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Advanced Orthomolecular Research

THE TRUTH ABOUT PALMATOYLETHANOLAMIDE (PEA)

THE TRUTH SERIES

THE TRUTH SERIES

As a discerning user of natural health products, you want what is best for your health. However, misinformation and deceptive marketing often make it challenging to identify fact from fiction. The Truth Series was created by Advanced Orthomolecular Research (AOR) to share the evidence-based truth about the most controversial and confusing topics within the natural health industry. At AOR, we believe that truth and transparency are the most important values for any organization to uphold. As visionaries, we are committed to continuous innovation so that we can advance the world of natural health. As such, the Truth Series aligns with our vision of providing optimal products without compromise.

Published in Canada by:
Advanced Orthomolecular Research Inc.

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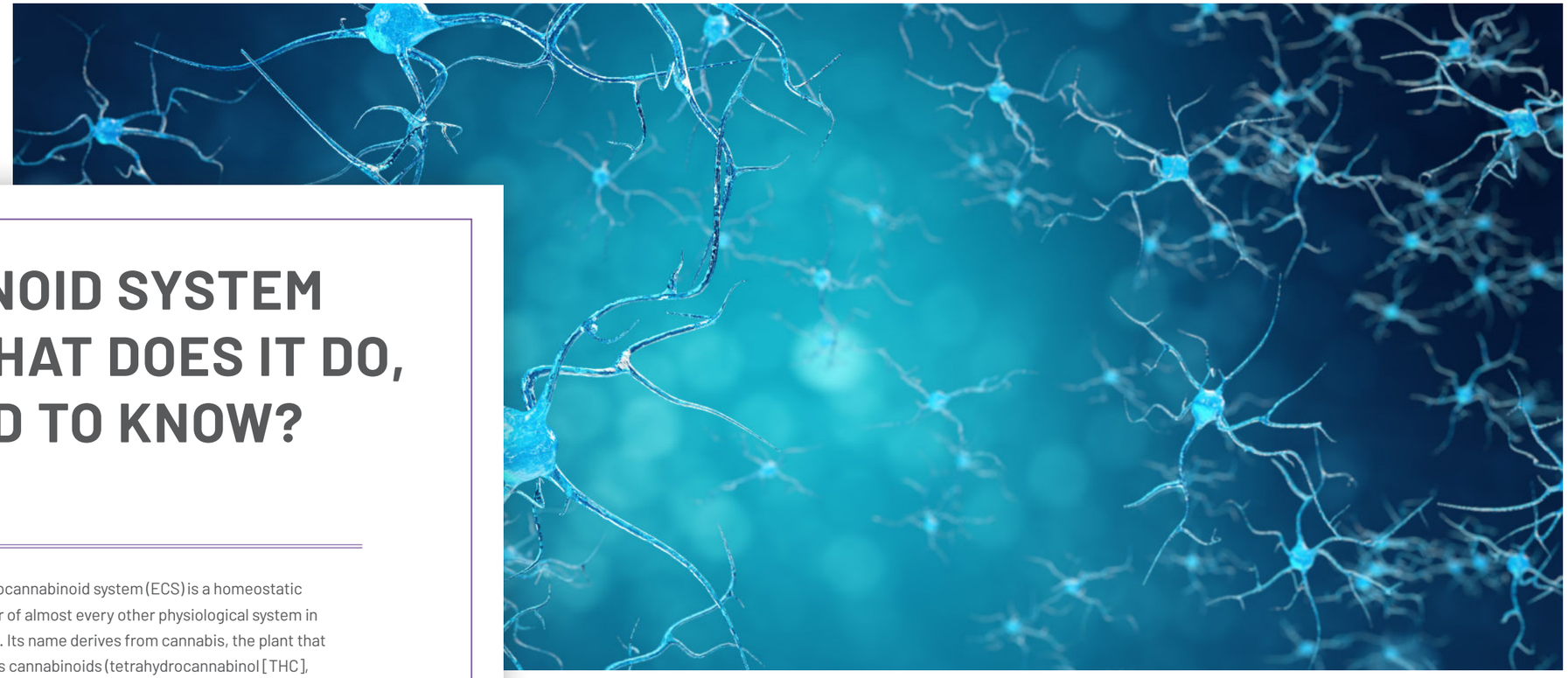


THE ENDOCANNABINOID SYSTEM (ECS) WHAT IS IT, WHAT DOES IT DO, AND WHAT DO I NEED TO KNOW?

By Dr. Traj Nibber, PhD

The endocannabinoid system (ECS) is a security and defense system that the body relies upon to keep us safe, whilst making sure checks and balances are in place to thwart attacks both from within and without.

The ECS is a vast signalling network that communicates with other well- known systems including the nervous, immune, hormonal or the endocrine, but also some that are rather more obscure, like the lymphatic or the enteric nervous system sometimes called the "second brain".

ECS's job is to relay important and timely information between these systems, but also prime, and prepare the body whenever danger arises. When called upon the ECS springs into action, and further protects, helps repair, and lessens body blows with deft and skill through its unique modulating abilities. It is much like tuning an expensive piano, one uses the services of a skilled technician who has an intimate understanding through pitch and volume of the piano to restore its balance.

The endocannabinoid system (ECS) is a homeostatic regulator of almost every other physiological system in the body. Its name derives from cannabis, the plant that produces cannabinoids (tetrahydrocannabinol [THC], cannabidiol [CBD], beta-caryophyllene [BCP], and others), and whose investigation explained the many functions of the ECS. In the past two decades, additional research has discovered that many other plants, and herbs modulate the ECS directly and indirectly.

The ECS responds to various insults, like injury, chronic inflammation, all forms of pain, and infections, whether bacterial or viral. As well, it safe guards fragile assets, like the mitochondria and nerve cells, which are highly sensitive and prone to damage. In addition, ECS keeps alert against other toxic insults, like carcinogens, solvents, UV light, pesticides, and many other.

WHERE IS THE ECS?

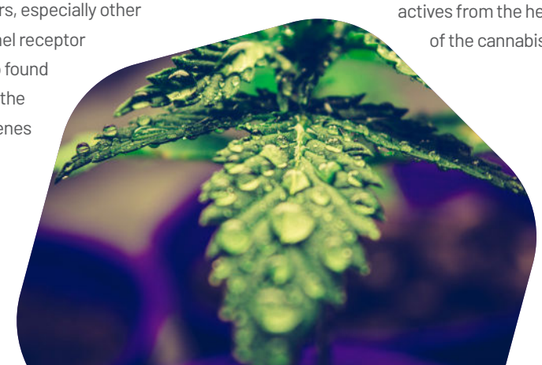
The ECS is distributed all over the body. Originally, it was believed to consist of two cannabinoid receptors, CB1 and CB2, two signalling messengers, or endocannabinoids (eCB's) made by the body namely, anandamide (AEA), and 2-acyl glycerol (2-AG), including the enzymes responsible for their synthesis (NAPE-PLD and NAT), and their breakdown (FAAH and NAAA). The receptors were originally thought to be distributed unevenly with CB1 being primarily located in the brain, and the CB2 receptors located in close proximity to the immune system, and in the peripheral tissues. However, scientists have discovered there is a significant overlap with the CB1 receptor found outside the brain, and the CB2 receptors also found within the brain.

In time, researchers discovered many other players, especially other receptors including GPR55, GPR119, and ion channel receptor TRPV1 through which pain is mediated. It was also found that the receptor PPAR-alpha, which is located in the nucleus of the cells and takes part in regulating genes associated with pain and inflammation, was also part of the ECS.

On top of that, other eCB-like molecules were discovered, like PEA, OEA and SEA. Eventually, scientists expanded these new discoveries to a more encompassing definition termed endocannabinoidome which correctly captures the current state of research of the ECS.

WHAT ACTIVATES THE ECS?

When harmful triggers like inflammation and injury act on the body, the ECS activates production of eCB's like AEA, 2-AG and PEA from the membranes of cells in the vicinity of the injury. EC's are produced on demand whenever the body requires their services. The advantage is that EC's can be produced quickly, locally and efficiently. However, exogenous or molecules not produced by the body can also stimulate the cannabinoid receptors CB1 and CB2. The most famous are the major actives from the hemp and marijuana varieties of the cannabis plant.



THC and CBD are the most popular but there are hundred or so other cannabinoids capable of acting on the ECS. THC, typically preferentially binds to CB1 receptors located mainly in the brain, and thus produces the psychotropic "high", while CBD only acts on CB2 receptors which are mainly located outside the brain. However, there are other plant species that also produce cannabis-like effects or cannabimimetic effects and some of these are the alkylamides from the Echinacea species, beta caryophyllene from clove, oregano, black pepper and other terpene fractions like limonene, linalool, pinene, myrcene and many others. All of these molecules activate the ECS to varying degree.

WHAT IS THE ENTOURAGE EFFECT?

Entourage effect is the enhancement of a biological effect by another molecule through various mechanisms. For example, it is commonly known that pure THC or CBD (isolates) is not as effective as the whole plant extract that contains CBD, THC and the many other components mentioned earlier. These other components like terpenes, flavonoids, etc. assist in an enhanced action of THC or CBD.

The entourage effect may occur through different mechanisms, e.g., preventing the breakdown of the eCB's by enzymes that are responsible for their destruction in which case the eCB's last longer in the body giving a prolonged and enhanced action, or improving the binding of eCB's on various receptors, or by activating other receptors, e.g., opening up ion channels that causes a synergistic effect of the major molecule e.g., THC or CBD.

ADVANTAGES OF ECB'S OVER PHYTOCANNABINOIDS?

EC's are produced by the body and these have significant advantages over exogenous or foreign cannabinoids like the phytocannabinoids. For example, eCB's are locally produced. They are molecules the body recognizes and is familiar with. The amount the body produces is in proportion to the demand, and the dose is well known. Additionally, these molecules act fast because they are produced locally, and once they have performed their service they are quickly broken down by the body and recycled back to the components of cellular membranes from which they originated. However, phytocannabinoids, are not natural molecules to the body. Moreover, their dose is not well known. For example, CBD is widely popular, but the effective dose varies greatly between individuals, which can be anywhere from 20 mg to 1,200 mg or more! So determining the right dose is a challenge. In addition, the effect of CBD varies greatly in people. Finally, phytocannabinoids can and do produce adverse effects, and can linger in the body, plus in the case of THC at least there is a chance of dependency.

In summary the ECS is a versatile defense system that exists in all plant and animal species, which the body heavily relies upon in protection, healing and recovery.

References

1. Alhouayek M and Muccioli GG. Harnessing the anti-inflammatory potential of palmitoylethanolamide Drug Discovery Today 2014 ; 19: 1632-1639
2. Aizpurua-Olaizola O. *et al.* Targeting the endocannabinoid system: future therapeutic strategies. Drug Discovery Today 2017; 22: 105-110
3. Chiurchiù V. *et al.* Bioactive Lipids and Chronic Inflammation: Managing the Fire Within. Front Immunol. 2018; 9: 1-11
4. Maccarrone M. *et al.* Endocannabinoid signaling at the periphery: 50 years after THC Trends in Pharmacological Sciences 2015; 36: 277-296
5. Witkamp R. Fatty acids,endocannabinoids and inflammation. European Journal of Pharmacology 2016; 785: 96-107
6. Goutopoulosa A. and Makriyannis A. From cannabis to cannabinergics: new therapeutic opportunities Pharmacology & Therapeutics 2002; 95: 103-117
7. Pertwee R. Endocannabinoids Handbook of Experimental Pharmacology 2015; 231: 1-477
8. Witkamp R. The role of fatty acids and their endocannabinoid-like derivatives in the molecular regulation of appetite Molecular Aspects of Medicine 2018; 64: 45-67

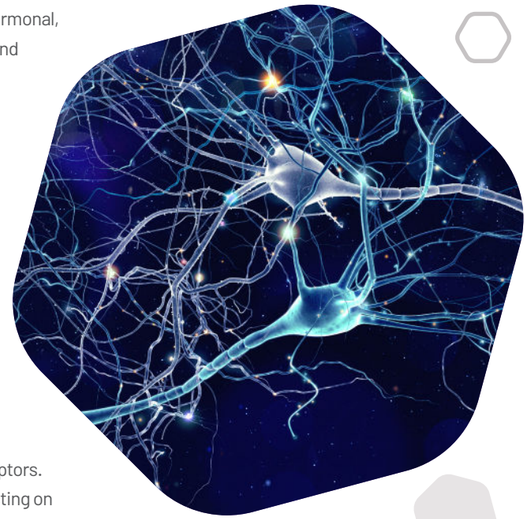
MEDIATING THE PHARMACOLOGICAL EFFECTS OF CANNABIMIMETICS

By Dr. Traj Nibber, PhD

The cannabis plants, both indica and sativa, produce close to 100 different cannabinoid molecules like CBD, THC, CBC, CBG, CBN as well as many of their acidic forms. Whilst these molecules get all the attention in the cannabis research world, there are hundreds of other cannabinoids that many other plants produce including spilanthes, Echinacea, hops, black pepper, oregano, peppermint, rosemary to name a few.

