GH Medical

Therapeutic Cannabinoids

At GH Medical we research cannabinoids, their natural role in the human body and their potenial to prevent and cure diseases.

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Cannabis medically revisited

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It probably has not escaped anyone that cannabis is getting a lot of media attention lately. In the public eye, the image of cannabis is rapidly shifting from gateway drug to universal cure. What people may have missed though, is why cannabis is suddenly receiving all this positive attention.

The endocannabinoid system guards life's most critical functions.

The reason for this revolution is a fairly recent discovery in biology: the endocannabinoid system. The endocannabinoid system is what separates us from amoebae. The human body consists of hundreds of billions of cells. The fact that we are not just a big blob of cells but precisely sculpted, functional human beings is due to the endocannabinoid system. This system governs life's most critical functions such as the control of cell division, metabolism, immune system and brain activity (Figure 1).

Failure to control cell division may lead to cancer on the one hand and to degenerative diseases like Alzheimer's, Parkinson's or Huntington's on the other.

Similarly, energy levels need to be tightly controlled. Failure to do so can lead to anorexia on the one hand and bulimia on the other. A strong connection between cannabis and feeding behavior has always been suspected, but now science is uncovering the underlying mechanism. Being able to discriminate self from non-self is another crucial condition for life. Failure results in autoimmune disease like Crohn's (irritable bowel syndrome), multiple sclerosis, psoriasis or debilitating inflammation.

Finally, intelligent life requires tight control of behavior or brain activity. Failure to maintain this balance can manifest itself as epilepsy, autism, migraine, schizophrenia or depression.

For this reason, cannabis use has often been associated with these diseases. Only where cannabis was usually blamed for causing mental disorders, it is now increasingly recognized that many people are genetically predisposed to and might actually self-medicate to stave off these very disorders. Combined, a picture emerges where many seemingly distinct diseases share a common defect: a dysfunctional or overstressed endocannabinoid system. Since endocannabinoids are functionally very similar to plant cannabinoids, plant cannabinoids can be exploited to boost the endocannabinoid system and promote mental and

physical balance. This is the key to the therapeutic potential of plant cannabinoids.

What are cannabinoids?

Before we go deeper into the therapeutic qualities of cannabinoids, let's take a closer look at what cannabinoids are exactly and how they fit in our metabolism (Figure 2).

Everything we consume at some point passes the Citric Acid Cycle, the central hub in our metabolism. In the Citric Acid Cycle our food is broken down to its raw elements, mostly Carbon, Hydrogen, Oxygen, Nitrogen, Sulfur and Phosphorus, and reshuffled. Carbon, hydrogen and oxygen are sufficient to produce carbohydrates for energy and lipids for cell membranes. Adding Nitrogen, Sulfur and Phosphorus produces our genetic information/DNA and our cell machinery/ proteins.

Diacylglycerol (DAG) is a major source of lipids and fatty acids in our body, including all lipid endocannabinoids.[1] Dietary supplementation with omega-6 and especially omega-3 fatty acids feeds directly into this point to boost your endocannabinoid levels. This is why omega fatty acids are so healthy!

Isoprene is a basic building block for many essential oils, but also cholesterol, sex hormones and plant cannabinoids. Stacking isoprene units produces molecules with different functions: one isoprene unit forms the basis for the smell of pear, two for the smell of menthol and three for the smell of ginger for instance (see Figure 2). Plant cannabinoids are produced from a backbone of four isoprene units. Six units form cholesterol and sex hormones. Ten isoprene units form Q10, which is often used in creams to rejuvenate the skin. Adding more isoprene units produces more viscous substances such as latex, which is made of 30 isoprene units.

Thus, both endocannabinoids and plant cannabinoids are natural compounds that are directly derived from or compatible with our core metabolism and share structural and functional properties with our steroid hormones.

[1] With the exception of a recently discovered class of endocannabinoids which are derived from hemoglobin, the oxygen carrier in our blood.

How do cannabinoids work?

