

Notes from Carl Germano's new book - **The Road to Ananda by Carl Germano, CNS**, CDN ISBN 978-0-578-44792-6 - published 2018

This is a great new book with an introduction written by Dr. Raphael Mechoulam - the worlds authority on the endocannabinoid system. **Please purchase the book to support his work !**

Dr Mechoulam - The ECS - endocannabinoid system

Helps govern:

Neurotransmission
Inflammatory cycling in the cell
Pain signaling to the brain
Insulin sensitivity
Building bones

Phytocannabinoids to nourish the ECS for treating many diseases including:

Neurological - anxiety, depression, stress, PTSD, Autism, Parkinson's, Alzheimers ect. (ALS ?)
- Concussion recovery.

Inflammatory - general pain / inflammation, Irritable bowel syndrome, Crohn's, Ulcerative Colitis, Fibromyalgia

Insomnia

Ocular - glaucoma, macular degeneration

Bone - Osteoporosis

Cardiovascular conditions

Diabetes

Our own bodies endocannabinoids are called Anandamide and 2-AG and are made from lipids and are taken up and broken down rapidly by enzymes in the cell. The enzymes that break down anandamide is FAAH and MAGL - degradation can be rapid.

The ECS is a significant collection of cell receptors - endocannabinoid receptors - and compounds we produce that attach and influence those receptors (endocannabinoids) Endocannabinoid receptors can be influenced by both the our bodies or those present in the plants - hemp/cannabis being the most abundant source of all.

ECS - plays a crucial role in governing neurotransmission and neuron communication. As such it influences numerous functions in the brain, including memory, mood, pain perception, cognition, emotions, motor function, reward, and anti-inflammatory effects.

CB1 & CB2 receptors are found in all the major organs of the body: Brain, Lungs, Liver, Stomach, Bone Marrow, Bladder, Skin, Heart, Intestines, Pancreas Spleen, Kidneys

CB1 - regulates neuron development, pain signaling, learning & memory processing, movement, motor control, inflammation, bone mass, and many other functions.

CB2 - regulates immune modulation & autoimmunity, enhancing bone mass, protecting the brain, pain and inflammation, lier support, and healthy stress response.

There are more endocannabinoid receptors than the neurotransmitter receptors of serotonin and dopamine. The total number of endocannabinoid receptors in the body is believed to be greater than all the other neurotransmitter receptors combined.

Receptors are proteins that act as doorways on the surface of cells for messengers to deliver information into the cell. They act as the cells "eyes and ears"

Anandamide is the “bliss” molecule and attaches to the CB1 receptor - the same one THC attaches to - it has positive effects on our mood, feelings and perceptions. It also attaches to the CB2 receptor. Neurologically it is a neurotransmitter that helps produce new nerve cells, reduces inflammation in the brain, and regulates functions that produce memory, creative thought processes, reward and motivation processes, control of movement in the body, emotion response and many other functions. Its ability to form new brain cells and acts as a mood elevator and stabilizer, useful in the treatment of depression and mood disorders. It also helps with cell division and helps control cell proliferation, survival and programmed cell death. Runners high - anandamide levels are significantly increased after exercise and tied to endorphin and opioid receptors. It is not nearly as potent as THC. CBD - full spectrum hemp - helps to interfere with the **FAAH enzyme** that degrades anandamide and therefore keeps levels high. FAAH is the enzyme that breaks down anandamide. Dark Chocolate combined with CBD - inhibits anandamide destruction in the brain. Dark Chocolate mimics (N-oleoylethanolamide and N-linoleoylethanolamide) act as cannabinoid mimics

Arachidonoylglycerol (2-AG) is a neurotransmitter that attaches to both CB1 and CB2 receptors. 2-AG acts as a full CB2 agonist. 2-AG is the most prevalent endocannabinoid ligand (molecule that binds to a receptor) in the brain and throughout the body where it helps to regulate immune function, pain management. Levels of 2-AG in the brain are 170X higher than anandamide. Reduction of inflammation, pain signaling, mood, stress, anxiety. In inflammation it decreases the COX-2 enzyme in the brain (protecting neurons) and throughout the body. It inhibits the spread of certain cancer cells as well. 2-AG activates receptors in the bones that help prevent the break down of bone osteoclasts and favor the production of osteoblasts that build up the bone.

2-AG has been shown to potentiate GABA receptors.
Supports diabetes management with insulin regulation too.