The WHO reports that 70% of the world's population resort to some sort of natural remedies for their wellbeing. Recently, numerous herbal agents and food plants beyond cannabis have been examined for their possible modulatory effects on the endocannabinoid system (ECS).

The ECS was only discovered in the last thirty years, and was named after cannabis due to the fact the two newly discovered receptors of the ECS, CB1 and CB2, were acted upon by THC from the cannabis plant.



The body relies upon the ECS to communicate with other systems in the body: nervous, hormonal, immune etc., to help protect the body against disease, damage and danger, both internal and external. ECS uses a wide variety of fatty acids at its disposal as signaling molecules, and networks with other systems, tissues, cells throughout the body, and modulates various disease processes. The ECS, therefore is very amenable to modifications that readdress the diseased or unbalanced state, back into health and equilibrium or a balanced state. As such ECS has become a particular target of drugs both natural and synthetic.

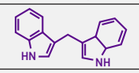
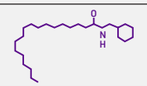
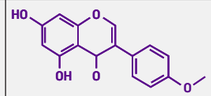
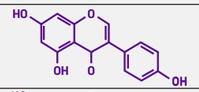
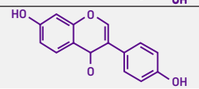
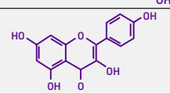
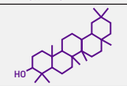
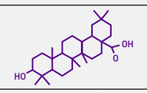
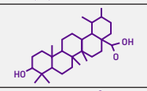
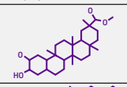
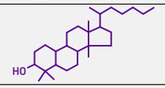
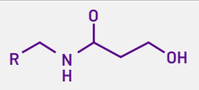
From a natural perspective, there are two types of cannabinoids: exocannabinoids, those produced outside the body and ingested from various plants including cannabis, and endocannabinoids, which are produced within the body.
Let us discuss these separately.

First, the exocannabinoids. Beside the cannabis species, there are hundreds of plants that have been found to produce molecules that impact the ECS. Many of these molecules interact with receptors beyond the first two that were discovered CB1 and CB2.
These include: GCPR 55, GPR 118, PPAR- alpha as well as TRPV1 and other ion channel receptors.
Therefore, a broader term has come into use: "*cannabinomimetics*", meaning molecules acting on various receptors of the ECS, but not derived from the cannabis plant.

Table 1 and also Figures 1, 2, 3 and 4 list a few of the molecules from various herbal species and their action on various receptors.

Oregano - *origanumvulgare L.*
Rosemary - *Rosmarinusofficinalis*
Cinnamon Cinnamomum spp.
Black pepper - *Piper nigrum L*
Clove – *Szygiumaromaticum*
Purple cone flower - *Echinacea purpurea - alkylamides*
Toothache tree or Prickly ash - *Zanthoxylum*
Maca - *Lepidiummeyenii*

Table 1: Phytochemicals in diet that may modulate the ECS

Plant Secondary Metabolite	Chemical Structure	Dietary Origin	Target/Effect	Potency (IC50, K i)/Efficacy	In Vivo Evidence	Selected References
BCP		Most widespread, numerous food plants, spices	CB_2 receptor agonist	~200 nM/partial (in vitro), full (in vivo)	strong	Gertsch *et al.*, 2008; Horváth *et al.*, 2012; Klauke *et al.*, 2014
DIM		Brassicaceae vegetables	CB_2 receptor agonist	~1 µM/partial	missing	Yin *et al.*, 2009
Falcarinol		Apiaceae, carrots (Daucus carrota), ginseng	CB_1 receptor inverse agonist	~200 nM/full	missing (indirect)	Leonti *et al.*, 2010
Macamide		Macca (Lepidium meyenii)	AEA reuptake inhibitor (CB_1 binding)	~200 nM/partial	missing	Hajdu *et al.*, 2014
Guineensine		Piper spp., black pepper	AEA reuptake inhibitor	~200 nM/full	good	Nicolussi *et al.*, 2014
Biochanin A		Soybeans (Glycine max), chickpeas (Cicer arietinum)	FAAH1 inhibitor	0.5–2 µM/full	some	Thors *et al.*, 2010
Genistein		Fava beans (Vicia faba), lupin (Lupinus spp.), soy	FAAH inhibitor/AEA uptake inhibitor	1–3 µM/full	missing	Thors *et al.*, 2007; Thors *et al.*, 2010
Daidzein		Fava beans (Vicia faba), lupin (Lupinus spp.), soy	FAAH inhibitor/AEA uptake inhibitor	2–4 µM/full	missing	Thors *et al.*, 2007; Thors *et al.*, 2010
Kaempferol		Widespread in food plants	FAAH inhibitor	2–4 µM	missing	Thors *et al.*, 2008
ß-amyrin		Widespread in vegetables	MAGL/ABHD6/ ABHD12 inhibitor	~1 µM/partial	some	Bento *et al.*, 2011b; Chicca *et al.*, 2012
Oleanolic Acid		Relatively widespread in food plants (olive oil)	ABHD12 inhibitor	~1.5 µM/full	some	Parkkari *et al.*, 2014
Ursolic Acid		Widespread in food plants	ABHD12 inhibitor	~2 µM/partial	missing	Parkkari *et al.*, 2014
Pristimerin		Scarce in food, Celastraceae	MAGL inhibitor	100 nM/full reversible	missing	King *et al.*, 2009
Euphol		Scarce in food	MAGL inhibitor	300 nM/full reversible	missing	King *et al.*, 2009
NAEs	 R = FA acyl chain	Chemical Formula: Present in higher plants, widespread in fresh food plants	FAAH and NAAA inhibitors	nM metabolized in vivo	some	Gachet *et al.*, 2017; Petrosino and Di Marzo, 2017

Source: Gertsch 2017, Br J Pharmacol 174, 1464-1483

FIGURE 1. Plant-Based CB1 Agonists.

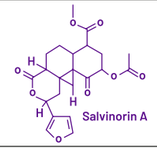
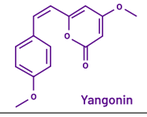
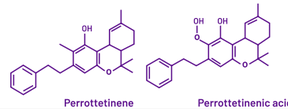
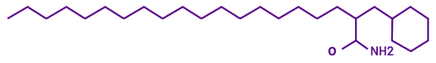
Salvia divinorum	*Salvia divinorum*	Salvinorin A	 Salvinorin A
Daucus carota	Carrot	Falcarinol (carotatoxin)	 Falcarinol
Piper methysticum	Kava Kava	Yangonin	 Yangonin
Radula marginata	New Zealand liverwort	Perrottetinene Perrottetinenic Acid	 Perrottetinene Perrottetinenic acid
Lepidium meyenii	Maca tuber Powder	"Macamide" *N*-benzyloleamide	 "Macamide" *N*-benzyloleamide

FIGURE 2. Plant Sources of Transient Receptor Potential Vanilloid 1 (TRPV1) Agonists.

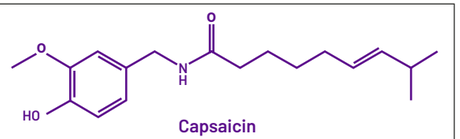
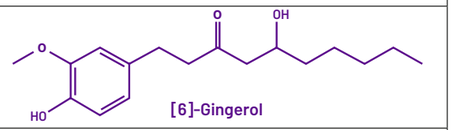
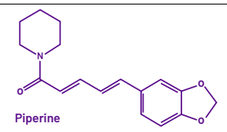
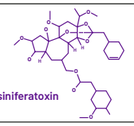
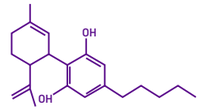
Capsicum annuum	Chili peppers	Capsaicin	 Capsaicin
Zingiber officinale	Ginger	Gingerol, zingerone	 [6]-Gingerol
Piper nigrum	Black pepper	Piperine	 Piperine
Euphorbia resinifera	Resin spurge	Resiniferatoxin	 Resiniferatoxin
Cannabis sativa	CBD trichomes	Cannabidiol	 Cannabidiol

FIGURE 3. ß-Caryophyllene, a CB2Agonist, and its Essential Oil Sources. (A) b-Caryophyllene molecule; (B) unfertilized female flower, Cannabis sativa; (C) copaiba balsam from Copaifera officinalis; (D) peppercorns, Piper nigrum; (E) lemon balm, Melissa officinalis; (F) cloves, Syzygium aromaticu m; (G) hops, Humulus lupulus. (All images: EBR.).

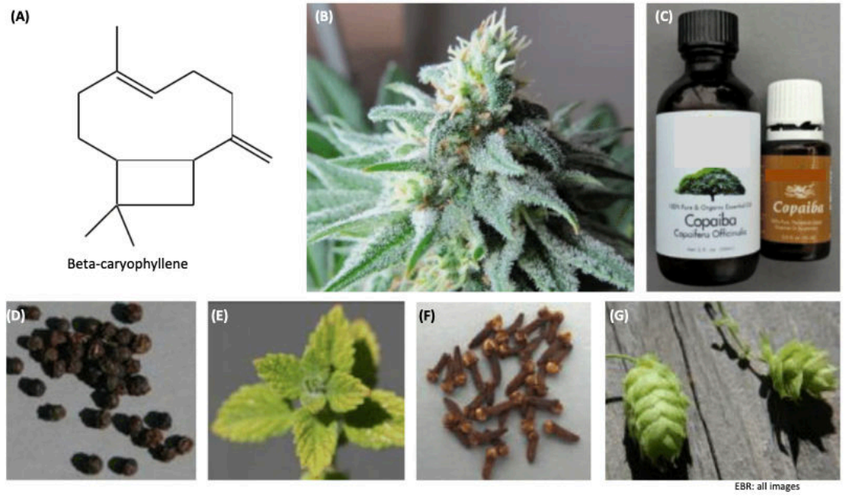
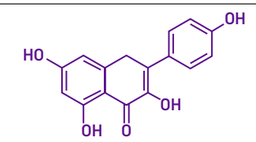
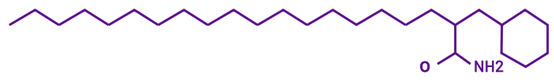
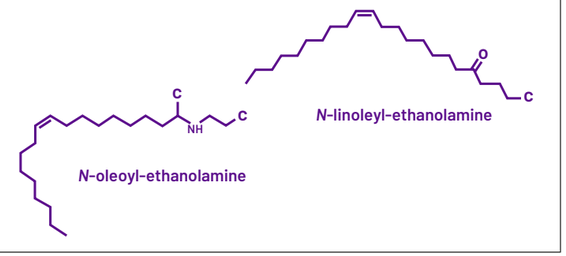


FIGURE 4. Plant Sources of Fatty Acid Amide Hydrolase (FAAH) Inhibition.