Now that we have a global idea what cannabinoids are, let's look at how they work. When a cell is activated or otherwise appropriately stimulated, the cell will respond by releasing endocannabinoids from its plasma membrane (the lipid coat covering the cell, see figure 3). The general rule is that more activation means more released cannabinoids means more target activity. This is the case for TRPV1 and CB1/2 in figure 4 but for instance mTOR shows decreased activity with increased cannabinoid dose. To date, 18 endocannabinoids have been described that bind to cannabinoid receptors. One cannabinoid receptor can have multiple targets (for instance CB1/2). This is divergence. Vice versa, multiple cannabinoid receptors can have the same targets and multiple targets can influence the same process (for instance energy production in mitochondria). This is convergence. With 18 endocannabinoids, 32 plant cannabinoids and 42 cannabinoid receptors (see below), combined with the principles of convergence and divergence, the cannabinoid system forms a web of 1000s of biochemical interactions that keep life within carefully monitored limits.

Mitochondria, the cells' own power plant and the endoplasmic reticulum, the cells' protein factory are two major targets for many components of the endocannabinoids system.

All incoming endocannabinoid signals inform the cell about its energy state and its redox or stress state.

The energy state is determined by the ratio of ATP, the charged version of the universal energy carrier in nature and ADP, the uncharged version. The redox state is determined by the ratio of reduced to oxidized elements in the cell. Oxidized elements cause damage to the cell and can even induce DNA damage, mutations etc. This is what anti-oxidants in our diet prevent. Coincidentally, cannabinoids are the best anti-oxidants in nature! When ATP is high, ADP is low and reduced and oxidized elements are in balance, this signals to the cell nucleus that all is well and the cell can continue what it is doing (dividing or growing etc.). When ATP is in balance with ADP and so are reduced and oxidized elements this signals moderate stress to the cell nucleus. The cell will respond by adapting what it is doing until the signal is 'all green' again.

When ATP is low, ADP is high, reduced elements are low and oxidized elements are high this signals considerable stress to the cell nucleus. The cell will respond by initiating a cell-autonomous suicide program called apoptosis. Through apoptosis a single cell sacrifices itself for the greater good of the system (the whole body).

Under the most severe stress, there is no energy/ATP and only uncharged ADP left. In addition the oxidized elements heavily outweigh the reduced elements. In this case, the cell is beyond apoptosis and the immune system kicks in to eliminate the overstressed cell.

The cannabinoid receptors involved and subsequent signaling cascades may depend on the physiological situation or on the disease at hand but in general this is how the endocannabinoid system works.[1]

[2] Adapted from: Philosophical Transactions of the Royal Society B, Nunn et al., 2012

