 2014 (review)
- CB1 receptor blockade reduces the motivational aspects of social play behavior in rats
 - Achterberga et al., 2016
- Direct and, more consistently, indirect CB1 activation reverse social impairment.
 - Ahmed et al., 2022 (review)

Social Behavior and Play

- Nonfamiliar social encounters increased striatal AEA levels in rats, particularly important for coping response to novel social contexts.
 - Marco et al., 2011
- Peer-rejected adolescent female rats increased CB1 levels in the amygdala and thalamus, increased levels of AEA, decreased FAAH, with lasting consequences in social behavior and pain sensitivity.
 - Schneider et al., 2016
- The ECS interacts with oxytocin, the neuropeptide that reinforces social bonding and social reward
 - Oxytocin drives AEA mobilization in the mouse nucleus accumbens, leading to reinforcement of social reward behavior.

– Wei et al., 2015

Exercise

- Medium to high-intensity voluntary exercise increases ECS signaling, via increased serum AEA levels, and possibly increased CB1 expression.
- Forced exercise does not increase AEA and can decrease CB1.

McPartland, 2014 (review)

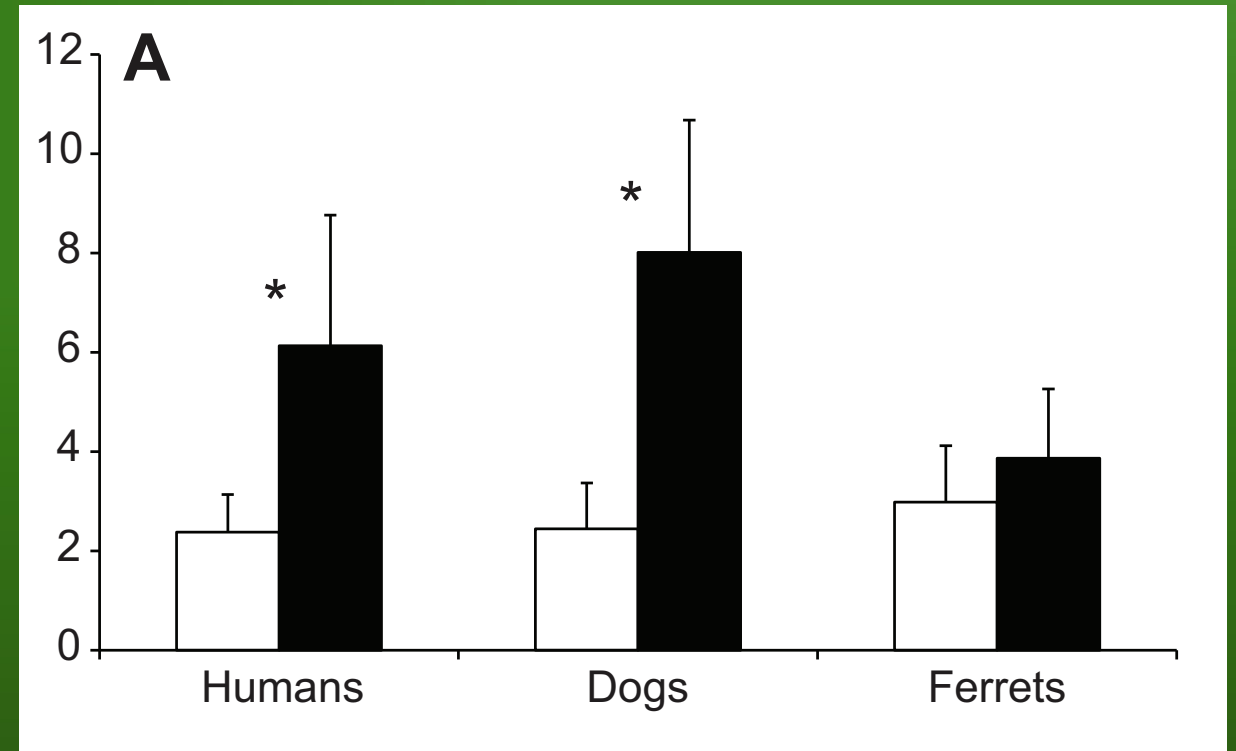
Exercise – Make Sure You Enjoy It!