Kaemperia galenga	Galangal	Kaempferol	 Kaempferol
Lepidium meyenii	Maca root powder	Macamide	 "Macamide" *N*-benzyloleamide
Theobroma cacao	Chocolate	N-oleoyl-ethanolamine N-linoleyl-ethanolamine	 *N*-linoleyl-ethanolamine *N*-oleoyl-ethanolamine

The active molecules can be classified into several main categories including: terpenes, alkylamides, flavonoids, or polyacetylenes and so on.

See *FIGURE 1* for structures of some of the main categories.

Terpenes are fat soluble compounds that easily cross cell membranes and are easily absorbed including into the blood brain barrier.

For example:

- D-limolene from the citrus essential oils has anxiolytic, anti-cancer and immune-stimulating properties
- Beta-myrcene from hops has analgesic and anti-inflammatory properties
- Alpha-pinene- prevents acetylcholine uptake so may help in memory and cognition
- Linalool found in lavender may have anticonvulsant, anti-inflammatory, analgesic and anti-anxiety properties
- Beta-caryophyllene (BCP) which is a sesquiterpene, is widely present in black pepper, cloves, and many other plants has anti-inflammatory and gastro-protective properties. Interestingly, BCP binds selectively to CB2 receptor like CBD and could be considered a phytocannabinoid without having any psychoactive side effects. Research has shown that BCP inhibits triggering of toll like receptors complex CD14/TLR4/MD2, which leads to production of inflammatory cytokines as well as enhanced Th1 response. BCP has been found to down regulate (inhibit) leucocyte proliferation, promote both T cells and restore the Th1/Th2 balance. In fact, a team of Canadian researchers from Dalhousie University in Halifax have proposed the use of BCP in treating sepsis in hospital emergency care. BCP is also an FDA approved food additive which is effective in fairly low doses of 350 mg per day.
- Beta-amyrin- is an anti-bacterial, anti-fungal and anti-inflammatory

Mechanisms of Action

PLANT MOLECULES HAVE VARIOUS MECHANISMS INCLUDING:

CB_1 - THC (+), FALCARINOL (-)

CB_2 - POSSIBLY CBD (+), BCP (+), BETA-AMYRIN (+)

PPAR-GAMMA- PEA (+), OEA (+)

TRPV1- PEA (-)

GCPR55-PEA (+)

GCPR118-(+)

ION CHANNELS (+) OR (-)

FAAH ENZYME- PEA (-) thus prolonging action of endocannabinoids like AEA in what is known as the entourage effect

(+) = ACTIVATION (-) = INHIBITION

Second, endocannabinoids (eCB), are cannabinoid-like molecules with a fatty acid structure that are produced by the body. Examples include AEA and 2-AG but also a host of other molecules like palmitoylethanolamide (PEA), oleylethanolamide (OEA) etc. In addition, there are other molecules that may also act on the ECS including fatty acid amino acids like N-Acyl taurine, fatty acid dopamine etc.

The advantage of eCB's, unlike other exocannabinoids, is they are produced by the body only on demand and whenever the body requires them, usually against disease and danger, and once they have completed their action they are quickly broken down and recycled back into the building blocks of the cellular membranes that they originally derived of. The eCB's are produced locally and act locally, unlike exocannabinoids, and their action is fairly quick since the body determines whether any eCB are required in the first place.
Let us examine one such molecule that the body produces when the need arises, PEA.

PEA is rapidly produced by the body and, due to its fat like chemical structure, moves easily into various tissues, and cells such as the brain, heart, kidneys, skin and so on, where it can modify disease pathology. Once it arrives, it quickly restores intracellular homeostasis. Simply put, it recreates chemical stability by quenching raging fires of inflammation, or reducing excessive cellular chatter among different cells. Cross-talk or exchanging information between different cells and systems is healthy and much needed, but excessive talk or "gossiping" among such players is unhealthy. In doing so, PEA helps in restoring normal service, putting out raging inflammatory fires, or just telling everyone to chill-out and promoting repair and regrowth of tissues.

Similarities and differences between exo and endocannabinoids

	Excocannabinoids	Endocannabinoids
	THC, CBD, others	PEA, OEA, Fatty acid amides, etc.
Mechanism of action	CB1 or CB2 receptors	PPAR, TRPV1, GPR55, ion channels, etc.
Entourage effect	Yes	Yes
Where produced?	Outside - plants	In the body
Onset of action	Quick	Quick
Dependency	THC but not CBD	None
Present in the body for how long?	Varies, can be long	Short effect
Tolerance issues	Possibly	None
Side-effects	THC - psychotropic, CBD?	None
Dose	with CBD - Individual variation	Known, 1,200 mg per day

References

1. Russo E. Beyond Cannabis: Plants and the Endocannabinoid System Trends in Pharmacological Sciences, 2016; 37: 594-605
2. Gertsch, J. *et al.* Beta-caryophyllene is a dietary cannabinoid. Proc. Natl. Acad. Sci. U.S.A. 2008; 105: 9099–9104 48.
3. Gertsch, J. Anti-inflammatory cannabinoids in diet: towards a better understanding of CB2 receptor action? Commun. Integr. Biol. 2008;1: 26–28
4. Tambe, Y. *et al.* Gastric cytoprotection of the non-steroidal anti-inflammatory sesquiterpene, b-caryophyllene. Planta Med. 2006; 62: 469–470
5. Di Marzo, V. *et al.* Trick or treat from food endocannabinoids? Nature 1998; 396: 636–637
6. Pacher, P. and Kunos, G. Modulating the endocannabinoid system in human health and disease–successes and failures. FEBS J. 2013; 280: 1918–1943
7. McPartland, J.M. *et al.* Care and feeding of the endocannabinoid system: a systematic review of potential clinical interventions that upregulate the endocannabinoid system. PLoS ONE 2014; 9: e89566 5.
8. Russo, E.B. Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? Neuroendocrinol. Lett 2004; 25: 31–39
9. Hanus O.L. Pharmacological and Therapeutic Secrets of Plant and Brain (Endo) Cannabinoids. Med Res Rev 2009; 29: 213–271
10. Gertsch J. Cannabimimetic phytochemicals in the diet – an evolutionary link to food selection and metabolic stress adaptation? British Journal of Pharmacology 2017;174:1464–1483
11. Leonti M. *et al.* Falcarinol is a covalent cannabinoid CB1 receptor antagonistand induces pro-allergic effects in skin. BiochemPharmacol 2010; 79:1815–1826.
12. Nicolussi S. *et al.* Guineensine is a novel inhibitor ofendocannabinoid uptake showing cannabimimetic behavioraleffects in BALB/c mice. Pharmacol Res 2014; 80: 52–65
13. Thors L., Belghiti M., Fowler CJ. Inhibition of fatty acid amide hydrolase by kaempferol and related naturally occurring flavonoids. Br J Pharmacol 2008; 155: 244–252
14. Chicca A. *et al.* Functionalization of ß-caryophyllene generates novel polypharmacology in the endocannabinoid system. ACS ChemBiol2014; 9: 1499–1507.

PEA: AN OLD DOG WITH NEW TRICKS

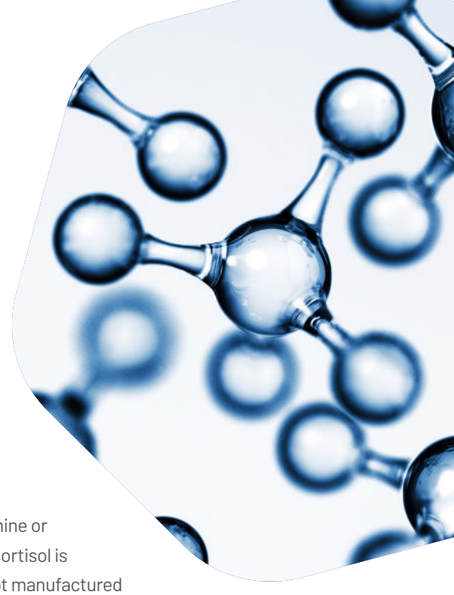
By Pamela Ovadje, PhD

For many years, lipids or fats were considered to be uninteresting oils with their only function being as an energy source, and building blocks for cell membranes. Today, lipids are recognized as critical players in different intracellular signaling processes throughout the body.

In 1929, the husband and wife research team of George and Mildred Burr, discovered that omega 6 fatty acids (e.g., from borage) were essential for health, and vital precursors in the biosynthesis of arachidonic acid a key molecule in health and disease. With the discovery in the early 1960s of prostaglandins from arachidonic fatty acid, a new and exciting era of lipid research was initiated. Edward Dennis of University of California at San Diego wrote:

> *"LIPIDS ARE IN MANY WAYS THE MOST IMPORTANT OF THE BIOMOLECULES BECAUSE THEY ARE THE ULTIMATE CONTROLLERS AND REGULATORS OF OUR BODILY PROCESSES; THEY ARE KEY TO SIGNALING EVENTS IN CELLS. FURTHER, IMBALANCES IN LIPIDS ARE IMPLICATED IN MANY ILLNESSES, SUCH AS HEART DISEASE, STROKE, ARTHRITIS, DIABETES AND ALZHEIMER DISEASE. IF WE ARE GOING TO SOLVE THESE DISEASES, WE MUST KNOW WHAT THE LIPIDS ARE AND WHAT THEY DO."*

The endocannabinoid system (ECS) is an extensive communication network which relies upon the endocannabinoids (eCB's) unique lipid signaling molecules. This lipid signaling network is a key modulator of physiological functions in many of the other network and signaling systems including the nervous system, the endocrine network, immune system, gastrointestinal tract, and the reproductive system, as well as other systems.



A unique feature of eCB's compared to classical neurotransmitter molecules, e.g., acetylcholine, dopamine or even hormones like cortisol is that the eCB's, are not manufactured in distant organs and then transported as packaged vesicles to other sites across the body, rather they are directly released from membranes at the site of disease and danger. This is a distinguishing feature of the eEC's as we shall see later!

Palmitoylethanolamide or PEA is a slightly tweaked, sixteen carbon chain fatty acid similar to the fatty acids found in palm, coconut, olive and other plant sources. A variety of plants are rich sources (e.g., alfalfa, corn, egg yolk, peanuts and particularly soy lecithin).

PEA is produced by the body whenever the demand arises. For example, when the body is under attack from bacterial or viral infections, UV damage, excess damage to the blood vessels by reactive oxygen species, or even when the blood glucose levels are consistently high.

PEA is a go-to-molecule that the body relies upon not only to communicate danger throughout the body with other organ systems, but also to counteract the immediate danger through PEA's wide and varied actions. So, it is both a signalling and a protective molecule.

Within the body, PEA is produced by specific enzymes that break down the phospholipid component of the cell membranes. This allows PEA to be called into action at a short notice, making it a key player for our body's defenses.

Strangely, few people have heard of PEA outside Europe despite its known health benefits for over sixty years!

The origins of PEA research started in 1939 when clinicians and researchers, Alvin Coburn and Lucille Moore, were looking to see how they could prevent the incidence of rheumatic fever in poor children living in New York who were highly susceptible to streptococcal throat infections. They discovered that four egg yolks could prevent and reduce rheumatic fever. But it took until 1957 for scientists at Merck Sharp and Dome to identify and isolate PEA as the molecule that provided this protection against streptococcal infection and rheumatic fever.

However, it wasn't until 1993 that research on PEA began in earnest when the mechanism of action of PEA was finally worked out. This was the work of Rita Levi-Montalcini, an Italian scientist, who back in 1954 had discovered the nerve growth factor (NGF), and thirty years later was awarded the Nobel Prize for this work.

Her discovery was that NGF activated specific immune cells called mast cells which caused inflammation and allergic reactions. And almost forty years later, Rita Levi-Montalcini discovered how another molecule, PEA, stopped the activation of mast cells thereby preventing inflammation and allergies. Furthermore, Levi-Montalcini discovered that PEA was produced locally by cells under threat from noxious and injurious external triggers, like UV-A, various toxins, allergens, infectious agents as well as other inflammatory agents, thereby reducing their threat. PEA was not only produced locally but also acted locally.

