A follow up medical 420 info, research, study links guide for TKMT video topics:

Link: https://www.youtube.com/channel/UC0pi1XHmPbGPlAyVlGXrI-g/videos?view=0&sort=dd&shelf_id=0

**Topic: [Opiate & Cannabinoid Synergy: Reducing & Coming Off Opiates With The Help Of Cannabis]**
Video Link: https://www.youtube.com/watch?v=1ertF7RBogY

Video Published on Jul 14, 2016
In this episode of "The Kootenay's Medicine Talk", Jim discusses the benefits of using opiates and cannabis together (or "synergistically"), including enhanced pain control, safety, in addition to reducing or potentially coming off opiates altogether.

FollowUp: Show Pain Control Interaction/Synergy Cannabinoid, Opioid, TRPV1 receptors, Microbiome

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**Topic: Opioid & Cannabinoid & TRPV1-n & Microbiome Synergy**

- [VIDEOS]: Opiate & Cannabinoid Synergy
- [VIDEOS]: Endocannabinoid System Introduction
- [Introduction]: Endocannabinoid System
- [VIDEOS]: Endogenous Opioid System Introduction
- [Introduction]: Endogenous Opioid System
- [Interaction]: Cannabinoid & Opioid & Pain Relief
- [VIDEOS]: TRPV1-n Receptor Introduction, Nociceptive Pain & Temperature
- [Introduction]: TRPV1 Receptor
- [Interaction]: Cannabinoid, Opioid, TRPV1-n, Pain Relief
- [VIDEOS]: Human Microbiome Introduction
- [Introduction]: Human Microbiome
- [Synergy]: Gut Endocannabinoid - Opioid - Microbiome

Follow Update Includes:

[The “Triumvirate” triangle of cannabinoid, TRPV1 and opioid receptors]
Link: https://www.researchgate.net/figure/283446665_fig1_Fig-1-The-Triumvirate-triangle-of-cannabinoid-TRPV1-and-opioid-receptors-For

[Endocannabinoid Gut Microbiome Synergy by Cloak N Dabber]
Link: http://kootenaysmedicinetree.ca/endocannabinoid-gut-microbiome-synergy

by Pix i | Jan 2, 2017 | Theories of the Cloak and Dabber

I hope this 420 medical info links guide will be helpful and educational to all: medical 420 users, 420 info nerds, students, teachers, researchers, caretakers....everyone. (CloakNDabber Ver 06 030717)
[VIDEOS]: Opiate & Cannabinoid Synergy

[Opiate & Cannabinoid Interactions, with Sandra Welch]

Video Link: https://www.youtube.com/watch?v=JRFnGS1XPe4

Finding a synergistic action between THC and opiates in treatment of acute and chronic pain, Sandra Welch, PhD addresses 2004 Cannabis Therapeutics Conference. Hosted by Patients Out of Time. DVDs are available.

[Dr. Donald Abrams Compares Cannabis To Opiate-based Medicines]

Video Link: https://www.youtube.com/watch?v=cGPtirNqGtM

Donald Abrams, M.D. explains he first learned how medical marijuana helped patients in various ways through many studies - dating back through the 90’s. Dr. Donald Abrams is the Chief of Hematology-Oncology at San Francisco General Hospital, as well as Professor of Clinical Medicine at the University of
[VIDEOS]: Opiate & Cannabinoid Synergy

["The Fentanyl Crisis & Cannabis": The Kootenay's Medicine Talk]

Video Link: https://www.youtube.com/watch?v=kQ7tJhfE Afw
Published on Nov 17, 2016
In this episode of The Kootenay’s Medicine Talk, Jim Leslie discusses the current #fentanyl #crisis impacting #Canadians, the role that #cannabis could play in curbing this #epidemic, and provides guidance around #safe and #reasonable #access to cannabis.

[Dr. Wardell discussing fentanyl, street opiates and marijuana in pain management]

Video Link: https://www.youtube.com/watch?v=sIJ7j2fuhTU Published on Sep 15, 2015

[Dr. Wardell talks about carfentanyl and pill addiction in Alberta]

Video Link: https://www.youtube.com/watch?v=4XnFISqsCgQ Published on Sep 23, 2016

[Dr. Wardell discussing fake oxy 80's laced with Fentanyl]

Video Link: https://www.youtube.com/watch?v=86kKCORIlpM Published on Sep 11, 2016
Dustin Sulak, D.O. is a renowned integrative medicine physician based in Maine, whose practice balances the principles of osteopathy, mind-body medicine and medical cannabis. Regarded as an expert on medical cannabis nationally, Dr. Sulak educates medical providers and patients on its clinical use, while continuing to explore the therapeutic potential of this ancient yet emerging medicine.

Dr. Sulak received undergraduate degrees in nutrition science and biology from Indiana University, a doctorate of osteopathy from the Arizona College of Osteopathic Medicine, and completed an internship at Maine-Dartmouth Family Medicine Residency.

We are in the throes of an opioid abuse crisis and are desperately searching for an answer. It’s time we acknowledge the solution that’s right in front of us and make this life-saving treatment available for those dependent on opioids. Cannabis has been proven to relieve chronic pain while reducing and replacing the use of opioids. It also relieves the symptoms of opioid withdrawal and decreases opioid craving. There is no toxic or lethal overdose of cannabis, and thousands of patients are already effectively using cannabis to replace opioids and other addictive substances.
**[Videos]: Endocannabinoid System Introduction**

["An Introduction To Cannabinoids": The Kootenay's Medicine Tree Talk]

Video Link:  [https://www.youtube.com/watch?v=I1M2qgwHO74](https://www.youtube.com/watch?v=I1M2qgwHO74)

Kootenay's Medicine Tree  Published on May 18, 2016

This week on "The Kootenay's Medicine Talk", director of The Kootenay's Medicine Tree Jim Leslie, provides an introduction to cannabinoids and the endocannabinoid system.

![An Introduction To Cannabinoids](https://www.youtube.com/watch?v=I1M2qgwHO74)

**[Your Endocannabinoid System Explained]**

Video Link:  [https://www.youtube.com/watch?v=PZYjJf0t2OQ](https://www.youtube.com/watch?v=PZYjJf0t2OQ)

Healer.com  Published on Aug 11, 2015

In this educational video medical cannabis expert Dr. Dustin Sulak explains your endocannabinoid system and the role it plays in maintaining harmony and balance within your body.

![Your Endocannabinoid System Explained](https://www.youtube.com/watch?v=PZYjJf0t2OQ)

**[Visualization of the endocannabinoid signaling system]**

Video Link:  [https://www.youtube.com/watch?v=jznQfMj9RWM](https://www.youtube.com/watch?v=jznQfMj9RWM)

Published on May 7, 2012

Visualization of the endocannabinoid signaling system.

![Visualization of the endocannabinoid signaling system](https://www.youtube.com/watch?v=jznQfMj9RWM)
[Videos]: Endocannabinoid System Introduction

[The Human Endocannabinoid System]
Video Link: https://www.youtube.com/watch?v=CUEvzNBTPxc
Published on May 25, 2012 Robert Weber
The Human Endocannabinoid System - a complete overview of the Endocannabinoid system as presented by the Univ of Kansas- Wichita

[CANNABIS BASICS - THE ENDOCANNABINOID SYSTEM]
Video Link: https://www.youtube.com/watch?v=Z-OEpwgv6aM
Published on Aug 27, 2016
It is now irrefutable the Cannabis possesses vast healing potential for A LOT of mental & physical conditions that modern medicine is drastically inferior in treating. But how does Cannabis work? How does it take effect when we consume it? The secret to this lies in the Endocannabinoid system of our bodies - a complex system of interdependent neurotransmitters and endogenous chemicals, and the series of receptors that transmit them.