2-AG is susceptible to degradation by a different enzyme in the body called **MAGL** (monoacylglycerol lipase) - an active component of Boswellia called b-amyryn has been shown to inhibit MAGL which can result in increasing 2-AG tone. CBD + Boswellia

PTSD - patients with PTSD have been shown to have depressed endocannabinoid levels in both hair and blood. Reduced levels of 2-AG and Anandamide promote aversive emotional memories in PTSD patients.

The ECS influences every conscious thought, perception or feeling. The ECS is responsible for things that determine if you are thinking clearly, our personality traits, focus, being laid back and relaxed, anxiety, etc.

The Gut, Brain immune and endocannabinoid system.

70% of our immune system is in the gut. The gut has 100 million neurons (brain cells) in it. The ECS orchestrates communication between the gut, brain and immune system. The ECS regulates gastrointestinal motility, control of nausea and intestinal inflammation and is pivotal in reducing the activity of the HPA pathway which helps relieve stress and anxiety. Conversation between the ECS and the gut bacteria - the endocannabinidiome meets the microbiome.

Vagal nerve - is impacted by the ECS

ECS tone in athletic and exercise is very important

Omega - 3 & your endocannabinoid system

Omega 3's are involved in the production of endocannabinoids (anandamide, 2-AG), activating cannabinoid receptors in the body has well as regulating inflammation and immunity.

Scientists have discovered a pathway in the body that converts omega 3 fatty acids - DHA and EPA into more potent molecules called omega 3 endocannabinoid epoxides.

Anandamide and 2-AG are produced in part from the presence of omega-3 fatty acids and some omega 6 fats. Some studies show that DHA/EPA influence the gene expression of CB1 receptors. A compound called DEA (doco-sa-hexaenoylethanolamide) is synthesized from DHA and is structurally similar to anandamide. Other studies reveal that EPA significantly increased production of neural stem cells, which is associated with higher levels of the endocannabinoid 2-AG

Omega 3's and phytocannabinoids act like a "multi-vitamin" for the ECS

PAIN - Full spectrum Hemp CBD complex + Fish Oils EPA/DHA + Boswellia

CB1 Receptor - neuropathic pain - CNS - Central Nervous System

CB2 Receptor - peripheral nervous system - GI tract

Hemp phytocannabinoids, such as beta caryophyllene, CBG and CBD can support our endocannabinoid system's participation in controlling inflammation and pain

Nociceptors are pain stimuli - they are pain signaling receptors - up regulation of CB1 and CB2 have the anti-nociception activity .

FAAH enzyme breaks down anandamide

MAGL enzyme breaks down 2AG - when it breaks down 2AG the body produces more arachidonic acid - arachidonic acid produces inflammation

The eicosanoid pathway from omega 3s - fish oils positively interact with the ECS

In the limbic area of the brain, CB1 receptors help regulate the transmission of pain to the brain by inhibiting neurotransmitters associated with pain sensation.

In the spinal cord CB1 is expressed in the excitatory neurons and helps regulate the transmission of pain stimulation to the brain by blocking neurotransmitter release. In addition, CB1 receptors have analgesic effects in peripheral tissues by delaying pain signals.

In peripheral tissue, CB2 receptors are widely located on immune cells and are a perfect target for influencing inflammatory pain processing. They modulate

The ECS positively interacts with the opioid system

ECS - Gut - Brain - immune system

ECS - plays important roles in controlling intestinal inflammation and the link between stress and abdominal pain.

Clinical studies on patients with inflammatory bowel disease.

ECS and Sleep

One interesting sleep inducing dietary cannabinoid-like molecule that acts on the CB1 and GABA receptors and helps inhibit the breakdown of anandamide is the fatty acid oleamide.

Oleamide (Omega - 9) is a molecule produced in the body from oleic acid as found in **olive oil**. Oleamide uses up FAAH, saves anandamide degradation and thereby keeping anandamide

levels high. Oleamides's interaction with GABA receptors produces sleepiness and promotes the healthy deep sleep cycle called REM. Oleamide exhibits potent sleep inducing properties, shortens the time to induce sleep, and lengthens the time spent in one of the deepest phases of sleep.

A neuron called orexin and receptors - these neurons and their receptors have the ability to communicate with the ECS - these neurons regulate the sleep/wake cycle.

ECS - Stress and Anxiety

TRPV1 - blocking this receptor results in reducing anxiety.