The endocannabinoid system guards life's most critical functions

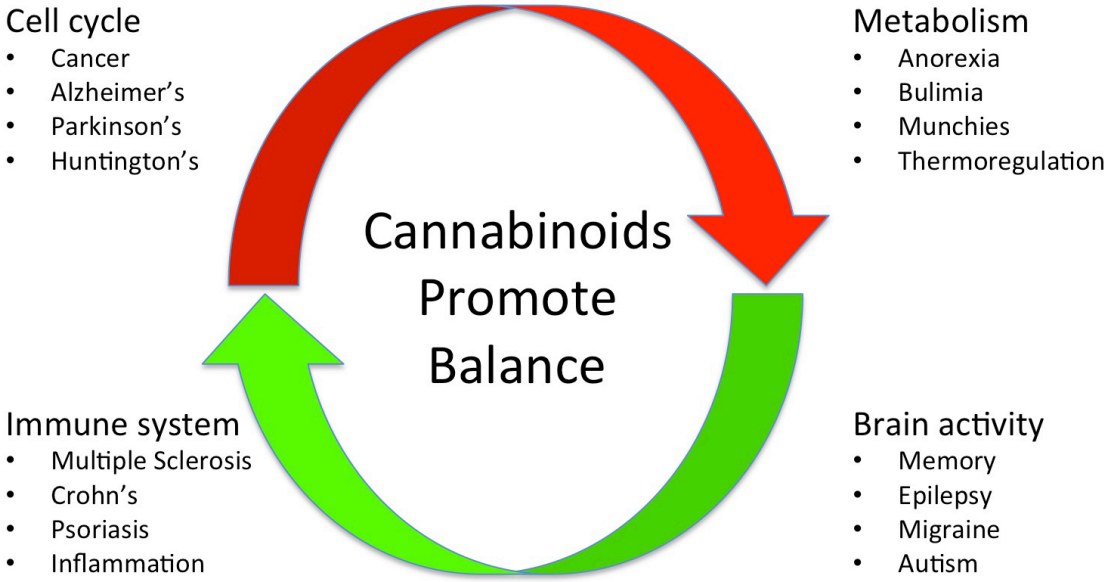
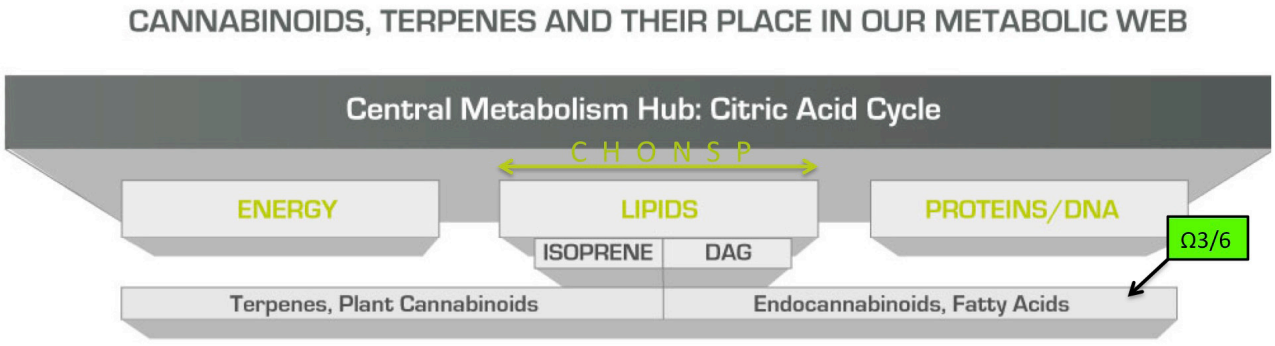


Figure 1



Carbon	Isoprene	Terpene	Terpenoid examples
5	1	hemiterpene	Pear, Smelly Feet
10	2	monoterpene	Menthol, Most Essential Oils/Classical TERPENES
15	3	sesquiterpene	Ginger, Hop, Cloves, Sex/Stress Hormones
20	4	diterpene	CANNABINOIDS, Vitamin A
30	6	triterpene	Cholesterol (Sex/Stress Hormones)
40	8	tetraterpene	Carotene, Lycopene, Anti-oxidants, Colorants
more	poly	polyterpene	Q10/Ubiquinone (Energy production), Latex