[3D Image Shows Clearest Picture Of Human Cannabis Receptor]
Video Link: https://www.youtube.com/watch?v=4xR0G5Vxfk8
Published on Dec 7, 2016
How does cannabis interact with the brain? The latest 3D imaging of the cannabis receptors and THC molecule are stunning to see how the brain reacts to marijuana. Get the full story at Cannabis.net, click here https://cannabis.net/blog/medical/thi...
[Introduction]: Endocannabinoid System

[What Is The Endocannabinoid System?]
Link: http://norml.org/library/item/introduction-to-the-endocannabinoid-system
Dustin Sulak, DO Healer.com
[Introduction]: Endocannabinoid System

- CB1 receptors are located in cells of the:
  - Brain/CNS/Spinal cord (CB1)
  - Cortical regions (CB1): (neocortex, pyriform cortex, hippocampus, amygdala)
  - Cerebellum (CB1)
  - Brainstem (CB1)
  - Basal ganglia (CB1): globus pallidus, substantia nigra pars, reticulata
  - Olfactory bulb (CB1)
  - Thalamus (CB1)
  - Hypothalamus (endocrine-brain link CB1)
  - Pituitary (CB1)

- CB1 and CB2 receptors are located in cells of the:
  - Eye (CB1 and CB2): retinal pigment epithelial/RPE cells
  - Stomach (CB1 and CB2)
  - Heart (CB1 and CB2)
  - Pancreas (CB1 and CB2)
  - Digestive tract (CB1 and CB2)
  - Bone (CB1 and CB2)

- Non-CB1 and non-CB2 are located in cells of the:
  - Upper airways (of mammals CB1)
  - Liver (CB1): kupffer cells (macrophage immune cells), hepatocytes (liver cell), hepatic stellate cells (fat storage cell)
  - Adrenals (endocrine gland CB1)
  - Ovaries (gonads and endocrine gland CB1)
  - Uterus (myometrium CB1)
  - Prostate (CB1): epithelial and smooth muscle cells
  - Testes (gonads and endocrine gland CB1): leydig cells; sperm cells

- Mind body medicine:
  - Disease is a message
  - Beliefs create
  - Expression/Release
  - Love/Gratitude/Forgiveness
  - Self-acceptance
  - Pleasure/Happiness/Positive Affect
  - Conscious choice

- CB2 receptors are located in cells of the:

- Lymphatic and Immune system:
  - Spleen (CB2)
  - Thymus (CB2)
  - Tonsils (CB2)
  - Blood (CB2) lymphocytes (p. 15)
  - Non-immune cell CB2 receptors are found in the Skin keratinocytes (p. 15)
**The Endocannabinoid System**

Brain cells (neurons) communicate with each other by sending chemical messages. The chemicals (neurotransmitters) cross a gap between neighboring neurons before attaching to their specific receptors.

**Presynaptic:** The neuron sending a message by releasing a chemical when signaled to do so.

**Postsynaptic:** The neuron receiving the message when its receptors are activated by specific chemicals (neurotransmitters).

**Neurotransmitters:** The chemical messengers that travel from one brain cell to another.

**Receptors:** Activated by neurotransmitters, receptors trigger a set of events that allows a message to be passed along to other neurons.

**Cannabinoids:** Natural chemicals (anandamide and 2-AG) that bind to cannabinoid receptors in the brain and the body.

**THC:** The main active ingredient in marijuana; THC, also a cannabinoid, interferes with the normal functioning of the endocannabinoid system.

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**Concentrations of CB₁ receptors**

- **Basal Ganglia¹** - Movement
- **Cerebral Cortex¹** - Higher cognitive function
- **Cerebellum¹** - Movement
- **Hypothalamus²** - Appetite
- **Hippocampus¹** - Learning, memory, stress
- **Medulla³,⁴** - Nausea/vomiting, chemoreceptor trigger zone (CTZ)
- **Spinal Cord¹** - Peripheral sensation including pain

[Introduction]: Endocannabinoid System
Introduction: Endocannabinoid System
[Videos]: Endogenous Opioid System Introduction

[How Opioids Work]
Video Link: https://www.youtube.com/watch?v=BKMIHNq1QsM
Erin Published on Oct 16, 2014

Short animation for class showing how opiates travel through your system.

[Opioid Tolerance]
Video Link: https://www.youtube.com/watch?v=W2QjbdYfakg
Dennis Wei Uploaded on Aug 12, 2010

This animation describes one particular hypothesis regarding the development of opioid tolerance. The hypothesis supports the idea that a shift in equilibrium between the recycling and degradation of the opioid receptors may result in receptor down-regulation, which consequently results in tolerance.

[Central Nervous System Mechanisms of Pain Modulation]
Video Link: https://www.youtube.com/watch?v=FbJF8qijf8EFirelight Media Group Uploaded on Apr 19, 2011
[Videos]: Endogenous Opioid System Introduction

[The Science of Opioids]  
Video Link: https://www.youtube.com/watch?v=AqDo4LiKz-c  
Published on May 9, 2016

The Science of Opioids - How do opioids work? We look at the physiological processes that let opioids produce their effects in human bodies.

[Opioid pharmacology part 1-2: mu,kappa and delta receptors]  
Video Link https://www.youtube.com/watch?v=YCz5A8ZkavM  
Video Link https://www.youtube.com/watch?v=LT80LeQNO10  
Video Link https://www.youtube.com/watch?v=2DNj8vVACE  
Pharmacology Corner Uploaded on Aug 19, 2011

[Mechanism of Action: μ-Opioid Receptor Agonists and Antagonists (Vivitrol)]  
Video Link: https://www.youtube.com/watch?v=T5lbBX56OWw  
https://www.vivitrol.com/HCP/Treatment... Published on Nov 2, 2016
[Introduction]: Endogenous Opioid System

[Opioid]
Link: https://en.wikipedia.org/wiki/Opioid

[Opioid analgesics & antagonists]
Slide Show Link: https://www.slideshare.net/rajud521/opioid-analgesics-antagonists

[Opioid pharmacology - A comprehensive subject seminar on Opioids]
Slide Show Link: https://www.slideshare.net/rohankolla/opioid-pharmacology-a-comprehensive-subject-seminar-on-opioids

[Cross-Talk Between Cannabinoid and Opioid Systems ]

[Opioid Receptors – The Basis of Pain Relief and Addiction: Bidirectional]
Slide Show Link: http://slideplayer.com/slide/701349/

[The endogenous opioid system and clinical pain management]

Abstract
The endogenous opioid system is one of the most studied innate pain-relieving systems. This system consists of widely scattered neurons that produce three opioids: beta-endorphin, the met- and leu-enkephalins, and the dynorphins. These opioids act as neurotransmitters and neuromodulators at three major classes of receptors, termed mu, delta, and kappa, and produce analgesia. Like their endogenous counterparts, the opioid drugs, or opiates, act at these same receptors to produce both analgesia and undesirable side effects. This article examines some of the recent findings about the opioid system, including interactions with other neurotransmitters, the location and existence of receptor subtypes, and how this information drives the search for better analgesics. We also consider how an understanding of the opioid system affects clinical responses to opiate administration and what the future may hold for improved pain relief. The goal of this article is to assist clinicians to develop pharmacological interventions that better meet their patient's analgesic needs.