It seemed like PEA was called into action whenever when the body needed protection not only against outside triggers but also when the body was under threat from within, for example against ageing, or whenever the immune system was overactive as in various autoimmune disorders, which occur when the body stops recognizing friend from foe, and starts acting against itself. Mast cells are key components of the inflammatory response and PEA plays a major role in deactivating or "chilling" the mast cells.

Levi-Montalcini succinctly pointed out the interaction between PEA and the mast cell:

> *"...Unregulated mast-cell activation constitutes a considerable risk to the health of the organism, and it is not unreasonable to expect that nature should have devised a means for the host to defend itself against such damage. It has recently been proposed that saturated N-acyl-ethanolamides is like PEA, which accumulate in tissues following injury and which down modulate mast-cell activation, exert a local, and anti-injury function via mast cells. Palmitoylethanolamide is orally active in reducing tissue inflammation and mast cells."*

Once the mechanism of action of PEA was identified, there was a flurry of research on PEA, and new and interesting health benefits were soon discovered. Most of this research was from Italy which leads the world on research of this fascinating molecule.

As early as 1980, Dennis Epps pointed out that PEA had a tendency to accumulate in the damaged heart muscle due to ischemia or deprivation of oxygen, and this might be of physiological importance because of its anti-inflammatory properties. It was Epps who first suggested that these fatty molecules played a protective role, and that their presence, "may signify a response of myocardial tissue to injury directed at minimizing damage and promoting survival". In other words, PEA and PEA like molecules were quick to be at the site of danger to offer protection.

More recent studies have confirmed what Epps and his colleagues were saying. It has been shown in various animal disease models, and human tissue analysis that PEA protects various tissues: the colon, kidney and particularly the nervous tissue e.g., spinal cord injury, shock, stroke, MS and Alzheimer's. PEA blood levels are being considered as a biomarker for several of these diseases.

Currently there are number of animal and human studies on the application of PEA in the following conditions:

- Endometriosis
- Benign prostatic hyperplasia (BPH)
- Burning mouth syndrome
- Inflammatory bowel disease and syndrome (IBD/IBS)
- Depression
- Autism
- Transient brain injury
- Arthritis
- Pain, of various origins
- Coronary heart disease
- Chronic kidney disease
- Atopic dermatitis and eczema
- Vulvodynia
- Cannabis dependence
- Migraine
- Infectious diseases

Clinical Research: Immunomodulatory

Virtually all the initial studies on PEA have been conducted in Europe, especially worth mentioning are the five large-scale human studies in adults and one in children conducted in the 1970s in the former Czechoslovakia. These studies were very well planned and rigorously conducted. The results in every study was at least 30% to 60% protection compared to subjects not on PEA. There was reduced fever, pain, sore throats, coughs, muscle pain, feeling of weakness and loss of days at work or in school. PEA was found to "increase tolerance to bacterial toxins", in other words a general enhancer of the immune system and protection against colds and flu. Another huge advantage various health authorities noticed was PEA could be deployed quickly, efficiently and without side effects, against all sorts of influenza viruses, compared to vaccines which normally take time to prepare because of the time required to identify of what type of virus will be prominent that season.

CONCLUSION

In conclusion, PEA is an endogenously, and locally produced anti-injury molecule, whose sole function is to offer immediate protection, and down-modulate disease processes, and act against toxic insults in various systems of the body. It is highly likely that nature, in her infinite wisdom, devised such a system to call upon whenever demand arose.

PEA is unique because it is naturally produced by the body, it is a true orthomolecule, it is very safe, and the doses are well known for the anti-inflammatory, analgesic, neuro-protective effects like cognition and sleep. PEA may prove to be helpful in the opioid crisis as well as cannabis dependency, now that cannabis is legalized in many countries. These qualities are in contrast to the phytocannabinoids like THC or CBD from hemp or marijuana plant where the dose of CBD can fluctuate widely from 20 mg to over 1,200 mg and some patients may see different effects. From a practitioner's viewpoint, this makes prescribing particularly challenging. This isn't the case with PEA. Finally, PEA is safe in children and seniors and has no issues for use in sports or in people that may not want to use hemp or marijuana derived THC or CBD because of religious or moral issues.

References

1. Kuehl F.A. *et al.* (1957) The identification of N-2-hydroxyethyl-palmitamide as a natural occurring antiinflammatory agent. J Am ChemSoc 79: 5577-5578.
2. Epps D.E. *et al.* (1980) Accumulation of N-acylethanolamineglycerophospholipids in infarcted myocardium. BiochimBiophysActa 618: 420-430.
3. Esposito E, *et al.* (2011) Effects of palmitoylethanolamide on release of mast cell peptidases and neurotrophic factors after spinal cord injury. Brain BehavImmun 25: 1099-1112.
4. Keppel Hesselink J.M. and Hekker T.A. (2012) Therapeutic utility of palmitoylethanolamide in the treatment of neuropathic pain associated with various pathological conditions: a case series. J Pain Res 5: 437-442.
5. Petrosino S. *et al.* (2010) N-palmitoyl-ethanolamine: Biochemistry and new therapeutic opportunities. Biochimie 92: 724-727.
6. Gatti A. *et al.* (2012) Palmitoylethanolamide in the treatment of chronic pain caused by different etiopathogenesis. Pain Med 13: 1121-1130.
7. Keppel Hesselink, J. (2013) Professor Rita Levi-Montalcini on Nerve Growth Factor, Mast Cells and Palmitoylethanolamide, an Endogenous Anti-Inflammatory and Analgesic. Compound Pain Relief 2013, 2:1-5
8. Maccarrone, M. *et al.* (2015) Endocannabinoid signaling at the periphery: 50 years after THC Trends in Pharmacological Sciences, May 2015, Vol. 36, No. 5 277
9. Fezza, F. *et al.* (2014) Endocannabinoids, related compounds and their metabolic routes. Molecules 19, 17078–17106
10. Pacher, P. *et al.* (2006) The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol. Rev. 58, 389–462 28
11. Steffens, S. and Pacher, P. (2012) Targeting cannabinoid receptor CB2 in cardiovascular disorders: promises and controversies. Br. J. Pharmacol. 167, 313–323
12. Rapino, C. *et al.* (2014) Endocannabinoid as biomarkers of human reproduction. Hum. Reprod. Update 20, 501–516
13. Witkamp R. (2016) Fatty acids, endocannabinoids and inflammation. European Journal of Pharmacology785(2016) 96–107
14. Esposito, E.Cuzzocrea, S. 2013. Palmitoylethanolamide in homeostatic and traumatic central nervous system injuries. CNS Neurol. Disord.Drug Targets 12, 55–61.
15. Esposito, E. *et al.* 2011.Effects of palmitoylethanolamide on release of mast cell peptidases and neurotrophic factors after spinal cord injury. Brain Behav. Immun. 25, 1099–1112.
16. Fonseca, B.M. *et al.* 2013. Endogenous cannabinoids revisited: a biochemistry perspective. Prostaglandins Other Lipid Mediat.102–103,13–30.
17. Skaper, S. *et al.* 2013.Glia and mast cells as targets for palmitoylethanolamide, an anti-inflammatory and neuroprotective lipid mediator. Mol. Neurobiol. 48,340–352.
18. Skaper, S. *et al.* 2013. Palmitoylethanolamide, a naturally occurring disease-modifying agent in neuropathic pain. Inflammopharmacology, 1–16.
19. Skaper, S.D., DiMarzo,V. 2012. Endocannabinoids in nervous system health and disease: the big picture in a nutshell. Philos.Trans. R. Soc. B: Biol.Sci.367, 3193–3200.

INFLAMMATION AND THE ENDOCANNABINOID SYSTEM

By Dr. Traj Nibber, PhD

Inflammation is a defensive strategy present in higher organisms in reaction to the effects of tissue injury, microbial infection, and other harmful conditions. It is an important immune response by the body. However, inflammation is a double-edge sword.

Broadly speaking, inflammation can be classified into two types. The first, is the acute form, which is critical for body's ability to protect and heal itself, as well as preventing further damage. For example, following a cut or a badly twisted ankle, the damaged area quickly turns red, signifying increased circulation and activity of various inflammatory cells reaching the site of damage. There is swelling, which is accumulation of fluid, another sign of the presence of various players at the site of damage and pain, which is activation of pain and other receptors. The affected area increases in temperature to minimize infection, and finally, there is loss of function which is meant to restrict movement of the affected area so as to prevent further damage (see figure 1).

The second form is chronic, or the low-grade inflammation, which is highly damaging, and widely accepted as the basis for almost every other disease, from heart disease, various neurological diseases to even obesity and diabetes (see figure 2). Chronic inflammation is like being under a constant siege, or threat by barbarians ready to enter the gates or the battlements, which necessitates hastily (albeit poorly constructed) shoring up of the defenses. From a cellular perspective, this means formation of new connective tissue, which unfortunately, interferes with the structure and function of the normal tissue. In short, inflammation could be described as a response of living tissue to local injury which can be both beneficial or harmful, depending on the degree and duration of the inflammation.

FIGURE 1. The five cardinal signs of inflammation

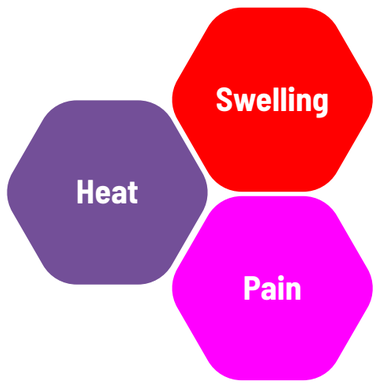
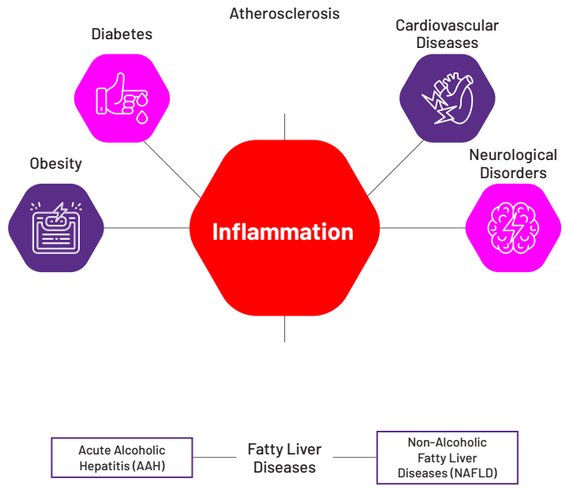


FIGURE 2. Inflammation and metabolic disorders



Understanding the Mechanism of Inflammation

Like all systems, there has to be a careful monitoring, and balance between the two states, thus ensuring that the acute form does not migrate into the chronic form. There are various players involved in the inflammatory process including cells, like macrophages (think of them as eater of the dead cells and cellular components!), receptors, such as toll-like receptors (TLRs), among others, all of which have a domino-like effect in orchestrating a cascade of activity in downstream systems like mitogen-activated protein kinase (MAPK), or the activation of a chemical called nuclear factor kappa-B (NF-κB).

NF-κB is a well-known inflammatory intermediary molecule that connects inflammation to various diseases. For example, pathogen-associated molecular patterns (PAMPs) from the surfaces of various pathogens (e.g., viruses) that stealthily enter the body, trigger cell surface receptors, called toll-like receptors (TLRs), which initiate a signaling pathway that activates NF-κB. NF-κB is one of the "bad" guys, and is normally found in the cytoplasm, where it is kept in check by an inhibitor molecule called of IκB. IkB binds the NF-κB in handcuffs, and prevents it from doing any mischief. However, interaction of cytokines or PAMP with cell surface TLRs begins a signaling sequence that brings another "bad guy", the inhibitor of κB kinase complex (IKK) into the picture. IKK "knocks out" IkB thereby freeing NF-kB to move into the nucleus where it turns on inflammatory genes.