Exercise

Changes in anandamide concentrations before and after 30 min. treadmill exercise.

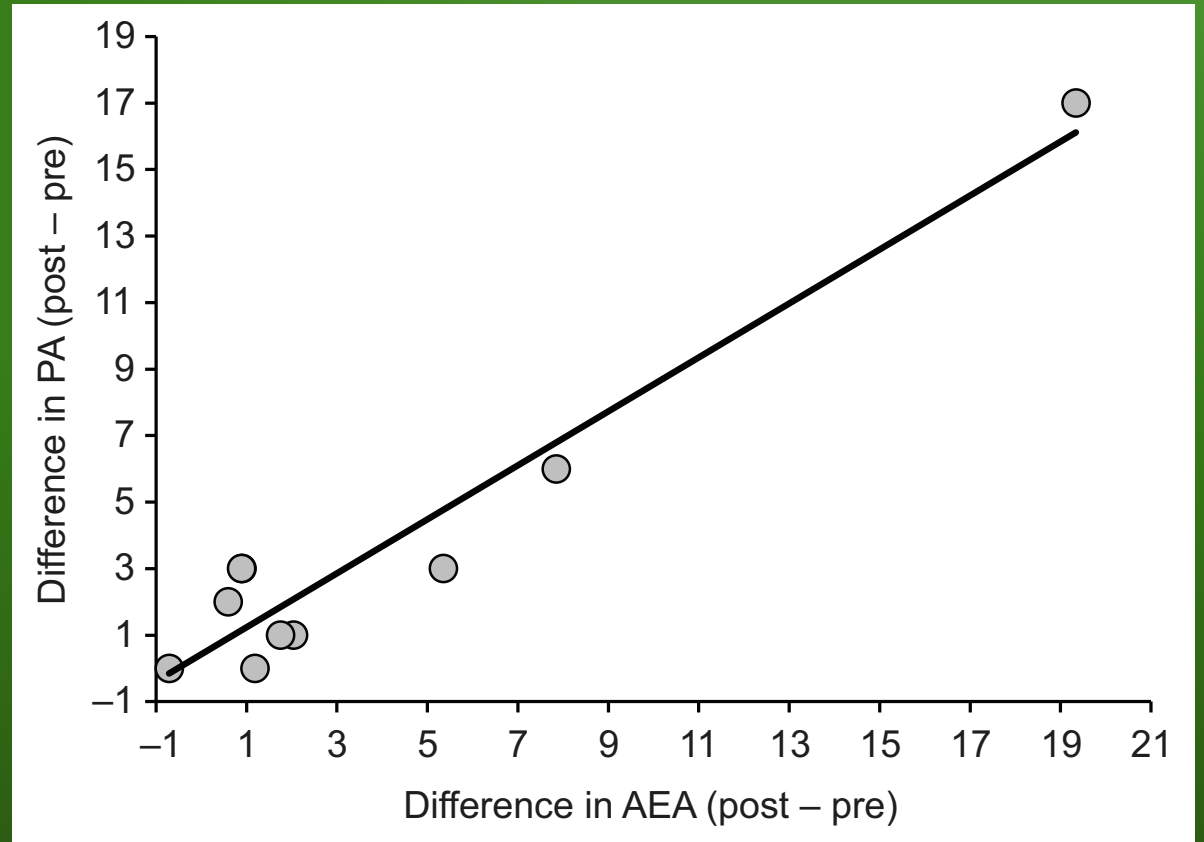
Raichlen et al., 2012



Exercise

Correlation
between positive
affect and AEA in
humans.