Endogenous Opioid Peptides

<table>
<thead>
<tr>
<th>OPIOID RECEPTOR CLASS</th>
<th>EFFECTS</th>
<th>ASSOCIATED ENDOGENOUS ENDOPHIN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mu 1</td>
<td>Euphoria, supraspinal analgesia, confusion, dizziness, nausea, low addiction potential</td>
<td>Endormorphin 1,2&gt;Beta-endorphin &gt;Enkephalin=Dynorphin</td>
</tr>
<tr>
<td>Mu 2</td>
<td>Respiratory depression, CVS and GI effects, miosis, urinary retention</td>
<td>Beta-endorphin&gt;Endormorphin 1,2&gt;Enkephalin=Dynorphin</td>
</tr>
<tr>
<td>Delta</td>
<td>Spinal analgesia, Opioid reinforcement, CVS depression, decreased brain and myocardial oxygen Demand</td>
<td>Enkephalin=Beta-endorphin&gt;Dynorphin</td>
</tr>
<tr>
<td>Kappa</td>
<td>Supraspinal, Spinal ,Peripheral analgesia, dysphoria, psychomimetic effects, feedback inhibition of endorphin system</td>
<td>Dynorphin A=Beta-endorphin&gt;Enkephalin</td>
</tr>
</tbody>
</table>
[Introduction]: Endogenous Opioid System

Link: http://flipper.diff.org/apptagsaccount/items/6573
Opioids bind to the receptors that modulate pain perception, hunger, thirst, mood, and other processes. Whether produced naturally in the brain or a poppy pod, or synthetically in the laboratory, opioids typically have an inhibitory effect on the firing of the nerve cells they interact with. Upon binding to opioid receptors on the cell membrane, the drugs, like their endogenous relatives, lead to an increase in the charge difference between the interior and exterior of the cell. This hyper-polarization makes it more difficult for the cell to depolarize and generate an action potential, or nerve impulse. (See illustration.) Opioid receptors are dense in neurons involved in pain transmission, such as those in the dorsal horn of the spinal cord. By quelling the activity of these neurons, opioids block the sensation of pain.
Cannabinoids and Opioids: A Historical Perspective

Cannabinoids

- 3000 BC: First evidence of medicinal use in China
- 500 BC: W.B. O’Shaughnessy’s work popularizes cannabis use
- 1800’s: Medicinal cannabis use declines
- 1900’s: 9-THC identified as main psychoactive agent in Cannabis sativa plant
- 1964: CB1, receptor identified
- 1988: CB2, receptor cloned
- 1992: Anandamide discovered, CB2 receptor identified
- 1993: CB2 receptor cloned
- 1998: Endogenous cannabinoid ligands shown to be analgesic

Opioids

- 1522: Earliest known reference for opium-based elixir
- 1604: Paracelsus reference to “laudanum”, opium-based elixir, as a potent painkiller
- 1804: Morphine extracted from opium poppy plant
- 1817: Morphine first marketed in Germany as analgesic
- 1874: Morphine analogs synthesized
- 1874: Heroin (diacetylmorphine)
- 1900’s:Codeine, dihydromorphine, oxycodeine, pethidine, oxymorphone
- 1970’s: Discovery of opioid receptors - μ (mu), κ (kappa), δ (delta)
- 1975: Discovery of endogenous opioid peptides - endorphins

2. Notoull W., 2004
As you can see from the image below, there are 2 channels leading to every single pain receptor in the body (the place where the feeling of pain starts) – the opioid channel, and the cannabinoid channel.

**Opioid Channel**

The opioid channel is blocked only by opioids (like Morphine, Heroin, Codeine, Vicodin, Oxycodone etc.). They are considered "essential" today for the treatment of pain, but they are not – they are only one (of two) methods of blocking pain.

They work quite well, but the side effects are debilitating: addiction and horrific withdrawal, low energy/sedation, confusion, nausea, constipation... even brain, liver & kidney damage, anxiety... the list goes on and on.

**Cannabinoid Channel**

Blocking the cannabinoid channel is equally as effective in blocking pain, but the only side effects are a sense of bliss, peace, and well being.

The cannabinoid channel is blocked ONLY by Cannabinoids.
[Interaction]: Cannabinoid and Opioid and Pain Relief

[Novel synergistic opioid-cannabinoid codrug for pain management]
Link: http://www.google.st/patents/US20080176885

Synergistic enhancement of the antinociceptive effect of morphine in combination with THC in the thermal tail flick test

Values are means ± S.E.M. n=6-10

Extrapolated Additive Effect

Morphine and delta-9-tetrahydrocannabinol (THC) were administered alone or in combination via the intraperitoneal route. THC was administered 30 min. prior to morphine.
**[Interaction]: Cannabinoid and Opioid and Pain Relief**

**[Interaction between kappa opioid and cannabinoid receptors]**
Link: [http://jn.physiology.org/content/84/5/2356](http://jn.physiology.org/content/84/5/2356)

Illustration of putative interaction between kappa opioid and cannabinoid receptors on $I_K$ amplitude. *Left*: filled diamonds illustrate the fact that kappa receptors appear to have endogenous ligand or constitutive tonic activity. Largest current trace reflects condition in which the antagonist (nor-BNI) alone is bound to the receptor (Fig. 5). *Right*: triangles show endogenous cannabinoids not bound to the CB1 receptor under control conditions because application of the antagonist alone (SR 141617A) has no effect on $I_K$. Smallest current trace reflects reduction in $I_K$ amplitude via activation of either kappa or CB1 receptors. Median trace reflects control condition. *Middle*: interaction between both receptors is hypothesized to occur via stimulation of $G_s$ protein and activation PKC (or possibly arachidonic acid stimulation of PKC), which alters $I_K$ (Fig. 4).

**[Synergistic interactions between cannabinoid and opioid analgesics]**

**Abstract**

Cannabinoids and opioids both produce analgesia through a G-protein-coupled mechanism that blocks the release of pain-propagating neurotransmitters in the brain and spinal cord. However, high doses of these drugs, which may be required to treat chronic, severe pain, are accompanied by undesirable side effects. Thus, a search for a better analgesic strategy led to the discovery that delta 9-tetrahydrocannabinol (THC), the major psychoactive constituent of marijuana, enhances the potency of opioids such as morphine in animal models. In addition, studies have determined that the analgesic effect of THC is, at least in part, mediated through delta and kappa opioid receptors, indicating an intimate connection between cannabinoid and opioid signaling pathways in the modulation of pain perception. A host of behavioral and molecular experiments have been performed to elucidate the role of opioid receptors in cannabinoid-induced analgesia, and some of these findings are presented below. The aim of such studies is to develop a novel analgesic regimen using low dose combinations of cannabinoids and opioids to effectively treat acute and chronic pain, especially pain that may be resistant to opioids alone.
Abstract
Cannabinoids and opioids are distinct drug classes historically used in combination to treat pain. Delta(9)-THC, an active constituent in marijuana, releases endogenous dynorphin A and leucine enkephalin in the production of analgesia. The endocannabinoid, anandamide (AEA), fails to release dynorphin A. The synthetic cannabinoid, CP55,940, releases dynorphin B. Neither AEA nor CP55,940 enhances morphine analgesia. The CB1 antagonist, SR141716A, deferentially blocks Delta(9)-THC versus AEA. Tolerance to Delta(9)-THC, but not AEA, involves a decrease in the release of dynorphin A. Our preclinical studies indicate that Delta(9)-THC and morphine can be useful in low dose combination as an analgesic. Such is not observed with AEA or CP55,940. We hypothesize the existence of a new CB receptor differentially linked to endogenous opioid systems based upon data showing the stereoselectivity of endogenous opioid release. Such a receptor, due to the release of endogenous opioids, may have significant impact upon the clinical development of cannabinoid/opioid combinations for the treatment of a variety of types of pain in humans.

[The Cannabinoid-Opioid Neuropathway Connection]

Heidi Heilman Published on February 10, 2016

Studies are now revealing that the cannabinoid-opioid systems of the brain are intimately connected. If you modify one system, you automatically change the other. Specifically, there is a functional interaction between the mu and Cb1 receptors of the brain. In the areas of the brain where cannabinoids bind, opioids bind as well. The mechanism is not yet well understood; more research is needed. But ultimately cannabinoids and opioids are known to strictly interact in many physiological and pathological functions, including addiction. Overall, evidence confirms a neurobiological convergence of the cannabinoid and opioid systems that is manifest at both receptor and behavioral levels.
[Interaction]: Cannabinoid and Opioid and Pain Relief

[Inhibiting the breakdown of endogenous opioids and cannabinoids to alleviate pain]
Link: http://www.nature.com/nrd/journal/v11/n4/full/nrd3673.html

Cannabinoids act on many of the same pain neural pathways as opioids

Endogenous Neurotransmitters:

- Opioids (Enkephalins) => Opioid Receptors
- Endocannabinoids (Anadaminde) => Cannabinoid Receptors

Similar locations of these receptors:

- Peripheral nocioceptive nerves (Source of pain)
- In the sensory neuron tranduction pathway
- In the descending modulatory pathways

With a key Difference although CB receptors are found in similar pain circuits as opioids, their absence in the brain-stem makes them safer than opioids.