Other pro-inflammatory chemical mediators, which include large families called cytokines and chemokines, are responsible for calling other inflammatory cells to the site of injury, and ensuring they are primed and armed to react. It is this overreaction that is the root cause of trouble in chronic inflammation.

Some of the cells called upon very early in the inflammatory process are the mast cells (MCs). Mast cells are known to be key players in the immune system, especially during allergic reactions. MCs are mobile chemical factories which are responsible for releasing a whole bunch of chemicals like proteases, histamine, leukotrienes, and many cytokines like tumour necrosis factor alpha (TNF-κ). When activated, MCs can either help defeat the invaders, or they can inflame an already worsening situation.

In humans, MCs preferentially reside in tissues that have access to the external environment, like the skin, lungs and the gastrointestinal tract, placing them in a prime position to encounter pathogens, and other external inflammatory stimuli.

Persistent inflammation can also induce pain that can progress from acute "nociceptive" pain to chronic "neuropathic" pain. There is evidence that MCs play an important role in the pathogenesis of chronic pain, and neuropathic pain in many diseases. MCs are key players in the pathology of allergies, endometriosis, migraine, primary MC disease, interstitial cystitis/bladder pain syndrome, chronic prostatitis, chronic pelvic pain, irritable bowel syndrome, vulvodynia, complex regional pain syndrome, fibromyalgia, and many more.

How do PEA, and other cannabimimetics reduce inflammation?

1. **MC stabilizers**
   Rita Levi Montalcini discovered in the early in the 1990s that PEA could stabilize the overactive MCs. It was like PEA coming to the scene with the raging and uncontrollable fires of inflammation all around the tissue, and putting cold water to dampen MCs activity and the ensuing fires. PEA is an excellent MC stabilizer, telling the rogue MCs to "chill out"! As such PEA could have application in all the conditions where MCs play a critical role.

   Preliminary observations showed that intake of a combination of PEA and various other ingredients like polydatin, a resveratrol precursor, reduced the severity of chronic pelvic pain and the size of endometriotic nodules in patients with endometriosis. The study has been completed, but the results have not yet been published. Other natural anti-inflammatories like quercetin, curcumin, boswellia etc. would make excellent combinations with PEA.

2. **Entourage effect via activation of PPARa, blocking of TRPV1, and reducing the breakdown of the eCBs**
   Number of studies suggest that PEA may be a key activator for peroxisome proliferator-activated receptor alpha (PPARa), which turns on the genes which reduce inflammatory. Likewise, PEA inhibits the TRPV1 receptor which is known to cause inflammation. Finally, a third anti-inflammatory mechanism of PEA maybe that it sacrifices itself to the enzymes that degrade eCBs like anandamide, allowing a longer effect of the eCBs which may explain the widely touted "entourage effect".

Neuroinflammation

Much remains to be learned about the signaling mechanisms that regulate neuroinflammation which may be the cause of many neurodegenerative diseases like Alzheimer's, Parkinson's, multiple sclerosis, ALS, dementia, depression and pain. However, it is becoming increasingly clear that the nerve cell or the neuron is constantly subjected to excessive "crosstalk" by a microglia–astrocyte–mast cell network, as a result of inadequate checks and balances of this network of cells, which results in the neuron becoming overwhelmed with excessive information with the end result of inflammation (Fig 4).

Skaper and colleagues in Italy have looked at the effects of PEA in controlling this excessive chatter between the microglia–astrocyte–mast cell network thereby reducing the assault on the neuron, thereby effectively reducing inflammation and pain.

Targeting endogenous regulators of neuroinflammation may therefore prove to be a viable way in dealing with diverse array of nervous system disorders. The capacity of PEA to modulate the protective responses of animals during inflammation and pain has led to the hypothesis that PEA may be an important player in homeostatic system controlling the basal threshold of both inflammation and pain. The production of PEA during inflammatory conditions supports this role, and emerging data that selective inhibition of PEA degradation is anti-inflammatory provides more direct evidence for the involvement of PEA in the control of pain and inflammation.

Inflammation and Metabolic Disorders

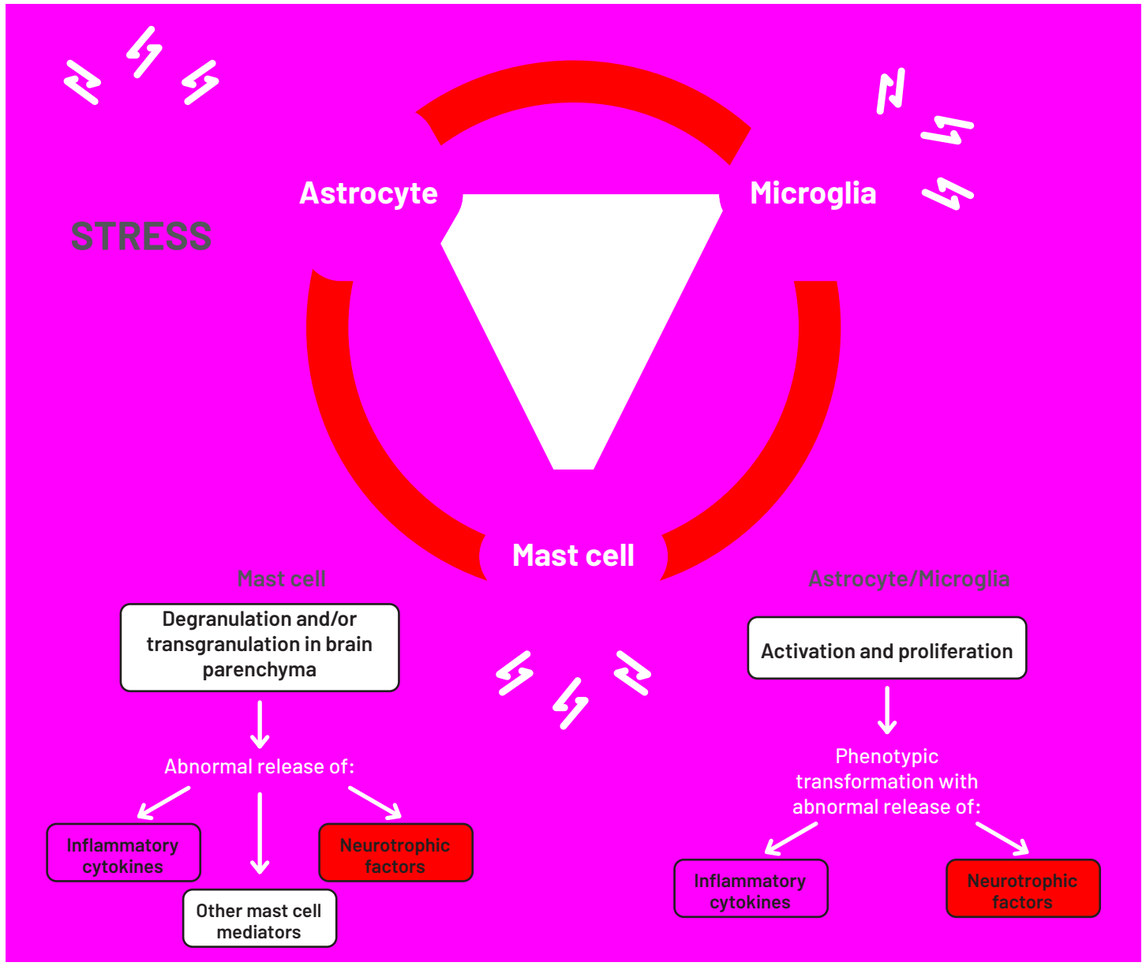
A high caloric intake coupled with inactive lifestyle leads to an increased incidence of obesity, type 2 diabetes, and cardiovascular diseases. Metabolism and inflammation are interrelated. Metabolic disorders display a strong inflammatory foundation, and inflammation is also linked to metabolic changes.

Whilst not many human studies have been conducted, it is conceivable that PEA and other cannabinmimetics could have a beneficial effect in metabolic syndrome as well as insulin resistance.

A recent human study showed a relationship between plasma PEA and metabolic risk factors as well as depression scores, with metabolic evolution being possibly mediated by PEA. Among patients with metabolic syndrome at baseline, 75% have resolved their cardio-metabolic risk factors at 12 months. In addition to weight loss and improvement of cardio-metabolic profile, the weight loss program could be beneficial in terms of psychological outcomes, eating disorders, and quality of life (QoL) improvement, even in subjects with no weight loss during the program. Of course this should be confirmed by larger clinical studies.

In summary, ECB like PEA may play a major role in controlling inflammation and pain through a variety of mechanisms.

FIGURE 3. Excessive interaction between astrocytes, MCs and microglia (cross-talk) as the cause of neuro-degeneration



Changes in palmitoylethanolamide levels during neuroinflammation

Disease; tissue or body fluid	Change	Main finding
Chronic relapsing experimental allergic encephalomyelitis; spinal cord	↑	~Twofold increase
Experimental acute stroke; striatal and cortical infarcted hemisphere	↑	~25-fold increase compared with controlateral (non-infarcted) areas
Experimental focal cerebral ischaemia; ischaemic cerebral cortex	↑	~25-fold increase compared with sham-operated animals; at 24 hr post-focal cerebral ischaemia
Cerebral ischaemia in man; penumbral tissue surrounding the primary ischaemic lesion (microdialysis study)	↑	Significantly increased levels within the first day after ischaemia
Chronic migraine or probable chronic migraine and probable analgesic-overuse headache; cerebrospinal fluid	↑	Significantly higher levels in the two patient groups (without significant difference between them) compared with control subjects
Chronic widespread pain and chronic neck-shoulder pain in women; microdialysis dialysate of the trapezius	↑	Significantly higher levels compared to healthy subjects, and correlation with pain intensity

Preclinical studies showing anti-neuroinflammatory and/or neuroprotective effects of palmitoylethanolamide

Model	Action
Compression model of spinal cord trauma in mice	Reduces spinal inflammation/tissue injury, ameliorates recovery of motor limb function Limits mast cell infiltration and activation; reduces activation of microglia and astrocytes
Traumatic brain injury in mice	Reduces edema and infarct size Improves neurobehavioural functions
MPTP mouse model of Parkinson's disease	Protects against MPTP-induced neurotoxicity, microglial and astrocyte activation, and functional deficits
Stroke (middle cerebral artery occlusion in rats)	Reduces oedema and infarct size Improves neurobehaviour impairments
β-Amyloid peptide injection in rat brain	Counteracts reactive gliosis Reduces behavior impairments
Chronic constriction injury in sciatic nerve	Anti-allodynic and anti-hyperalgesic effects Reduces mast cell activation Preservation of nerve structural integrity
Acute inflammation (formalin, dextran, carrageenan injection in rat hindpaw)	Reduces mast cell activation, tissue oedema, inflammatory/ mechanical hyperalgesia
WAG/Rij rat model of absence epilepsy	Anti-epileptic action