(Raichlen et al., 2011)



An Analysis of Endocannabinoid Concentrations and Mood Following Singing and Exercise in Healthy Volunteers

 **frontiers**
in Behavioral Neuroscience

ORIGINAL RESEARCH
published: 26 November 2018
doi: 10.3389/fnbeh.2018.00269

Nicole L. Stone¹, Sophie A. Millar¹, Philip J. J. Herrod¹, David A. Barrett², Catharine A. Ortori², Valerie A. Mellon³ and Saoirse E. O'Sullivan^{1}*

- 9 healthy female volunteers (mean age 61) recruited from a local choir.
- Singing for 30 min increased plasma levels of anandamide by 42% ($P < 0.05$), PEA by 53% ($P < 0.01$) and OEA by 34% ($P < 0.05$) and improved positive mood and emotions ($P < 0.01$), without affecting hunger scores.
 - Stronger than cycling or dancing in this group

The New Runner's High? Examining Relationships Between Cannabis Use and Exercise Behavior in States With Legalized Cannabis

Sophie L. YorkWilliams^{1*}, Charleen J. Gust¹, Raeghan Mueller¹, L. Cinnamon Bidwell², Kent E. Hutchison¹, Arielle S. Gillman¹ and Angela D. Bryan¹

 **frontiers**
in Public Health

ORIGINAL RESEARCH
published: 30 April 2019
doi: 10.3389/fpubh.2019.00099

Using cannabis with exercise associated with 43.4 more min of weekly aerobic exercise ($p < 0.01$).

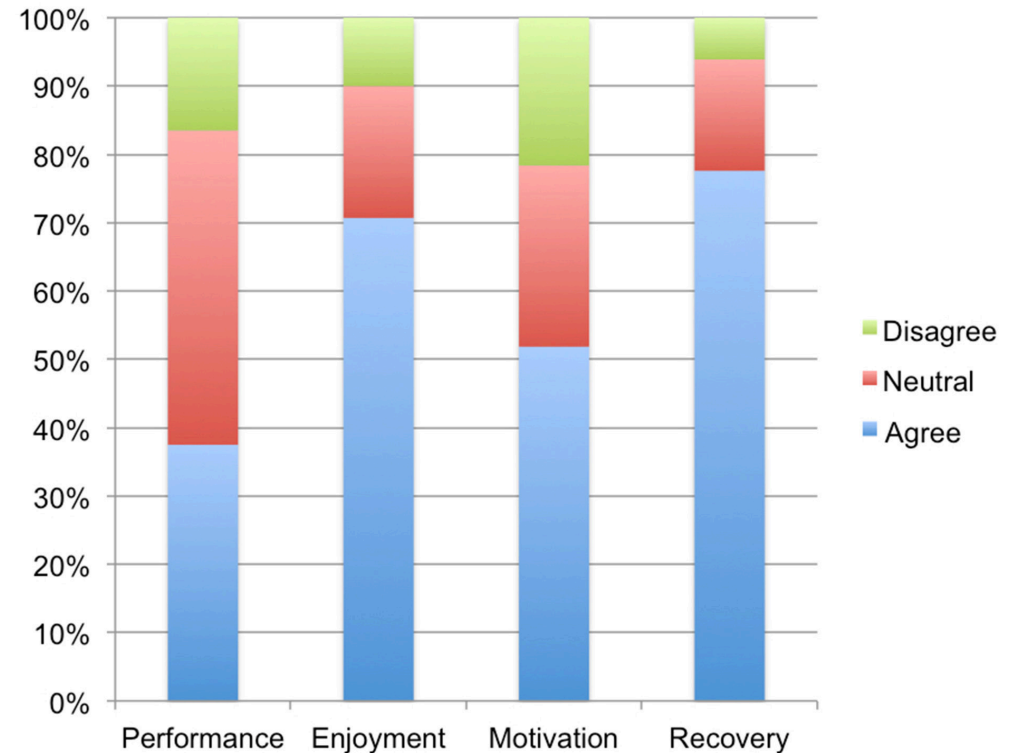


FIGURE 1 | Percentage of co-using participants who agreed, disagreed, or felt neutral toward whether use of cannabis shortly before and/or after exercise enhanced exercise performance, enjoyment, motivation, and recovery.