Figure 2: Endogenous opioids and endogenous cannabinoids are present at all three levels of pain
[Interaction]: Cannabinoid and Opioid and Pain Relief

[Endogenous opioid and endogenous cannabinoid signalling: differences in synthesis, secretion mechanisms and metabolism]

Link: http://www.nature.com/nrd/journal/v11/n4/fig_tab/nrd3673_F1.html


a | Both of the endogenous enkephalins, Met-enkephalin and Leu-enkephalin, bind to μ-opioid receptors (MORs) and δ-opioid receptors (DORs). Enkephalins have a higher affinity for DORs (~tenfold higher) than for MORs, whereas morphine has a higher affinity for MORs than for DORs. The arrows denote the sites of enkephalin cleavage by aminopeptidase N (APN) and neprilysin (NEP).

b | N-arachidonoyl ethanolamide (AEA), like Δ9-tetrahydrocannabinol (Δ9-THC), binds to cannabinoid receptor 1 (CB1R) and CB2R with about 100 times lower affinity than Δ9-THC. Fatty acid amid hydrolase (FAAH) cleaves AEA (as illustrated by the arrow) into the metabolites ethanolamine and arachidonic acid, which are both devoid of affinity for AEA targets.

c | Enkephalins are synthesized intracellularly from enzymatic processing of the gene-derived precursor preproenkephalin (PENK). Stored in large synaptic vesicles, they are released (under basal or phasic conditions) by a Ca\(^{2+}\)-dependent exocytosis mechanism. Outside the cells, enkephalins interact with opioid receptors only, and their signal is interrupted by the concomitant action of two zinc metallopeptidases — NEP and APN — that generate inactive metabolites. The circulating concentrations of enkephalins, which modulate the physiological analgesic response, are enhanced by dual enkephalinase (DENK) inhibitors.

d | AEA is synthesized from membrane phosphoglycerides through a multi-enzymatic process involving N-arachidonoyl-phosphatidyl-ethanolamine transferase (NAT) and a selective phospholipase D (PLD)\(^{88, 130}\). AEA is released from the cells both by passive membrane diffusion and using the catalytically silent intracellular transporter FAAH-like anandamide transporter (FLAT)\(^{38}\). The same dual mechanisms are also used for the reuptake of synaptic AEA and delivering it to FAAH. FLAT may act as a shuttle delivering AEA to the cell membrane for secretion or, conversely, desorbing it from the membrane to transport it to the FAAH site. Outside the cells, AEA binds to various receptors such as cannabinoid receptors, transient receptor potential subfamily V member 1 receptor (TRPV1) and peroxisome proliferator-activated receptor-α (PPARα). The AEA signal is interrupted inside the cells by FAAH-induced degradation.
[Interaction]: Cannabinoid and Opioid and Pain Relief

[Cannabidiol is an allosteric modulator at mu- and delta-opioid receptors]

Link: https://www.ncbi.nlm.nih.gov/pubmed/16489449

Abstract
The mechanism of action of cannabidiol, one of the major constituents of cannabis, is not well understood but a noncompetitive interaction with mu opioid receptors has been suggested on the basis of saturation binding experiments. The aim of the present study was to examine whether cannabidiol is an allosteric modulator at this receptor, using kinetic binding studies, which are particularly sensitive for the measurement of allosteric interactions at G protein-coupled receptors.

[Cannabis and Opioid Induced Constipation]

Link: http://cannabisdigest.ca/cannabis-and-oic-opioid-induced-constipation/
Rudolf Schicho; Martin Storr

Constipation of intestinal reflexes may be alleviated by the anti-emetic properties of cannabis. Relief of constipation was one of the original cannabis indications cited by Shen-Nung five thousand years ago. Virtually every historical medical reference since that time has included similar observations. On the other hand, opiates commonly cause very severe constipation.

[Cannabinoid–Opioid Interaction in Chronic Pain]

Link: https://www.researchgate.net/publication/51765229_Cannabinoid-Opioid_Interaction_in_Chronic_Pain

Abstract November 2011
Cannabinoids and opioids share several pharmacologic properties and may act synergistically. The potential pharmacokinetics and the safety of the combination in humans are unknown. We therefore undertook a study to answer these questions. Twenty-one individuals with chronic pain, on a regimen of twice-daily doses of sustained-release morphine or oxycodone were enrolled in the study and admitted for a 5-day inpatient stay. Participants were asked to inhale vaporized cannabis in the evening of day 1, three times a day on days 2-4, and in the morning of day 5. Blood sampling was performed at 12-h intervals on days 1 and 5. The extent of chronic pain was also assessed daily. Pharmacokinetic investigations revealed no significant change in the area under the plasma concentration-time curves for either morphine or oxycodone after exposure to cannabis. Pain was significantly decreased (average 27%, 95% confidence interval (CI) 9, 46) after the addition of vaporized cannabis. We therefore concluded that vaporized cannabis augments the analgesic effects of opioids without significantly altering plasma opioid levels. The combination may allow for opioid treatment at lower doses with fewer side effects.
[Interaction]: Cannabinoid and Opioid and Pain Relief

[Interaction of the cannabinoid and opioid systems in the modulation of nociception]

Link: https://www.ncbi.nlm.nih.gov/pubmed/19367508

Abstract

Cannabinoids and opioids produce antinociceptive synergy. Cannabinoids such as Delta-9-tetrahydrocannabinol (THC) release endogenous opioids and endocannabinoids such as anandamide (AEA) also alter endogenous opioid tone. Opioids and cannabinoids bind distinct receptors that co-localize in areas of the brain involved with the processing of pain signals. Therefore, it is logical to look at interactions of these two systems in the modulation of both acute and chronic pain. These drugs are often co-abused. In addition, the lack of continued effectiveness of opioids due to tolerance development limits the use of such drugs. The cost to society and patients in terms of dollars, loss of productivity, as well as quality of life, is staggering. This review summarizes the data indicating that with cannabinoid/opioid therapy one may be able to produce long-term antinociceptive effects at doses devoid of substantial side effects, while preventing the neuronal biochemical changes that accompany tolerance. The clinical utility of modulators of the endocannabinoid system as a potential mimic for THC-like drugs in analgesia and tolerance-sparing effects of opioids is a critical future direction also addressed in the review.

[Opioids and cannabinoids interactions: involvement in pain management]

Link: https://www.ncbi.nlm.nih.gov/pubmed/20017728

Abstract

Among several pharmacological properties, analgesia is the most common feature shared by either opioid or cannabinoid systems. Cannabinoids and opioids are distinct drug classes that have been historically used separately or in combination to treat different pain states. Indeed, it is widely known that activation of either opioid or cannabinoid systems produce antinociceptive properties in different pain models. Moreover, several biochemical, molecular and pharmacological studies support the existence of reciprocal interactions between both systems, suggesting a common underlying mechanism. Further studies have demonstrated that the endogenous opioid system could be involved in cannabinoid antinociception and recent data have also provided evidence for a role of the endogenous cannabinoid system in opioid antinociception. These interactions may lead to additive or even synergistic antinociceptive effects, emphasizing their clinical relevance in humans in order to enhance analgesic effects with lower doses and consequently fewer undesirable side effects. Thus, the present review is focused on bidirectional interactions between opioids and cannabinoids and their potent repercussions on pain modulation.
Abstract