References

1. Hotamisligil, G.S. Inflammation and metabolic disorders. Nature 2006, 444, 860–867.
2. Libby, P. *et al.* Inflammation in atherosclerosis: Transition from theory to practice. Circ. J. 2010, 74, 213–220.
3. Dantzer, R. *et al.* From inflammation to sickness and depression: When the immune system subjugates the brain. Nat. Rev. Neurosci. 2008, 9, 46.
4. Naseri, R. *et al.* Anthocyanins in the Management of Metabolic Syndrome: A Pharmacological and Biopharmaceutical Review. Front. Pharm. 2018, 9.
5. Farzaei, M.H. *et al.* An update on dietary consideration in inflammatory bowel disease: Anthocyanins and more. Expert. Rev. Gastroenterol. Hepatol. 2018, 12, 1007–1024.
6. Farzaei, M.H. *et al.* Mechanistic review on plant-derived natural compounds as dietary supplements for prevention of inflammatory bowel disease. Expert. Rev. Gastroenterol. Hepatol. 2016, 10, 745–758
7. Graziottin A. *et al.* Mast cells in chronic inflammation, pelvic pain and depression in women Gynecol Endocrinol, 2014; 30: 472–477
8. Skaper S. *et al.* Mast cells, glia and neuroinflammation: partners in crime? Immunology, 2013; 141: 314–327
9. Keppel Hesselink J. M. Evolution in pharmacologic thinking around the natural analgesic palmitoylethanolamide: from nonspecific resistance to PPAR-α agonist and effective nutraceutical. Journal of Pain Research 2013:6 625–634
10. Keppel Hesselink J. M. Palmitoylethanolamide (PEA)–'Promiscuous ' anti-inflammatory and analgesic molecule at the interface between nutrition and pharma. PharmaNutrition 2014; 2: 19–25
11. Palazzo E. *et al.* Role of N-Acylethanolamines in the Neuroinflammation: UltramicronizedPalmitoylethanolamide in the Relief of Chronic Pain and Neurodegenerative Diseases. Neuropsychiatry (London) 2019; 9: 2035–2046

GETTING TO THE ROOT OF CHRONIC PAIN

By Dr. Pamela Ovadje, PhD

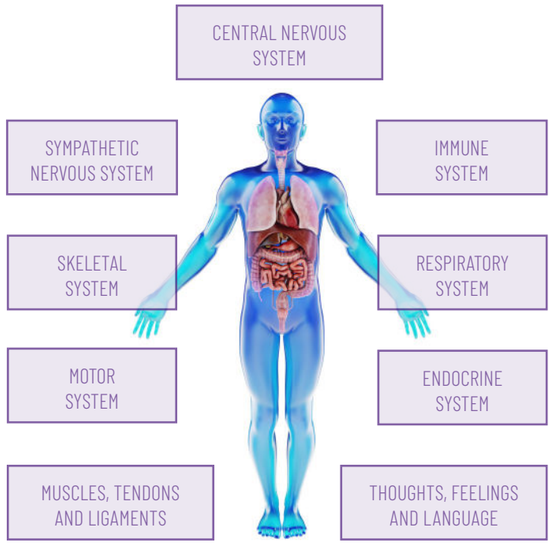
PAIN

The old school way of thinking about pain is usually centered around the idea that pain is a sign of tissue damage or pathology and is an accurate indication of your health, as it was caused by pain pathways. Pain and tissue damage are poorly related, as pain is an unreliable indicator of the presence of amount of tissue damage and one can exist without the other. This old way of thinking is not necessarily inaccurate, but it does leave a lot of room for unaccounted issues. Generally, pain is a very complex experience and individuals experience, perceive, respond to and manage pain differently.

The new understanding of pain takes into account that pain is a sign of the perceived need of an individual's need to protect body tissue. It understands that all pain is meaningful and there is a biopsychosocial recognition. This model is more holistic and ensures that pain is assessed by looking at all body systems.

WHAT IS INVOLVED IN PAIN EXPERIENCES?

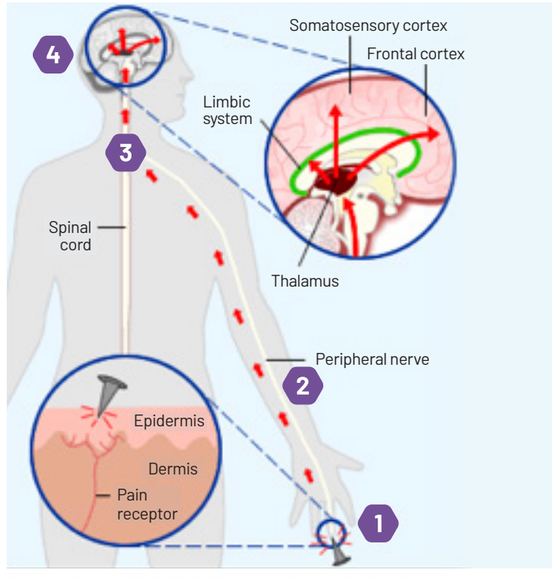
Short answer? Everything is involved! Longer answer, Figure 1 (adapted from Alberta Health Services Primary Health Care Resource Centre) looks at all the systems involved in the pain experience.



All of these systems provide information to the brain and that determines how we experience pain. When we feel pain, sensory receptors in different parts of our bodies send messages through nerve fibres to the spinal cord and brainstem and then onto the brain, which registers the type of pain and results in the sensation of pain.

The nature of pain is highly personal. Pain has both sensory (somatic) and psychological (affective) components (Welch, 2009).

HOW YOU FEEL PAIN: THE PAIN PATHWAY



WHAT IS CHRONIC PAIN?

Pain is generally classified as either acute or chronic. Acute pain is considered a normal reaction to injury and should not last very long; it is usually gone within three months following assault/injury. Persistent or chronic pain happens with longer exposure to pain signals. This is longer-lasting pain, which can be intermittent and may vary with intensity or remain persistent and generally lasting longer than three months. It is sometimes a result of an underlying health condition, such as chronic fatigue syndrome, arthritis, fibromyalgia, inflammatory bowel disease to name a few.

Over the last two decades, the consensus from published articles suggest that, irrespective of gender differences, approximately 40-50% of the population experiences persistent pain lasting longer than three months, especially longer than six months. The disparity was found in the intensity of perception of pain and the interference of pain on daily life activities. This prevalence of pain increases with age and most of the pain reported (approximately 90%) is localized to the musculoskeletal system (Andersson *et al.*, 1993; Gibson & Lussier, 2012; Souza *et al.*, 2017). It is important to note that there is increased dissatisfaction with chronic pain management, as such requiring better pain management options.

Chronic pain (CP) is a multidimensional health condition, which is more related to peripheral and central nervous sensitization than to exclusive duration time. CP is not just considered a symptom but a disease, classified as R 52.1 under the wrong name of intractable diseases. It is considered a health crisis, due to its increased prevalence and associated physical and emotional incapacity (Gureje *et al.*, 1998; Merskey and Bogduk, 2012; Katz *et al.*, 2015; Lynch 2015). CP is classified according to its pathophysiology – nociceptive pain, neuropathic pain and pain without a known somatic background.

Neuropathic pain (NPP) is a faction of chronic pain caused by a lesion or dysfunction of the peripheral or central nervous system. It can result from surgery and various health conditions, including diabetes, infections, multiple sclerosis, spinal cord lesions and cancer. NP is underdiagnosed and difficult to treat, and with a prevalence anywhere between 1% and 18% of the population, this does represent a significant health crisis (Bouhassira *et al.*, 2008; Cruccu & Truini, 2017; Attal, Bouhassira, & Baron, 2018). This is a long-term pain characterized as a burning, tingling, shooting pain or electric sensations. It is associated with physical damage to nerves and a failure of the spinal cord to dampen down the pain sensations.

1. Pain receptors (nociceptors) in the skin are activated by tissue damage.
2. A signal travels up the peripheral nerve to the spinal cord.
3. Within the spinal cord, chemical messengers (neurotransmitters) are released. These activate other nerves that pass signals to the brain.
4. The thalamus relays the signals on to the somatosensory cortex (sensation), frontal cortex (thinking) and limbic system (emotional response)

DEALING WITH CHRONIC PAIN

Managing or treating chronic pain is essential, as unattended pain can have far-reaching effects, including social isolation, psychological effects and economic impacts, due to a struggle/inability to work for people experiencing severe chronic pains.

Chronic pain is a frequent reason for many physician visits, especially in the elderly population.

Treating or managing chronic or neuropathic pain requires understanding of the underlying cause of the pain and the pain pathways that are associated with it. Pain management is usually multidisciplinary, with the main goal being the improvement in the quality of life of those living with pain. Pain management involves the use of opioid, non-opioid or alternative medicines. Although non-opioid medications, such as NSAIDs (non-steroidal anti-inflammatory drugs) or acetaminophen-based drugs, are initially recommended, depending on the type and source of pain, opioid recommendations still see a high use among medical practitioners, compared to other pain management techniques. Unfortunately, medical practitioners cannot predict which patients will develop an addiction, and as such believe that withholding, interrupting or withdrawing treatment corresponds to causing more harm (Gatchel *et al.*, 2014; Reuben *et al.*, 2015; Dowell *et al.*, 2016; Busse *et al.*, 2017).

Outside of disease conditions, like cancer, chronic pain is strongly linked chronic inflammation, so outside of pharmaceutical drugs for inflammation, like NSAIDs, an anti-inflammatory diet or supplementation can be beneficial in dealing with pain caused by chronic inflammation. Regrettably, the available research focusing on anti-inflammatory diets and supplements are rare, which makes it difficult to come to a consensus on the best treatment options for inflammation and pain (Dowell *et al.*, 2016;Busse *et al.*, 2017).

It has been established that more than half of the patients dealing with chronic pain are dissatisfied with their treatment options, indicating a need for safer, more effective pain treatment/ management options.

THE ENDOCANNABINOID SYSTEM AND CHRONIC PAIN

Since the discovery of the first cannabinoid receptor, over 30 years ago, advances in research have identified the important system that has a major control in the human body. The Endocannabinoid System (ECS), identified about 50 years ago and determined to be a separate system in the 1980s, is one of the most sophisticated, pleiotropic signalling systems that exists in vertebrates – it is present all over the human body. This system, when in prime condition, has far-reaching effects throughout the body, supporting many basic needs. It is involved in all aspects (Piomelli *et al.*, 2000; Bifulco, 2009).

Although the ECS was discovered thanks to all the research into the benefits of the cannabis plant, it should be noted that the ECS does not exist because of this plant. It exists because we naturally produce compounds that interact with the cannabinoid receptor and have downstream effects (paraphrased from Dr. Raphael Mechoulam).

The ECS is composed of the cannabinoid receptors, the endocannabinoids that target these receptors and the biochemical machinery to produce these lipids (enzymes that help synthesize and break down the endocannabinoids). New research has identified new players in the ECS. These include other receptors, protein channels and fatty acid amides with structural similarities to the original endocannabinoids, anandamide, 2-arachidonoylglycerol and N-arachidonoyl dopamine. This network plays an important role in stress response, metabolism, cognitive health, energy, pain, inflammation, muscle control, gut health and vision (Jhaveri *et al.*, 2007; Di Marzo & Wang, 2014; Walker, 2016).

The auto-protective role of endocannabinoids has been widely documented in several pathological conditions: thermal, neuropathic and inflammatory pain, multiple sclerosis, cancer, intestinal disorders, post-traumatic stress or phobias or anxiety, excitotoxicity and traumatic brain injury, hemorrhagic, septic or cardiogenic shock, hypertension, and atherosclerosis (Piomelli *et al.*, 2000). Specifically, the role of the ECS in pain development and management has been of major interest, since research has shown that the ECS has a major role in regulating pain sensation, with modulatory actions at all stages of pain processing pathways. Additionally, the introduction of the theory of clinical endocannabinoid deficiency (CECD), which suggests that a physiological decrease in endocannabinoid levels can contribute to the development of several conditions, including a lowered pain threshold (Guindon & Hohmann, 2012; Russo, 2016; Woodhams *et al.*, 2017), leading to increased perception of pain.

Since endocannabinoids modulate pain under physiological conditions (Welch, 2009), developing pharmacological approaches that enhance the functioning of the endocannabinoid system,

e.g., by increasing levels of endogenous cannabinoids, inhibiting enzymes that control endocannabinoid deactivation or blocking the reuptake of the endocannabinoids, could be used to improve therapeutic potential of the ECS.

THE CONNECTION BETWEEN PEA, THE ECS AND CHRONIC PAIN

Current typical pain management interventions for chronic pain may well lack long-term benefits, even discounting the side effects commonly associated with common treatment options like opioids and NSAIDs. These treatment options are linked to long-term addiction/misuse issues, in the cases of opioids, and serious gastrointestinal issues, in the case of NSAIDS (Sostres *et al.*, 2010; Gatchel *et al.*, 2014).