Studies with animals that have genetic deficiencies of 2-AG induce anxiety and depression while increasing 2-AG reduces anxiety stress behavior.

In clinical studies with patients with PTSD - higher levels of CB1 receptors are found in regions of the brain associated with fear and anxiety as compared to controls. PTSD patients have significantly reduced levels of both anandamide and 2-AG. The anandamide levels are too low, the brain compensates by increasing the number of CB1 receptors since they are involved in the extinction of traumatic memories. Chronic stress exposure enhances the activity of FAAH which lowers anandamide levels and inhibits our capacity to adapt to daily onslaught of stressors.

When under heavy stress FAAH fosters poor neurological communication and function in the brain.

Stress increases FAAH which decreases Anandamide which increases HPA axis resulting in the release of cortisol - chronic elevation of cortisol is inflammatory and destructive to the body.

When CB1 signaling in the body is impaired, anxiety and poor physiological response to stress occurs. For CB1 signaling to be most efficient our body must have an ample supply of anandamide.

The best way to improve anandamide levels is via the consumption of full spectrum phytocannabinoid rich hemp oil standardized for its cannabidiol (CBD) content. CBD is uniquely able to inhibit the rapid breakdown of anandamide by FAAH and also influences other targets of stress and anxiety.

CBD increases levels of serotonin.

Brain circuits involved in anxiety and HPA axis involved in our stress response work more efficiently with an ample supply of anandamide.

Decreasing levels of MAGL - monoacylglycerol lipase the enzyme that degrades 2-AG - causes reductions in the symptoms of anxiety by keeping endocannabinoid tone high.

Low levels of 2-AG were observed in patients with major depressive disorders. Depression after heart surgery - can be supported with full spectrum CBD too.

ECS & Bone Health -

Both endocannabinoids, 2-AG and anandamide and their receptors, CB1 and CB2 are present in osteoblasts and osteoclasts. Specifically anandamide stimulates CB1 receptors in bone. CB1 sends signals to suppress the release of norepinephrine - a hormone that inhibits bone

formation. Activation of CB1 receptors influences brain to bone communication. CB2 receptors increases bone mass by increasing the number and activity of bone building osteoblasts. Osteoporotic patients exhibit TRPV1 (vanilloid type 1) stimulation and a reduction of CB2 receptors in osteoclast cell. TRPV1 is known to inhibit calcium access to skeletal tissue, which has a damaging effect on bone density.

The phytocannabinoid **beta caryophyllene**, found in hemp, clove, and pepper, is a potent CB2 agonist which may prove to be a novel anti-osteoporotic therapy.

Cancer -

The ECS plays a regulatory role in inflammation, immunity and anti-tumor activity. Supporting the ECS with phytocannabinoids can influence signaling pathways that help control tumor growth and maintenance. ECS is involved with tumor suppressive activity by inhibiting proliferation, increasing apoptosis, and blocking angiogenesis to tumors. CBD, CBG, CBC, NS CBDA HAVE BEEN SHOWN TO EXERT ANTI-PROLIFERATIVE / PRO-APOPTOTIC EFFECTS FOR A VARIETY OF TUMOR CELL LINES . Human breast, prostate, lung, colorectal, gastric adenocarcinoma. In rats - glioma, leukemia and thyroid cells.

In vitro studies of human tissue - glioma cells. In lung cancer cells in response to CBD - tumor cell lines exhibited increased levels of inflammatory prostaglandins, which in turn, induced cell death. In human leukemia cells (in vitro) CBD made it harder for the cancerous cells to survive.

CBD may provide similar benefits with regard to **multiple myeloma**, a plasma cell malignancy characterized by the accumulation of a monoclonal plasma cell population in the bone marrow. The activation of the TRPV2 by CBD - in studies with was also combined with bortezomib

CBD reduces multi-drug resistance in cancer cells. A recent report detailed how CBD and CBN inhibit ATP binding cassette (ABC) transporters which contributes to the multi-drug resistance of breast tumor cells.

CBD can also act as an anti-emetic - from chemotherapy nausea

It has been found to be supportive in preventing neuropathy in patients using paclitaxel (PAC)

Endocannabinidiome and the Microbiome connection

70% of your immune activity is in the gut. Several studies have demonstrate how gut bacteria activates GPCR receptors that are also targeted by the ECS

The ENDOCANNABIDIOME - The two primary cannabinoid receptors are called CB1 and CB2. CB1 receptors are more often responsible for stress response, relaxation, neurotransmission and involuntary motor control. CB2 receptors are primarily focused on immunomodulatory and inflammatory response in the body.