Opiates and exogenous cannabinoids, both potent analgesics used for the treatment of patients with neuropathic pain, bind to and activate class A G-protein-coupled receptors (GPCRs). Several lines of evidence have recently suggested that opioid and cannabinoid receptors can functionally interact in the central nervous system (CNS). These interactions may be direct, such as through receptor heteromerization, or indirect, such as through signaling cross-talk that includes agonist-mediated release and/or synthesis of endogenous ligands that can activate downstream receptors. Interactions between opioid and cannabinoid receptors may mediate many of the behavioral phenomena associated with the use of these drugs, including the production of acute antinociception and the development of tolerance and cross-tolerance to the antinociceptive effects of opioid and cannabinoid-specific ligands. This review summarizes behavioral, anatomical, and molecular data characterizing these interactions during the development of neuropathic pain and during antinociceptive treatment with these drugs alone or in combination. These studies are critical for understanding how the receptor systems involved in pain relief are altered during acute or chronic pain, and for designing better antinociceptive drug therapies, such as the combined use of opioid and cannabinoid receptor agonists or selective activation of receptor heteromers, that directly target the altered neurophysiology of patients experiencing pain.
[Videos]: TRPV1-n Receptor Introduction, Nociceptive Pain & Temperature

**[Pain and temperature | TrpV1 Receptor]**

Video Link: [https://www.youtube.com/watch?v=D-oAsFIHqbY](https://www.youtube.com/watch?v=D-oAsFIHqbY)

Published on Oct 11, 2013


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**[Phases of Nociceptive Pain]**

Video Link: [https://www.youtube.com/watch?v=PMZdkac4YLk](https://www.youtube.com/watch?v=PMZdkac4YLk)

Uploaded on Apr 19, 2011

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**[An Introduction to Pain Pathways and Mechanisms]**

Video Link: [https://www.youtube.com/watch?v=i5V_q7XqQN8](https://www.youtube.com/watch?v=i5V_q7XqQN8)

Published on Nov 19, 2013

This podcast is based on the article 'An Introduction to Pain Pathways and Mechanisms' which can be found on the UCL Centre for Anaesthesia medical students webpage:
Mutations in ion channels underlie multiple neurological disorders, including pathological pain states. Although previous work with knock-out mice has suggested that TRP channels play an important role in pain pathways, no human heritable disorders of pain sensation have been linked to mutations in TRP channels. Watch and listen as John Wood and colleagues take you on a personally guided tour of their findings that a point mutation in TRPA1 causes the human pain syndrome FEPS. Read more in Kremeyer et al., Neuron 66(5).
How do we feel cold or heat?

There are special temperature sensing channels called TRP channels (TRP stands for transient receptor potential, but you won’t see that much). TRP channels were first isolated in Drosophila (fruit flies) and responded to light. Now we know that some TRP channels actually respond to narrow ranges of temperatures (see figure above with responses of different TRP channels spanned across degrees centigrade) and are found in many organisms, including humans (mostly of the TRPV varieties, though TRPM8 and TRPA1 also seem to be important in humans). Essentially, when exposed to a temperature in their range, TRP channels open and let ions into the neuron, depolarizing it, causing an action potential and sending signals to the brain. This is a much more complicated process (as all signaling in neurons actually is) with changes occurring inside the cell due to their activation, but that is the general idea.

Some of these TRP channels are located on C-fibers (unmyelinated neurons that generally conduct pain signals) and that is why extreme hot or extreme cold can feel rather painful. TRP channels can also be activated by chemicals,
[Interaction]: Cannabinoid, Opioid, TRPv1-n Receptor and Pain Relief

[Anandamide and the vanilloid receptor (TRPV1)]
Link: https://www.ncbi.nlm.nih.gov/pubmed/19647120

Abstract
Arachidonylethanolamide (anandamide) was identified some 15 years ago as a brain constituent that binds to the cannabinoid receptor. After this seminal discovery, multiple new receptors for anandamide have been identified, including the vanilloid receptor (TRPV1), and anandamide is now frequently referred as an "endovanilloid." Characterization of the action of anandamide on TRPV1 revealed that (1) the potency and efficacy of anandamide on TRPV1 very much depend on the species and tissue, (2) anandamide responsiveness in vivo is significantly controlled by its local metabolism, (3) anandamide activation of cannabinoid receptors regulates TRPV1 responsiveness, (4) TRPV1 activation regulates anandamide synthesis, (5) anandamide metabolites affect TRPV1 responses, (6) the often observed convergent physiological actions of anandamide and TRPV1 agonists in neither case necessarily represent direct effects on TRPV1, and (7) coactivation of the cannabinoid receptors and TRPV1 often complicates the distinction between these pathways. These issues are reviewed here together with the potential implications for the pathophysiological and pharmacological regulation of inflammatory, respiratory, and cardiovascular disorders, as well as of appetite and fat metabolism.

[Why do cannabinoid receptors have more than one endogenous ligand?]  
Link: http://rstb.royalsocietypublishing.org/content/367/1607/3216

Abstract
The endocannabinoid system was revealed following the understanding of the mechanism of action of marijuana's major psychotropic principle, Δ⁹-tetrahydrocannabinol, and includes two G-protein-coupled receptors (GPCRs; the cannabinoid CB1 and CB2 receptors), their endogenous ligands (the endocannabinoids, the best studied of which are anandamide and 2-arachidonoylglycerol (2-AG)), and the proteins that regulate the levels and activity of these receptors and ligands. However, other minor lipid metabolites different from, but chemically similar to, anandamide and 2-AG have also been suggested to act as endocannabinoids. Thus, unlike most other GPCRs, cannabinoid receptors appear to have more than one endogenous agonist, and it has been often wondered what could be the physiological meaning of this peculiarity. In 1999, it was proposed that anandamide might also activate other targets, in particular the transient receptor potential of vanilloid type-1 (TRPV1) channels. Over the last decade, this interaction has been shown to occur both in peripheral tissues and brain, during both physiological and pathological conditions. TRPV1 channels can be activated also by another less abundant endocannabinoid, N-arachidonoyldopamine, but not by 2-AG, and have been proposed by some authors to act as ionotropic endocannabinoid receptors. This article will discuss the latest discoveries on this subject, and discuss, among others, how anandamide and 2-AG differential actions at TRPV1 and cannabinoid receptors contribute to making this signalling system a versatile tool available to organisms to fine-tune homeostasis.
Different functions at different receptors for brain anandamide and 2-AG. Anandamide (structure highlighted in pink) and 2-AG (structure highlighted in light green) are depicted as being produced (thin brown arrows) from both pre- and post-synaptic intracellular membranes and from post-synaptic plasma membranes, respectively.

**Anandamide, by acting at pre-synaptic CB1 receptors, may participate in ‘tonic’ suppression of GABAergic signalling in organotypic hippocampal cultures [40], whereas at pre-synaptic TRPV1 it stimulates glutamate release, thereby participating in some pathological conditions (shown in *italics*; see text).** By acting at post-synaptic **TRPV1**, anandamide either reduces glutamate signalling and produces long-term depression (LTD) by stimulating AMPA receptor (AMPAR) endocytosis [41, 42] or, as shown in MSNs of the striatum [43], it inhibits 2-AG biosynthesis and retrograde action at CB1 receptors [44], with potential consequences on endocannabinoid-mediated retrograde control of DSE and DSI, LTD and LTP. 2-AG can also act at post-synaptic CB1 receptors, thereby mediating ‘slow self-inhibition’ of neocortical interneurons [45].