Diet and the ECS



Dietary Polyunsaturated Fatty Acids

- Ω -3 consumption can reduce excessive AEA and 2-AG levels that may be causing CB1 desensitization (e.g. obesity).
– Bosch-Bouju & Layé, 2016
- Ω -3 rich diet vs SAD reduced pain, correlated with DHEA and 2-DHG, which may have other benefits via the ECS
– Ramsden et al., 2015

Dietary Polyunsaturated Fatty Acids

- Developmental dietary ω -3 deficiency in rodents resulted in decreased eCB-dependent synaptic plasticity in the prefrontal cortex and nucleus accumbens
- A diet rich in ω -3 polyunsaturated fatty acids maintained endocannabinoid-dependent plasticity in the nucleus accumbens following a chronic social defeat stress

– Bosch-Bouju & Layé, 2016

Hemp Seeds



Image by Susanna Sieg from Pixabay

Per 50 g serving (5 tbsp)
Par portion de 50 g (5 c. à soupe)

Amount Teneur	% Daily Value* % valeur quotidienne*
Calories / Calories 280 (1160 KJ)	
Calories from Fat/Calories des lipides 280 (1160 KJ)	
Total Fat/Lipides 18 g	28%
Saturated/ saturés 1.5 g +Trans/ trans 0 g	8%
Polyunsaturated/ polyinsaturés 14 g	
Omega-6/ oméga-6 10 g	
Omega-3/ oméga-3 3.5 g	
Monounsaturated/ monoinsaturés 2 g	
Cholesterol/ Cholestérol 0 mg	0%
Sodium/ Sodium 140 mg	6%
Potassium/ Potassium 380 mg	11%
Carbohydrate/ Glucides 16 g	5%
Dietary Fibre/ Fibres alimentaires 15 g	60%
Soluble Fibre/ Fibres solubles 1 g	
Insoluble Fibre/ Fibres insolubles 14 g	
Sugar/ Sucres 1 g	
Protein/ Protéines 13 g	

Small Cold-Water Fish



Images from Pixabay by stevepb, monicore

Trends in Pharmacological Sciences


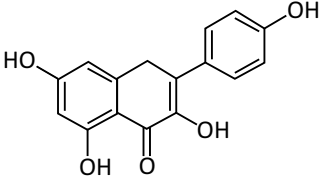

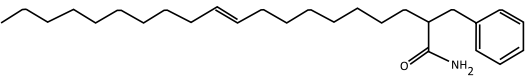

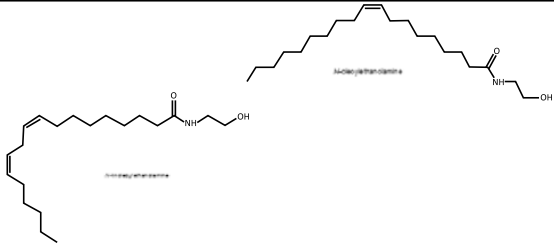
CellPress

Review

Beyond Cannabis: Plants and the Endocannabinoid System

Ethan B. Russo^{1,*}

Dietary FAAH Inhibitors: Galangal, Maca, Chocolate

<p><i>Kaempferia galanga</i></p>	 <p>Galangal</p>	<p>Kaempferol</p>	 <p>Kaempferol</p>
<p><i>Lepidium meyenii</i></p>	 <p>Maca root powder</p>	<p>Macamide</p>	 <p>"Macamide" <i>N</i>-Benzyloleamide</p>
<p><i>Theobroma cacao</i></p>	 <p>Chocolate</p>	<p><i>N</i>-oleoyl-ethanolamine <i>N</i>-linoleyl-ethanolamine</p>	

Reviewed in Russo, 2016

Probiotics, Lacto-Fermentation

Lactobacillus acidophilus NCFM



- Induced CNR2 mRNA expression in human epithelial cells
- Antinociception in rats that was reduced by a CB2 antagonist.