The use of phytocannabinoids, especially CBD and THC for chronic pain, and other health conditions, in anecdotal and increasing clinical evidence, point to the usefulness of the ECS in regulating health and disease states. Due to the lack of knowledge surrounding the exact mechanism of action of cannabis and its phytocannabinoids in human health, there are many ongoing and impending clinical trials, on clinicaltrials.gov alone, there are 592 studies registered for the use of CBD in health and diseases, with 110 studies just for CBD and its use in pain and 41 completed studies. Similar numbers are listed for THC's use in health and disease, especially in pain models. The completed studies trend towards the positive, with CBD or THC treatment providing a better pain response, compared to the comparative product/placebo.

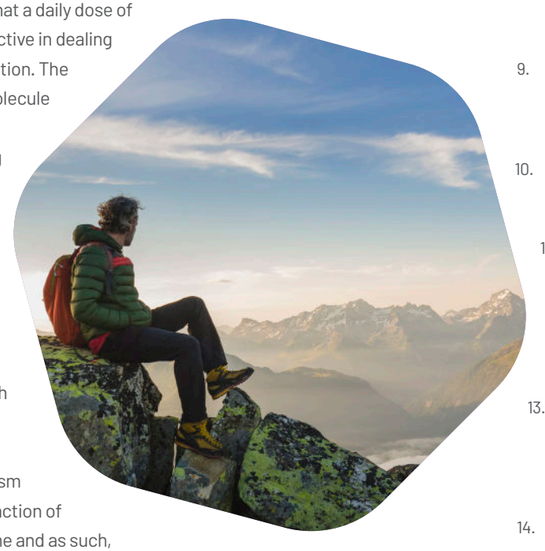
The issues with cannabis/CBD/THC or the other phytocannabinoids, even with all the ongoing clinical studies, is the lack of consistency. The products are different, the extraction methods are different, the study models are different and the clinical doses are vastly different. This makes it difficult to establish a common treatment plan with cannabis or its phytocannabinoids.

Palmitoylethanolamide (PEA) is a fatty acid amide, with a similar chemical structure to endogenous cannabinoids, anandamide (AEA). Both PEA and AEA belong to the family of lipids, known as N-acylethanolamines (De Petrocellis *et al.*, 2001; Paladini *et al.*, 2016). PEA is widely distributed in different body tissues and can be found in many different food sources. Following its discovery, research focused on the molecular mechanisms by which PEA exerts its activity. Initially thought to act by interacting directly with the CB2 receptor, research now shows that PEA acts through multiple mechanisms. The fact that PEA has only a weak affinity for the CB1 and CB2 receptors means that antagonists of conventional cannabinoid receptors do not inhibit the activity of PEA.(Petrosino and DiMarzo, 2017).PEA can act via direct activation of at least two different receptors: the PPAR-α and the orphan receptor, GPCR55. Additional evidence suggests that PEA directly inhibits the expression of FAAH, the enzyme responsible for the degradation of AEA, promoting further activity of AEA on downstream signalling through the ECS.

PEA can also indirectly activate the transient receptor potential vanilloid receptor type 1 (TRPV1) channels. These channels are also targets for endocannabinoids and endocannabinoid-like molecules. Since PEA inhibits the degradation of endogenous cannabinoids AEA and 2-AG, these molecules are free to interact with TRPV1, CB1 and CB2 receptors. The activation of TRPV1 channels and interactions with Peroxisome Proliferator-Activated Receptor alpha(PPAR-α), leading to increased expression of CB2 receptors shows the multi-reach of PEA, promoting what is now known as the "Entourage Effect" to establish its important therapeutic effects, both in the central and peripheral nervous system (Anand *et al.*, 2009; Hesselnik, 2012).

The research by Dr. Rita Levi-Montalcini led to the wide use of PEA as a painkiller, by neurologists and pain specialists, in the first decade of this century. Additional research has established the role of PEA in inflammation and pain.

It should be noted that, unlike cannabis and its phytocannabinoids, the mechanism of action of PEA and its effective doses and safety have been well established. Safety and efficacy doses of PEA are well known. Studies show that a daily dose of 1,200 mg of PEA is effective in dealing with pain and inflammation. The safety profile of this molecule ensures that non-responders to 1,200 mg can be prescribed higher doses of PEA, with little likelihood of serious adverse events. Furthermore, the PEA has a calming effect on overactive genes, which code for inflammation and pain signalling, to adapt cellular metabolism (Hesselnik, 2018). This action of PEA requires ample time and as such, PEA should be used long term, as it is not a quick fix but a long-term solution to balancing out the ECS for better health, improved response to pain signalling and reduction in the causes of chronic pain.



References

1. Andersson, H. I., Ejlertsson, G., Leden, I., & Rosenberg, C. (1993). Chronic Pain in a Geographically Defined General Population: Studies of Differences in Age, Gender, Social Class, and Pain Localization. The Clinical Journal of Pain, 9, 174–182. https://doi.org/10.1542/peds.2004-0682
2. Merskey, H and Bogduk, N. "Classification of chronic pain: descriptions of chronic pain syndromes and definitions of pain terms/prepared by the international association for the study of pain," in Task Force on Taxonomy, 2nd edition, 1994, Update 2012, http://www.iasp-pain.org/PublicationsNews/Content.aspx? ItemNumber=1673
3. Souza, J. B. De, Grossmann, E., Perissinotti, Di. M. N., Oliveira Junior, J. O. De, Fonseca, P. R. B. Da, & Posso, I. D. P. (2017). Prevalence of Chronic Pain, Treatments, Perception, and Interference on Life Activities: Brazilian Population-Based Survey. Pain Research and Management, 2017. https://doi.org/10.1155/2017/4643830
4. J. Katz, B. N. Rosenbloom, and S. Fashler, "Chronic pain, psychopathology, and DSM-5 somatic symptom disorder," Canadian Journal ofPsychiatry,vol.60,no.4,pp.160–167,2015
5. O. Gureje, M. von Korff, G. E. Simon, and R. Gater, "Persistent pain and well-being: a World Health Organization study in primary care," The Journal ofthe AmericanMedical Association, vol. 280, no. 2, pp. 147–151, 1998
6. M. E. Lynch,"What is the latest in pain mechanisms and management?" Canadian Journal of Psychiatry,vol.60,no.4, pp.157–159,2015
7. Cruccu, G., & Truini, A. (2017). Neuropathic Pain: The Scope of the Problem. Pain and Therapy, 6(S1), 1–3. https://doi.org/10.1007/s40122-017-0086-1
8. Attal, N., Bouhassira, D., & Baron, R. (2018). Diagnosis and assessment of neuropathic pain through questionnaires. The Lancet Neurology, 17(5), 456–466. https://doi.org/10.1016/S1474-4422(18)30071-1
9. Bouhassira, D., Lantéri-Minet, M., Attal, N., Laurent, B., & Touboul, C. (2008). Prevalence of chronic pain with neuropathic characteristics in the general population. Pain, 136(3), 380–387. https://doi.org/10.1016/j.pain.2007.08.013
10. Gibson, S. J., & Lussier, D. (2012). Prevalence and Relevance of Pain in Older Persons. Pain Medicine, 13(SUPPL. 2). https://doi.org/10.1111/j.1526-4637.2012.01349.
11. Dowell, D., Haegerich, T., & Chou, R. (2016). CDC Guideline for Prescribing Opioids for Chronic Pain—United States, 2016. JAMA, 315(15), 1624–1645. https://doi.org/10.1111/mcn.12149
12. Gatchel, R. J., McGeary, D. D., McGeary, C. A., & Lippe, B. (2014). Interdisciplinary chronic pain management. American Psychologist, 69(2), 119–130. https://doi.org/10.1037/a0035514
13. Reuben, D. B., Alvanzo, A. A. H., Ashikaga, T., Bogat, G. A., Callahan, C. M., Ruffing, V., & Steffens, D. C. (2015). National Institutes of Health Pathways to Prevention Workshop: The role of opioids in the treatment of chronic pain. Annals of Internal Medicine, 162(4), 295–300. https://doi.org/10.7326/M14-2775
14. Busse, J. W., Craigie, S., Juurlink, D. N., Buckley, D. N., Li, W., Couban, R. J., … Guyatt, G. H. (2017). Guideline for opioid therapy and chronic noncancer pain. Cmaj, 189(18), E659–E666. https://doi.org/10.1503/cmaj.170363
15. Piomelli, D., Giuffrida, A., Calignano, A., & Rodríguez de Fonseca, F. (2000). The endocannabinoid system as a target for therapeutic drugs. Trends in Pharmacological Sciences, 21(6), 218–224.
16. Bifulco, P. M. (2009). The endocannabinoid system: From biology to therapy. Pharmacological Research, 60(2), 75–76. https://doi.org/10.1016/j.phrs.2009.04.015
17. Walker, J. M. (2016). Endo- cannabinoid Signaling IN Series Editor. https://doi.org/10.1007/978-1-4939-3539-0
18. Di Marzo, V., & Wang, J. W. (2014). The Endocannabinoidome: The World of Endocannabinoids and Related Mediators. The Endocannabinoidome: The World of Endocannabinoids and Related Mediators. https://doi.org/10.1016/C2013-0-13461-7
19. Jhaveri, M. D., Richardson, D., & Chapman, V. (2007). Endocannabinoid metabolism and uptake: Novel targets for neuropathic and inflammatory pain. British Journal of Pharmacology, 152(5), 624–632. https://doi.org/10.1038/sj.bjp.0707433
20. Welch, S. P. (2009). Interaction of the cannabinoid and opioid systems in the modulation of nociception. International Review of Psychiatry, 21(2 SPEC. ISS.), 143–151. https://doi.org/10.1080/09540260902782794
21. Woodhams, S. G., Chapman, V., Finn, D. P., Hohmann, A. G., & Neugebauer, V. (2017). The cannabinoid system and pain. Neuropharmacology, 124, 105–120. https://doi.org/10.1016/j.neuropharm.2017.06.015
22. Guindon, J., & Hohmann, A. (2012). The Endocannabinoid System and Pain. CNS & Neurological Disorders - Drug Targets, 8(6), 403–421. https://doi.org/10.2174/187152709789824660
23. Russo, E. B. (2016). Clinical Endocannabinoid Deficiency Reconsidered: Current Research Supports the Theory in Migraine, Fibromyalgia, Irritable Bowel, and Other Treatment-Resistant Syndromes. Cannabis and Cannabinoid Research, 1(1), 154–165. https://doi.org/10.1089/can.2016.0009
24. Welch, S. P. (2009). Interaction of the cannabinoid and opioid systems in the modulation of nociception. International Review of Psychiatry, 21(2 SPEC. ISS.), 143–151. https://doi.org/10.1080/09540260902782794
25. Sostres, C., Gargallo, C. J., Arroyo, M. T., & Lanas, A. (2010). Adverse effects of non-steroidal anti-inflammatory drugs (NSAIDs, aspirin and coxibs) on upper gastrointestinal tract. Best Practice and Research: Clinical Gastroenterology, 24(2), 121–132. https://doi.org/10.1016/j.bpg.2009.11.005
26. Anand, P., Whiteside, G., Fowler, C. J., & Hohmann, A. G. (2009). Targeting CB2 receptors and the endocannabinoid system for the treatment of pain. Brain Research Reviews, 60(1), 255–266. https://doi.org/10.1016/j.brainresrev.2008.12.003
27. Paladini, A., Fusco, M., Cenacchi, T., Schievano, C., Piroli, A., & Varrassi, G. (2016). Palmitoylethanolamide, a special food for medical purposes, in the treatment of chronic pain: A pooled data meta-analysis. Pain Physician, 19(2), 11–24.
28. De Petrocellis, L., Davis, J. B., & Di Marzo, V. (2001). Palmitoylethanolamide enhances anandamide stimulation of human vanilloid VR1 receptors. FEBS Letters, 506(3), 253–256. https://doi.org/10.1016/S0014-5793(01)02934-9
29. Petrosino, S., & Di Marzo, V. (2017). The pharmacology of palmitoylethanolamide and first data on the therapeutic efficacy of some of its new formulations. British Journal of Pharmacology, 174(11), 1349–1365. https://doi.org/10.1111/bph.13580
30. Hesselink, J. M. K., & Hekker, T. A. M. (2012). Therapeutic utility of palmitoylethanolamide in the treatment of neuropathic pain associated with various pathological conditions: A case series. Journal of Pain Research, 5, 437–442. https://doi.org/10.2147/JPR.S32143
31. Hesselink, J. (2018). Chronic Pain and the Use of Palmitoylethanolamide. Austin Journal of Neurological Disorders & Epilepsy, 5(2), 1042.
32. Passavanti, M. B., Alfieri, A., Pace, M. C., Pota, V., Sansone, P., Piccinno, G., … Fiore, M. (2019). Clinical applications of palmitoylethanolamide in pain management: protocol for a scoping review. Systematic Reviews, 8(1), 18–21. https://doi.org/10.1186/s13643-018-0934-z