Finally, 2-AG is the likely agonist at the CB1 receptor on astrocytes, which is recently emerging as the possible mediator of a series of biological actions listed in the figure [46–49], and at CB2 receptors in the same cells as well as in microglia, with strong implications for the inhibition of neuroinflammation and potential therapeutic use in several neuroinflammatory disorders [50, 51]. MSN, medium spiny neurons; LTP, long-term potentiation; AMPA, 2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl) propanoic acid; DSE, depolarization-induced suppression of excitation; DSI, depolarization-induced suppression of inhibition.
The endocannabinoid system and transient receptor potential (TRP) channels have been recognized as important regulators of smooth muscle tone in the lower urinary tract. [54][55] Cannabinoid receptors, TRPA, and TRPV cooperatively mediate smooth muscle relaxation in the prostate, urethra, and bladder. [54][55] In this process, mechano-afferent signals cause activation of the cannabinoid receptor 2 (CB2) and TRP channels on sensory neurons, leading to the release of NO and cyclooxygenase activation by neurons, which finally results in postsynaptic smooth muscle relaxation [Figure 3]. [55] In contrast to animal models, where CB1 strongly inhibits bladder smooth muscle contraction, endocannabinoid effects in the human lower urinary tract are prevalingly mediated by CB2. [54][56]

Figure 3: Role of endocannabinoids and TRP channels for regulation of smooth muscle tone in the lower urinary tract. Mechano-afferent signals lead to activation of CB2 receptors and TRP channels (TRPA, TRPV) in sensory neurons. This causes the release of nitric oxide and cyclooxygenase-dependent neurotransmission, finally resulting in smooth muscle relaxation in the detrusor, prostate, and urethra. Consequently, activation of CB2 receptors by Cannabinor or FAAH inhibitors improves LUTS in animal models.
Abstract

Plant cannabinoids, like Δ(9)-tetrahydrocannabinol (THC) and cannabidiol (CBD), activate/desensitize thermosensitive transient receptor potential (TRP) channels of vanilloid type-1 or -2 (TRPV1 or TRPV2). We investigated whether cannabinoids also activate/desensitize two other 'thermo-TRP's', the TRP channels of vanilloid type-3 or -4 (TRPV3 or TRPV4), and if the TRPV-inactive cannabichromene (CBC) modifies the expression of TRPV1-4 channels in the gastrointestinal tract. TRP activity was assessed by evaluating elevation of \([\text{Ca}^{2+}]_i\) in rat recombinant TRPV3- and TRPV4-expressing HEK-293 cells. TRP channel mRNA expression was measured by quantitative RT-PCR in the jejunum and ileum of mice treated with vehicle or the pro-inflammatory agent croton oil. (i) CBD and tetrahydrocannabinolic acid (THCV) stimulated TRPV3-mediated \([\text{Ca}^{2+}]_i\) with high efficacy (50-70% of the effect of ionomycin) and potency (EC(50) 3.7 μm), whereas cannabigerovarin (CBGV) and cannabigerolic acid (CBGA) were significantly more efficacious at desensitizing this channel to the action of carvacrol than at activating it; (ii) cannabidivarin and THCV stimulated TRPV4-mediated \([\text{Ca}^{2+}]_i\) with moderate-high efficacy (30-60% of the effect of ionomycin) and potency (EC(50) 0.9-6.4 μm), whereas CBGA, CBBG, cannabinol and cannabigerol were significantly more efficacious at desensitizing this channel to the action of 4-α-phorbol 12,13-didecanoate (4α-PDD) than at activating it; (iii) CBC reduced TRPV1β, TRPV3 and TRPV4 mRNA in the jejunum, and TRPV3 and TRPV4 mRNA in the ileum of croton oil-treated mice. **Cannabinoids can affect both the activity and the expression of TRPV1-4 channels, with various potential therapeutic applications, including in the gastrointestinal tract.**
Abstract

Chronic inflammation in rheumatoid arthritis (RA) is accompanied by activation of the sympathetic nervous system, which can support the immune system to perpetuate inflammation. Several animal models of arthritis already demonstrated a profound influence of adrenergic signaling on the course of RA. Peripheral norepinephrine release from sympathetic terminals is controlled by cannabinoid receptor type 1 (CB₁), which is activated by two major endocannabinoids (ECs), arachidonylethanolamine (anandamide) and 2-arachidonylglycerol. These ECs also modulate function of transient receptor potential channels (TRPs) located on sensory nerve fibers, which are abundant in arthritic synovial tissue. TRPs not only induce the sensation of pain but also support inflammation via secretion of pro-inflammatory neuropeptides. In addition, many cell types in synovial tissue express CB₁ and TRPs. In this review, we focus on CB₁ and transient receptor potential vanilloid 1 (TRPV1)-mediated effects on RA since most anti-inflammatory mechanisms induced by cannabinoids are attributed to cannabinoid receptor type 2 (CB₂) activation. We demonstrate how CB₁ agonism or antagonism can modulate arthritic disease. The concept of functional antagonism with continuous CB₁ activation is discussed. Since fatty acid amide hydrolase (FAAH) is a major EC-degrading enzyme, the therapeutic possibility of FAAH inhibition is studied. Finally, the therapeutic potential of ECs is examined since they interact with cannabinoid receptors and TRPs but do not produce central side effects.

Introduction

Rheumatoid arthritis (RA) is a debilitating disease that affects around 1.3 million people in the US alone [1]. Important characteristics of RA are inflammation of the joint with subsequent destruction of cartilage, pannus formation and infiltrates of immune cells [2, 3, 4]. Ongoing inflammation also leads to systemic changes manifesting in co-morbidities like dyslipidemia, depression, fatigue, insulin resistance, activation of the sympathetic nervous system, and cachexia [5, 6]. Changes in sympathetic activity lead to a metabolic switch, which is in part responsible for the perpetuation of inflammation and the increase in cardiovascular risk in RA patients [7].

Cannabis has been used since 4000 BC for the treatment of spasms and post-operative pain [8]. In the 1990s, the two main receptors for cannabinoids (cannabinoid receptors I and II; CB₁ and CB₂) were identified [9, 10]. Both receptors are activated by the psychoactive component of cannabis, tetrahydrocannabinol (THC), and several other synthetic and plant-derived cannabinoids [11]. Two major endogenous cannabinoids (endocannabinoids, ECs), arachidonylethanolamine (anandamide, AEA) and 2-arachidonylglycerol (2-AG), were described shortly after the discovery of CB₁ and CB₂ [12, 13]. In recent years, other receptors such as transient receptor potential vanilloid 1 (TRPV1), GPR55, or GPR18 were found to bind cannabinoids, and activation of these receptors is responsible for the off-target effects of several cannabinoids [14, 15, 16, 17, 18]. Transient receptor potential channel (TRP) modulation by cannabinoids might be explicitly important since these receptors not only influence sensation of pain, but also support inflammation [19].

This review describes physiological aspects of CB₁ receptors, pharmacological roles of ECs and the EC-degrading enzyme fatty acid amid hydrolase (FAAH), functional crosstalk between ECs and TRPV1, the interaction between ECs and the sympathetic nervous system in RA, the influence of ECs on arthritis disease sequelae in mice and humans, and direct immunomodulatory effects of CB₁ signaling in the periphery and in the brain. Considering this knowledge we finally try to demonstrate an optimum therapeutic EC approach in RA.
Possible effects of fatty acid amid hydrolase (FAAH) inhibition on neuroinflammation. CB₁ and TRPV1 are expressed throughout the brain by several cell types, including microglia. In addition, FAAH-degradable N-acylethanolamines activate several other anti-inflammatory pathways supporting the role of CB₁.

Since no data are available regarding the effects of FAAH on sympathetic activity or microglia, the following sequence is hypothetical in nature.

Upon activation, microglia produce pro-inflammatory cytokines and CB₁ activation opposes this

1. Since CB₁ controls neurotransmitter release, hypothalamic norepinephrine is decreased by FAAH inhibition, restoring brain-immune system-joint communication
2. Damaged neuronal tissue generated by the pro-inflammatory milieu is regenerated by CB₁ activation
3. FAAH inhibition elevates mood and depressive symptoms in patients disappear due to decreased brain cytokines levels
4. Rheumatoid arthritis patients often suffer from bad sleep quality, and this is surpassed by FAAH inhibition
5. In general, CB₁ activation decreases neuronal excitability, and this supports the general anti-inflammatory effect on microglia, which are activated by glutamate
6. The STOP symbol indicates inhibition, the PRIORITY ROAD symbol indicates an enhancement of a given effect
[Interaction]: Cannabinoid, Opioid, TRPV1-n Receptor and Pain Relief

[The “Triumvirate” triangle of cannabinoid, TRPV1 and opioid receptors]
Link: https://www.researchgate.net/publication/283446665_Receptome_Interactions_between_three_pain-related_receptors_or_the_Triumvirate_of_cannabinoid_opioid_and_TRPV1_receptors
Link: https://www.researchgate.net/figure/283446665_fig1_Fig-1-The-Triumvirate-triangle-of-cannabinoid-TRPV1-and-opioid-receptors-For

Abstract

A growing amount of data demonstrates the interactions between cannabinoid, opioid and the transient receptor potential (TRP) vanilloid type 1 (TRPV1) receptors. These interactions can be bidirectional, inhibitory or excitatory, acute or chronic in their nature, and arise both at the molecular level (structurally and functionally) and in physiological processes, such as pain modulation or perception. The interactions of these three pain-related receptors may also reserve important and new therapeutic applications for the treatment of chronic pain or inflammation. In this review, we summarize the main findings on the interactions between the cannabinoid, opioid and the TRPV1 receptor regarding to pain modulation.
The “Triumvirate” triangle of cannabinoid, TRPV1 and opioid receptors

[Interaction]: Cannabinoid, Opioid, TRPV1-n Receptor and Pain Relief

The figure shows the interactions between the three receptor types according to Tables 1–3. Red arrows indicate inhibitory, while blue arrows indicate excitatory effects.