Rousseaux et al., 2007

Review

The Endocannabinoid System: A Bridge between Alzheimer's Disease and Gut Microbiota

Tiziana Bisogno ^{1,*} , Anna Lauritano ² and Fabiana Piscitelli ^{2,*} 

Molecular Psychiatry (2021) 26:6269–6276
<https://doi.org/10.1038/s41380-021-01147-5>

ARTICLE



Endocannabinoid system mediates the association between gut-microbial diversity and anhedonia/amotivation in a general population cohort

Amedeo Minichino ¹ · Matthew A. Jackson² · Marta Francesconi ³ · Claire J. Steves⁴ · Cristina Menni ⁴ · Philip W. J. Burnet¹ · Belinda R. Lennox ^{1,5}

European Journal of Nutrition (2021) 60:3703–3716
<https://doi.org/10.1007/s00394-021-02538-8>

ORIGINAL CONTRIBUTION



Mediterranean diet consumption affects the endocannabinoid system in overweight and obese subjects: possible links with gut microbiome, insulin resistance and inflammation

Manual Therapy

In subjects receiving osteopathic manipulation, serum levels of AEA obtained after treatment more than doubled the pre-treatment levels. No change was seen in control subjects.

McPartland, 2005



Manual Therapy

Increase in PEA in subjects with chronic low back pain at 30 minutes posttreatment was two times greater than the increase in control subjects.

Degenhardt et al., 2006



Cold Bathing and Winter Swimming Associated with Improvements in

- Immune function, cardiovascular function, antioxidant activity, and metabolism
 - Kolettis et al., 2003
- Insulin sensitivity
 - Gibas-Dorna et al., 2016
- Reduced inflammation and blood lipids
 - Pan et al., 2015
- Activation of anti-pain centers of the brain
 - Muzik et al., 2018



Endocannabinoid regulation in white and brown adipose tissue following thermogenic activation

Lucia M. Krott,^{1,*} Fabiana Piscitelli,^{1,†} Markus Heine,^{*} Simona Borrino,[†] Ludger Scheja,^{*}
Cristoforo Silvestri,[†] Joerg Heeren,^{2,*} and Vincenzo Di Marzo^{2,†}

- Exposure to cold caused an upregulation of endocannabinoid levels and biosynthetic enzymes in white adipose tissue (WAT).
- Activation of brown adipose tissue and browning of WAT in mice cause upregulation of endocannabinoid levels

**IF WE ALWAYS CHOOSE COMFORT,
WE NEVER LEARN THE DEEPEST
CAPABILITIES OF OUR MIND OR BODY.**

WIM "THE ICEMAN" HOFF



Fasting



Endocannabinoid levels in rat limbic forebrain and hypothalamus in relation to fasting, feeding and satiation: stimulation of eating by 2-arachidonoyl glycerol

***¹Tim C. Kirkham, ¹Claire M. Williams, ²Filomena Fezza & ²Vincenzo Di Marzo**

- Fasting increased levels of anandamide and 2-AG in the limbic forebrain and, to a lesser extent, of 2-AG in the hypothalamus.
- Hypothalamic 2-AG declined as animals ate.

Fasting



- The ECS is intimately involved in regulation of hunger, satiety, and energy utilization.
- While the interactions are complex, data suggest that fasting can both trigger increased production of eCBs and restore balance to the ECS in scenarios consistent with obesity and metabolic syndrome.

– Hillard, 2018 (review); McPartland et al., 2014

Summary: ECS-Enhancing Recommendations

1. Distress → Eustress via perceptual shift
2. Social interactions and play
3. Enjoyable exercise
4. Omega-3 PUFAS: hemp seeds, sardines, wild salmon
5. FAAH inhibition: Chocolate, maca, galangal
6. Fermented foods (for most)
7. Bodywork
8. Ice bathing
9. Fasting

Thank you!

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