ENDOMETRIOSIS, PAIN AND THE USE OF PALMITOYLETHANOLAMIDE (PEA)

By Dr. Sarah Zadek, ND

Endometriosis is a painful disorder characterized by the presence of endometrial (uterine) tissue in other locations, outside the uterus. This can include on or around the ovaries, on other structures within the pelvic cavity, and even in other locations around the body. Having space-occupying lesions can be intrusive enough, but because they are made of endometrial tissue, these lesions respond to hormonal signals such as estrogen. Therefore women often experience extreme pain throughout the menstrual cycle, often surrounding both ovulation and menstruation.

Pain in endometriosis can also commonly be experienced with intercourse (dyspareunia), with bowel movements (dyschezia), and can occur chronically without necessarily being linked to the menstrual cycle.

Because pain can occur so frequently and regularly, it makes standard treatment like non-steroidal anti-inflammatories (NSAIDs) common, but far from ideal and potentially dangerous.

A common side effect of NSAIDs are stomach aches and pain which can lead to the development of ulcers with chronic use. More disturbingly, in 2015 the FDA strengthened their warning on NSAID use stating that even short-term use, as little as a few weeks, can increase the risk of stroke, heart attack and death.[1] This risk may increase with longer use which makes women with endometriosis more vulnerable and in need of other safer, treatment options.

Among new approaches in endometriosis treatment is the use of palmitoylethanolamide (PEA): an endocannabinoid-like molecule being revered for its efficacy in decreasing chronic pain.

TREATING ENDOMETRIOSIS WITHOUT NSAIDS

Inflammatory responses play major roles in the development and progression of endometriosis. Endometriotic cells manage to escape destruction by the immune system by secreting chemical messengers called cytokines.[2] These cells also have increased expression of an enzyme called cyclooxygenase-2 (COX-2), which forms prostaglandin compounds involved in inflammation.3 As well, the activation of mast cells, which secrete histamine, may also contribute.[4] Mast cells, when activated, can communicate with pain nerve fibres, creating more hypersensitive pain reactions.

Endometriotic lesions can be surgically removed, but without controlling immune responses and hormonal signals, there is a risk of them recurring. This is why hormonal contraceptive medications are often used to help suppress and prevent growth of lesions. However, many women cannot tolerate hormonal birth control, or may be looking to become pregnant and therefore need to avoid hormonal contraceptives.

Naturopathic and orthomolecular medicines have much to offer in these situations as there are alternative anti-inflammatory, anti-tumour agents, and other options for pain. Most recently, researchers have been investigating the role of the endocannabinoid system in pain and inflammation.

PEA AND RESVERATROL

PEA in particular is a lipid mediator produced naturally in the body with analgesic and anti-inflammatory properties. Although PEA doesn't bind to cannabinoid receptors CB1 and CB2 itself, it acts as a mediator, communicating with other systems such as the nervous system and hormonal systems. As well, it can help increase the effect of the body's own endocannabinoids.

In cases when the body is stressed or injured, PEA is released to help direct the immune response. Most interestingly, PEA has been shown to stabilize mast cells and microglia cells, basically deactivating them. In doing so, PEA can reduce the hyper-sensitization of pain nerve fibers that would communicate with the nervous system, causing pain sensations.[4]

Multiple trials have shown that PEA is more effective than placebo in the treatment of chronic pelvic pain.[4] In endometriosis specifically, PEA has been used in multiple clinical trials with a resveratrol precursor called trans-polydatin.

Resveratrol has often been used in naturopathic treatment protocols for endometriosis due to its multiple anti-inflammatory, anti-oxidant and apoptotic actions.[5] Specifically, resveratrol can inhibit COX-2, and therefore the production of prostaglandins, and in experimental models has been shown to support the regression of lesions.[4,5]

The growth of lesions is often supported by the presence of vascular endothelial growth factor (VEGF): a compound that stimulates the production of new blood supply to tissue. One of the actions of resveratrol is as an anti-angiogenic substance, preventing tumours and lesions from developing their own blood supply. This helps prevent the funneling of even more immune and inflammatory molecules to these areas, and helps control the size of lesions.[3]

When combined, PEA and this resveratrol precursor have been shown to significantly reduce chronic pelvic pain in women with endometriosis. In a meta-analysis of four studies which included 80 patients with endometriosis-related pain, treatment significantly reduced pelvic pain, dysmenorrhea and dyspareunia within three months.[4] Not only were improvements in pain documented, but this was also in comparison to placebo. Dosing in most cases and trials used were 600 mg to 800 mg of PEA and 60 mg to 80 mg of polydatin daily, in divided doses.

Although researchers are still working out specific mechanisms on the development of endometriosis and the resulting pain, these new clinical studies are showing a lot of promise.

CONCLUSIONS

Pain management is a primary goal in the treatment of endometriosis. Although conventional treatments include the use of NSAIDs and hormonal contraceptives, these may not be viable options for many women, or may not be safe or tolerated.

Overall, inflammation and immune function play a huge role when it comes to managing the growth of lesions and the pain that accompanies them.

PEA's anti-inflammatory actions seem to work in conjunction with its ability to decrease both peripheral and central mechanisms of pain sensitization. More so, when combined with a resveratrol precursor, chronic pelvic pain is significantly reduced in addition to the potential action of shrinking or preventing the growth of lesions.

References

1. FDA Drug Safety Communication: FDA strengthens warning that non-aspirin nonsteroidal anti-inflammatory drugs (NSAIDs) can cause heart attacks or strokes. (2015) U.S. Food and Drug Administration https://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-strengthens-warning-non-aspirin-nonsteroidal-anti-inflammatory
2. Podgaec S. *et al.* "Th1 and Th2 immune responses related to pelvic endometriosis." Rev. Assoc. Med. Bras. 2010; 56(1): 92-98
3. Zito G. *et al.* "Medical Treatments for Endometriosis-Associated Pelvic Pain" Biomed Res Int. 2014; Article ID 191967.
4. Indraccolo U, Indraccolo SR, Mignini F. Micronized palmitoylethanolamide/trans-polydatin treatment of endometriosis-related pain: a meta-analysis. Ann Ist Super Sanita. 2017 Apr-Jun; 53(2): 125-34
5. Dull AM, Moga MA, Dimienescu OG, Sechel G, Burtea V, Anastasiu CV. Therapeutic approaches of resveratrol on endometriosis via anti-inflammatory and anti-angiogenic pathways. Molecules. 2019 Feb 13; 24(4). pii: E667

PEA: A NOVEL APPROACH TO THE MANAGEMENT OF COLDS AND FLU

By Dr. Sarah Zadek, ND

Cold and flu season is upon us, making it primetime for boosting the immune system and increasing our prevention tactics. There are many dietary and supplemental strategies to help improve immune function, especially in an effort to help decrease the need for antibiotics.

Palmitoylethanolamide (PEA) is a lipid signalling molecule that helps modulate immune system responses. This endocannabinoid-like molecule is made by the body in response to inflammation, injury and infection, but is also found in many foods such as egg yolks, soybeans, soy lecithin, peanut oil and alfalfa.

PEA FOR MANAGEMENT OF COLDS AND FLU

Research on PEA started decades ago and focused on using PEA to prevent and treat infections in children and adults. The first double-blind controlled trials on PEA tested its efficacy on upper respiratory tract infections (colds and flu), both for prevention and treatment.

The prevention trial included 899 volunteers who were given 600 mg of PEA three times daily for the first three weeks, then just 600 mg once daily for six weeks. Compared to a group given placebo, the PEA group had a significantly lower incidence (40%) of illness by the end of the six-week trial.

In children aged 11-15 years, those given 300 mg of PEA twice daily for eight weeks had 15.7% fewer acute respiratory tract infections than those given placebo.

In the treatment trial, 1304 patients were given 600 mg three times daily for 12 days. Those who took PEA had fewer episodes of fever, headache, and sore throat compared to the group given placebo. Fever and pain were significantly reduced by 45.5% and the duration of illness was also reduced in the PEA treatment group.

Even though PEA is an endocannabinoid-like molecule, it's not technically an endocannabinoid, nor does it have any psychotropic effects. It actually doesn't bind directly to CBD1 or CBD2 receptors, but instead acts as a modulator. Its ability to influence, enhance and affect immune and inflammatory pathways make it a key molecule for controlling both infections and inflammation.

AGE-RELATED IMMUNE DECLINE

Research on this incredible molecule hasn't stopped. More recently, researchers have tested how well PEA holds up in cases of the aging immune system. As we age, there are definite changes in how well the immune system functions. The result of this change is responsible for the decrease in vaccine responses and the increased incidence and severity of infections in the elderly.

PEA has been recognized as a supportive therapy in this population. Specifically, PEA can help limit the number of infections experienced in the elderly population, and counteract the excessive inflammation that occurs as a result of infection.

CLEARING INFECTION AND PROTECTING COGNITIVE FUNCTION IN THE ELDERLY

In animal studies, researchers have shown that PEA increases the activity of microglial cells. These are specialized immune cells specific to the brain and spinal cord. Their main job is to clear away damaged neurons and infections in the central nervous system.

In the elderly, microglial cells tend to be over-reactive and can prolong the inflammatory response when an infection occurs. Having this excessive inflammation can lead to cognitive deficits. When comparing the activity of young versus old microglia cells in animal studies, older cells cannot clear away bacterial infections as well.

As a modulator, PEA has been shown to eliminate bacteria in cases of bacterial meningitis. In a specific study, aged animals were pretreated with PEA and then infected with a pathogenic strain of E. coli (E. Coli K1 meningitis). Mice pretreated with PEA survived longer, but also had lower bacterial counts in the spleen, liver and blood than in non-PEA treated animals.

Researchers also found less pro-inflammatory mediators in circulation (signals and molecules known to cause tissue swelling and damage). Therefore PEA could be used as a supportive immune therapy to prevent excess inflammation, swelling, and the resulting cognitive defects from infections in the central nervous system.

CONCLUSIONS

PEA, a novel anti-inflammatory molecule, may be our next tool to help prevent and treat colds and flu. Additional benefits include decreased swelling in the central nervous system and a lessening of cognitive decline in the elderly from these types of infections.

References

1. Keppel Hesselink J.M. *et al.* Palmitoylethanolamide: A natural body-own anti-inflammatory agent, effect and safe against influenza and common cold. Int J Inflam. 2013; 151028. doi: 10.1155/2013/151028
2. Heide EC, Bindila L, Post JM, Malzahn D, Lutz B, Seele J, Nau R, Ribes S. Prophylactic palmitoylethanolamide prolongs survival and decreases detrimental inflammation in aged mice with bacterial meningitis. Front Immunol. 2018. 9: 2671

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