The ligands which are mediating the inhibitory or excitatory effects are presented within the arrows.

The dashed arrows denote the indirect effect between the two receptors through the indicated intermediers in square brackets.

The acute (ac.) and chronic (chr.) administration of the ligands are also indicated in brackets in black and yellow color, respectively.

Legends and abbreviations: 2-AGE: 2-arachidonyl glyceryl ether (endocannabinoid); ac.: acute treatment; AEA: anandamide (endocannabinoid); AM251: CB 1
[Videos]: Human Microbiome Introduction

[The Invisible Universe Of The Human Microbiome]
Video Link: https://www.youtube.com/watch?v=5DTrENdWvvM

The next time you look in a mirror, think about this: In many ways you’re more microbe than human. There are 10 times more cells from microorganisms like bacteria and fungi in and on our bodies than there are human cells.

[You are your microbes - Jessica Green and Karen Guillemin]
Video Link: https://www.youtube.com/watch?v=1X8p0vhsWRE
Published on Jan 7, 2013 View full lesson: http://ed.ted.com/lessons/you-are-you...

From the microbes in our stomachs to the ones on our teeth, we are homes to millions of unique and diverse communities which help our bodies function. Jessica Green and Karen Guillemin emphasize the importance of understanding the many organisms that make up each and every organism.
[Videos]: Human Microbiome Introduction

[The Hungry Microbiome: why resistant starch is good for you]

Video Link: https://www.youtube.com/watch?v=NI3KtR3LogM
Published on Apr 9, 2014
Bowel cancer is the second most common cancer in Australia. Research shows that eating fibre rich in resistant starch is one way we can combat this threat. This animation shows how resistant starch moves through the intestine, feeds the healthy bacteria of the gut Microbiome and helps prevent cancer. More information on our website: http://www.csiro.au/hungrymicrobiome/

[Mind-altering microbes: how the microbiome affects brain and behavior: Elaine Hsiao TEDxCaltech]

Video Link: https://www.youtube.com/watch?v=FWT_BLVOASI
Published on Feb 8, 2013
Elaine Hsiao is a postdoctoral fellow in chemistry and biology at Caltech. She received her undergraduate degree in microbiology, immunology and molecular genetics from UCLA and her doctoral degree in neurobiology from Caltech with Professor Paul Patterson. She studied neuroimmune mechanisms underlying the pathogenesis of neurodevelopmental disorders and uncovered a role for the commensal microbiota in regulating autism-related behaviors, metabolism, and intestinal physiology. Elaine has received several honors, including predoctoral fellowships from the National Institute of Health, Autism Speaks and the Caltech Innovation Program. She is currently studying the mechanisms by which microbes modulate host production of neuroactive molecules and aims to better understand how the human microbiota influences health and disease.
[Introduction]: Human Microbiome

[Microbiome 101: Understanding Gut Microbiota]
Link: http://www.prescript-assist.com/intestinal-health/gut-microbiome/

[Human microbiome]
Link: https://www.britannica.com/science/human-microbiome

[Human microbiota]
Link: https://en.wikipedia.org/wiki/Human_microbiota

Link: http://www.serestherapeutics.com/our-science/microbiome-overview

What the heck is ‘Endocannabinoid Gut Microbiome Synergy’, you ask? This article is packed with resources about the theories of the Cloak and Dabber. With research that explains the synergy, you’re sure to have your mind blown!

Research links showing (crosstalk) between Human Microbiome and Endocannabinoid System via the Brain Gut Axis and 2 examples of synergistic ECS gut microbiota.

- The Human Microbiome Intro
- The Endocannabinoid System
- Endocannabinoids in the Gut
- The Role of ECS and Synergistic Gut Microbiota via the Brain Gut Axis
- 2 Examples of helpful Synergistic ECS-Gut Brain Microbiota
- Lactobacillus Acidophilus
- Akkermansia Muciniphila

- Connection: cannabis, mango fruit, synergistic Akkermansia Mucinphila microbiota, gut brain health.
- Vitamin Weed & Life Style, Super Foods, Milk Kefir, Hemp Seed, Raw Cannabis Juice
- Synergistic Probiotics and Foods promoting ECS Brain Gut Health
- Body, Colon Cleanse Detox
Quebec City, QC – The Canadian Institutes of Health Research (CIHR) is providing $10 million over seven years to fund the research of Vincenzo Di Marzo at the Université Laval. A globally renowned biochemist and pharmacologist from Italy, Di Marzo will become a Canada Excellence Research Chair (CERC) dedicated to studying the relationship between neurochemical signalling and metabolic health.

**Dr. Di Marzo** is an expert in the brain’s *endocannabinoid system*, a group of chemical signals responsible for physiological processes such as appetite, pain sensation, mood and memory. His research will examine the links between this system and the complex community of micro-organisms that live in the digestive tracts; links believed to be responsible for numerous health issues like obesity. He aims to develop new therapeutic treatments for these disorders which will deliver significant social and health benefits for Canadians while reducing the strain on Canada’s healthcare system.

“We already know much about the intestinal microbiota,” he said. “It basically consists of bacteria, viruses and yeasts, some with beneficial effects on the body and others with less. We also know that a change in the relative composition of gut microbiota affects physiological functions. Indeed, such a change is closely related to certain bowel disorders including inflammatory bowel disease, obesity, metabolic and cardiovascular disorders and even cancer. I hope to clarify this issue. I want to study the microbiota interactions with the human body at the molecular level. The intestine plays an essential role in many biological functions, including metabolism and the immune system. It consists of good and bad bacteria, generally well balanced. But when this balance is broken, there occurs a so-called “dysbiosis” which disrupts the body.”

“**Over the past five years, enormous advances have been made in our understanding of the connection between gastrointestinal micro-organisms and the brain’s endocannabinoid system,**” said Alain Beaudet, president, CIHR. “Dr. Di Marzo and his team are working at the cutting edge of this burgeoning area of research and will help to position Canada as a world leader in this field. We are proud to support their efforts, which will ultimately lead to better treatments for a wide range of conditions, including obesity and cardiovascular disease.”
[Synergy]: Gut Endocannabinoid - Opioid - Microbiome

[Lactobacillus acidophilus modulates intestinal pain & induces opioid & cannabinoid receptors]
Link: http://www.nature.com/nm/journal/v13/n1/full/nm1521.html
Link: https://www.ncbi.nlm.nih.gov/pubmed/17159985
Link: https://www.researchgate.net/publication/6639667_Lactobacillus_acidophilus_modulates_intestinal_pain_and_induces_opioid_and_cannabinoid_receptors

Abstract
Abdominal pain is common in the general population and, in patients with irritable bowel syndrome, is attributed to visceral hypersensitivity. We found that oral administration of specific Lactobacillus strains induced the expression of mu-opioid and cannabinoid receptors in intestinal epithelial cells, and mediated analgesic functions in the gut-similar to the effects of morphine. These results suggest that the microbiology of the intestinal tract influences our visceral perception, and suggest new approaches for the treatment of abdominal pain and irritable bowel syndrome.