Increased levels of the endocannabinoid Anandamide and CB1 receptors are seen in tissue sample of those with colitis, diverticulitis, and celiac diseases Irritable bowel disease show enhanced expression of CB2 receptors.

Initially researchers found that cannabinoids such as THC, which binds to the CB1 receptor had an amazing impact on slowing motility especially in the presence of inflammatory related bowel diseases. Excess motility causes diarrhea. Full spectrum hemp extract has been shown to provide similar benefits of THC but does not produce an inebriated state. CBD is showing similar activity to THC, but beta caryophyllene (BC) specifically attaches to the CB2 receptor. CB2 receptors play a role in those specifically dealing with IBD - Inflammatory - related bowel disease. Patients with IBD are more likely to show increased CB2 expression - which in turn down the flames in the gut. This could help lessen pain and inflammation associated with IBD such as colitis.

IN THE GUT

CB1 - Decreases acid secretion
Decreases motility
Decreases Inflammation

CB2 - Decreases pain
Decreases inflammation and decreases motility

CBD affects cells in the gut called enteric glial cells (EGC) These have an important role in maintaining the health and balance of the intestinal tract (homeostasis) by defending against pathogens and actively participate in the progression of intestinal inflammation

ECS and Eye Health - The eye is an extension of our nervous system and very much connected to our brain. The ECS is functional in all aspects of our vision and health of ocular tissue. The retinal ECS - the ECS is present throughout most tissues in the eye - there are CB1 and CB2 receptors there and anandamide and 2AG in humans there is significantly higher amounts of 2AG in the retina as compared to anandamide. The ECS helps modulate visual perception and function as well as pressure within the eye known as intraocular pressure (IOP) In the capillaries in the retina - normal levels of 2-AG and anandamide promote relaxing effects (vasorelaxation) - whereas disrupted levels are implicated in eye disorders. The ECS is involved in macular degeneration, glaucoma and other eye conditions. The ECS helps to maintain homeostasis within the entire visual system

In Diabetes - CBD helps protect the eye damage caused by this - CBD increases the enzyme that break down glutamate and preserving retinal functioning in diabetic animals. Saffron, Lutein and Zeaxanthin are all important supporting nutrients but added CBD helps them

ECS and Neurological Health -

The Brain weighs 3lbs

Keeping a healthy ECS is the key to keeping your brain healthy. The ECS is one of the most extensive signaling systems in our brain and assists in the regulation of:

1. Providing neurons to be more adaptogenic and provides greater flexibility for them to adjust to injury, disease or environmental changes.
2. Protecting the brain from excitatory glutamate, which can lead to death of neurons.
3. Protecting the brain from inflammation and inflammatory cytokines from the immune system.
4. Modulating neurotransmitter release, reducing oxidative stress involved with pain signaling.

ECS and neurological diseases - Epilepsy, Alzheimers, MS, Parkinson's and Traumatic Brain Injury

ECS - Physiological Functions - Builds brain cells, improves memory, reduces inflammation, reduces oxidative stress, governs neurotransmission

CB - receptors are concentrated in key functional areas of the brain such as basal ganglia (movement), cerebral cortex (cognition), cerebellum (movement), hippocampus (memory, stress), spinal cord (pain signaling). CB2 receptor activation results in anti-inflammatory activity - it is a target for further study into the treatment of Alzheimers, and MS

CB2 receptors are involved with MS -

Variations of Anandamide and 2AG are involved with ALS, Huntington's and Parkinson's disease.

When the ECS is over or under active the brain and CNS feel its effects positively or negatively depending on the nature of the activity.

CBD, HEMP & ITS FAMILY OF PHYTOCANNABINOIDS

Marijuana is shorter, squatter, and broader leaves

Hemp is very tall, long stalks, and narrower leaves.

CBD does not attach to the CB1 and CB2 receptors , but indirectly supports CB1 receptors by inhibiting the breakdown of anandamide which attaches to CB1. Beta caryophyllene a minor phytocannabinoid in hemp, is a strong agonist to the CB2 receptor. The collective compounds in hemp work together as a family to produce more effective benefits as compared too isolating one.