[The Discovery of a New Potent Analgesic Yogurt]
Link: http://mappingignorance.org/2015/03/27/the-discovery-of-a-new-potent-analgesic-yogurt/

By using as analogy an experimental model of colitis where opioid (µ-, δ- and κ-) and cannabinoid (CB2) receptors have been shown to alleviate pain and inflammation, they hypothesize that probiotics may upregulate the expression of similar receptors on epithelial cells which are responsible for the transmission of nociceptive information to the intestinal nervous system. To this end, they first look at five representative probiotic bacteria from the Lactobacillus and Bifidobacterium genera (L. acidophilus NCFM, L. sadivarius Ls-33, L. paracasei Lpc-37, B. lactis Bi-07 and B. lactis Bl-04) and their ability to modify the expression of these receptors involved in analgesia when cultured along with a human epithelial cell line. Among all, only L. acidophilus NCFM was shown to increase both the expression of OPRM1 and CNR2 mRNA (genes coding for µ-opioid and CB2 receptors, respectively), but more importantly a 25-60% from all epithelial cells had the receptors (meaning the mRNA is also translated) with no major adverse effects in the intestinal tract. Furthermore, by using a transgenic fibroblast mouse cell line in which the NF-κβ signalling pathway was impaired, the effect could be prevented (highlighting the critical role of the pro-inflammatory pathway for the gene receptor expression to happen).
Probiotics therapy has been shown to treat visceral hyperalgesia. For example, *Lactobacilli acidophilus NCFM* modulates intestinal pain and activates opioid and cannabinoid receptors. In addition, according to Dr. Manning, *L. reuteri* prevents colonic hyper-excitability and *L. plantarum* inhibits inflammatory distention and pain. Probiotics use has been reported to reduce anxiety and stress response, and improve mood in patients with irritable bowel syndrome and chronic fatigue syndrome. Tillisch et al has shown that consumption of a fermented milk product containing specific probiotics modulates brain activity affecting midbrain connectivity.²

One of the best strains of probiotics out there is Lactobacillus Acidophilus. Much like Lactobacillus Brevis, this strain of probiotic occurs naturally within the body. Not only does it promote digestive tract and immune system health, it also helps in the production of lactase.² This could provide some benefit to those with lactose intolerance. Some research suggests *L. acidophilus* may also provide some benefit for cardiovascular health by reducing cholesterol.³

It helps to maintain a healthy balance of bacteria in your digestive tract by producing vitamin K, lactase, acidophilin, acedolin, bacteriocin, and lactocidin. In doing so, Lactobacillus acidophilus helps your body naturally break down lactose into simple sugars. It even modulates immune system function.⁴ Some research even suggests it may provide some help with urinary tract infections, *irritable bowel syndrome*, and bacteria deficiencies caused by antibiotics.
[Synergy]: Gut Endocannabinoid - Opioid - Microbiome

[Chronic opioid use is associated with altered gut microbiota and predicts readmissions in patients with cirrhosis]

Link: https://www.ncbi.nlm.nih.gov/pubmed/27868217
Link: https://www.researchgate.net/publication/310603779_Chronic_opioid_use_is_associated_with_altered_gut_microbiota_and_predicts_readmissions_in_patients_with_cirrhosis

C. Acharya; N. S. Betrapally; P. M. Gillevet; R. K. Sterling; H. Akbarali; M. B. White; D. Ganapathy; A. Fagan; M. Sikaroodi; J. S. Bajaj

Abstract

Opioid use is epidemic in cirrhosis, which could precipitate hepatic encephalopathy (HE) potentially through gut dysbiosis and inflammation. To define the effect of opioids on readmissions and on gut microbiota composition and functionality. Cohort 1 had 200 cirrhotic in-patients (with/without opioid use) followed prospectively through the index hospitalisation and 6 months post discharge. Readmissions (HE-related/unrelated) were compared between patients discharged on opioids compared to the rest, including using a multi-variable analysis. Cohort 2 consisted of 72 cirrhotics on chronic opioids who were age/model for end-stage liver disease (MELD) and prior HE-balanced with 72 cirrhotics not on opioids. Stool microbiota composition (multi-tagged sequencing), predicted functionality (PiCRUST), endotoxemia and systemic inflammation (IL-6, IL-17) were compared. Cohort 1: Chronic opioid use was statistically similar between those admitted with/without HE, and was judged to be an HE precipitant in <5% of cases during the index hospitalisation. Of the 144 patients alive at 6 months, 82 were readmitted. The opioid users had a significantly higher all cause (69% vs. 48%, P = 0.008), but not HE-related readmissions (30% vs. 41%, P = 0.30). On regression, opioid therapy and female gender were predictive of readmission independent of MELD score and previous HE. Cohort 2: Significant dysbiosis was noted in the opioid cohort, especially in HE+opioid patients with lower autochthonous taxa and Bacteroidaceae relative abundance. PiCRUST showed highest aromatic amino acid and endotoxin production in opioid users. Opioid users also had higher endotoxemia and IL-6 but not IL-17. Chronic opioid use in cirrhosis is associated with increased endotoxemia, dysbiosis and all-cause readmissions.

[Natural Ways To Improve Mood By Increasing Our Opioids and Endorphins]

Link: https://saveourbones.com/fight-pain-naturally-and-increase-opioids-with-these-13-scientifically-backed-tips/

Your Brain And Opioids

Opioids are substances that connect with receptors in your brain, to influence your experience of stress or pain and to regulate motivation, emotion, attachment, hunger and satiety. Your brain has four major opioid receptors. They are:

- mu-opioid (MOR)
- delta-opioid (DOR)
- kappa-opioid (KOR)
- nociceptin (NOR)

These receptors receive different opioids and have different effects. Your body naturally produces opioids that pair with these receptors, creating useful positive effects. One well-known example is endorphins, a group of hormones that pair with mu-opioid receptors. You have probably heard endorphins mentioned in relation to their mood enhancing feel-good effects.
[Synergy]: Gut Endocannabinoid - Opioid - Microbiome

[The Role of Nutrition in Modulating Chronic Pain]

This topic was addressed by Heather Tick, MD, Clinical Associate Professor in the Departments of Family Medicine and Anesthesiology and Pain Medicine at the University of Washington Medicine, in Seattle, at PAINWeek 2016.¹

“Food is the first thing I talk about with most of my patients,” she states in the introduction to her presentation. “Why is that so important [to talk about food]?” she asks. “Basically, it is because every single time you eat, you change your body chemistry. And that is not an exaggeration: you either increase your inflammation, or you decrease your inflammation.”

[Opioid-induced gut microbial disruption and bile dysregulation leads to gut barrier compromise and sustained systemic inflammation]
Link: http://www.nature.com/mi/journal/v9/n6/full/mi20169a.html

Mucosal Immunology 9, 1418-1428 (November 2016)
S Banerjee, G Sindberg, F Wang, J Meng, U Sharma, L Zhang, P Dauer, C Chen, J Dalluge, T Johnson and S Roy

Abstract

Morphine and its pharmacological derivatives are the most prescribed analgesics for moderate to severe pain management. However, chronic use of morphine reduces pathogen clearance and induces bacterial translocation across the gut barrier. The enteric microbiome has been shown to have a critical role in the preservation of the mucosal barrier function and metabolic homeostasis. Here, we show for the first time, using bacterial 16s rDNA sequencing, that chronic morphine treatment significantly alters the gut microbial composition and induces preferential expansion of Gram-positive pathogenic and reduction in bile-deconjugating bacterial strains. A significant reduction in both primary and secondary bile acid levels was seen in the gut, but not in the liver with morphine treatment. Morphine-induced microbial dysbiosis and gut barrier disruption was rescued by transplanting placebo-treated microbiota into morphine-treated animals, indicating that microbiome modulation could be exploited as a therapeutic strategy for patients using morphine for pain management.