Figure 2

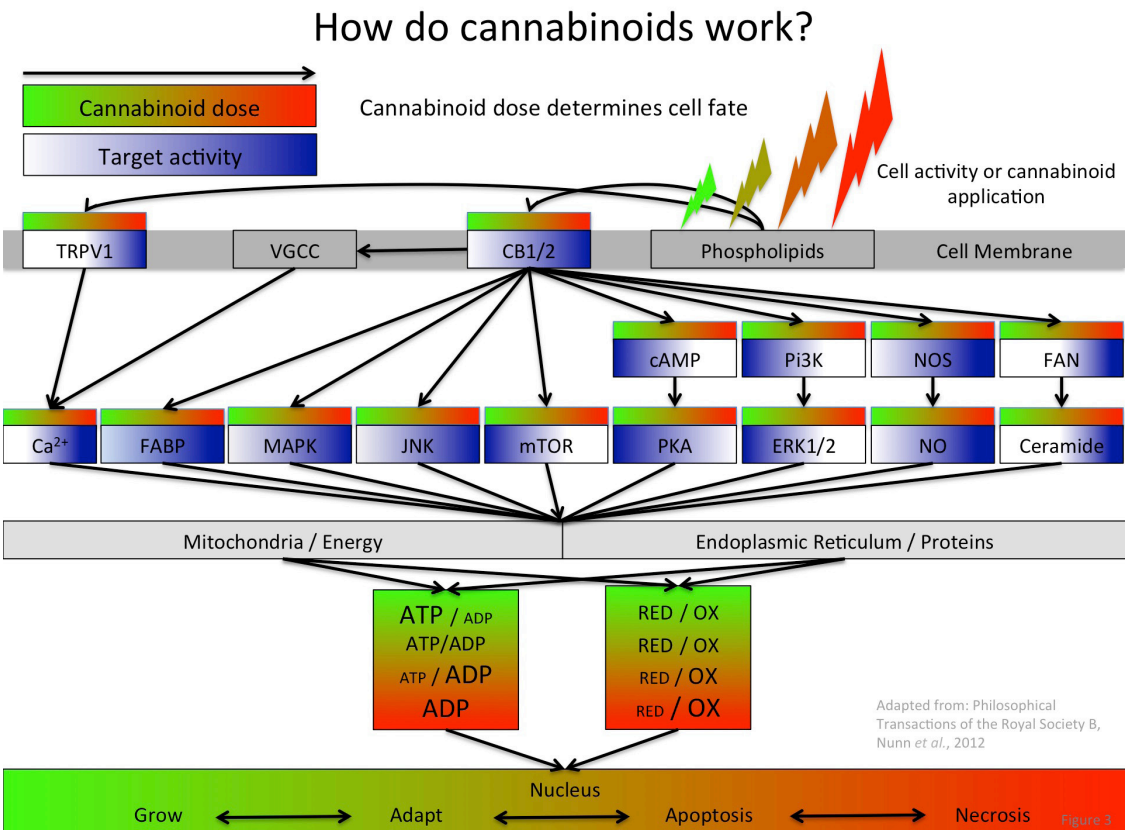


Figure 3

Cannabinoids can alleviate symptoms or even cure disease

1. Addiction
2. ADHD
3. AIDS
4. Alzheimer's disease
5. Anorexia
6. Anxiety
7. Arthritis
8. Autism
9. Bladder cancer
10. Bone cancer
11. Breast cancer
12. Bulimia
13. Cervical cancer
14. COPD
15. Crohn's
16. Cystitis
17. Depression
18. Diabetes
19. Eczema
20. Epilepsy
21. Glioblastoma
22. Huntington's
23. Hypoxic-ischemic encephalopathy
24. Insomnia
25. Klinefelter Syndrome
26. Leukemia
27. Malaria
28. MDMA come-down
29. Migraine
30. Morphine interaction
31. Multiple Sclerosis
32. Obesity
33. OCD
34. Pain
35. Parkinson's
36. Prostate Cancer
37. Psoriasis
38. Psychosis and Schizophrenia
39. PTSD
40. Stroke
41. Tinnitus
42. Tourette's

28,976 scientific papers published (June 2015)

99% of all research is focused on two cannabinoids:

THC, very therapeutic and makes you high / stoned

CBD, less therapeutic but does not make you high / stoned

Figure 4

Cannabinoids can alleviate symptoms or even cure disease

The therapeutic use of cannabinoids goes back thousands of years to places like India and China where cannabis was recommended for malaria, dysentery and constipation, to block rheumatic or menstrual pain, to induce sleep and to stimulate appetite.

Unfortunately, much evidence for the therapeutic value of cannabinoids is anecdotal and not backed by scientific method. Still, a wealth of scientific data exists that supports the therapeutic use of cannabinoids.

To date, there is scientific evidence for the therapeutic value of cannabinoids in many disorders (Figure 4). This includes some of the most debilitating and financially burdening diseases in the developed world: Alzheimer's, cancer, depression, diabetes, epilepsy, obesity, pain and others. For a detailed description of this evidence please see: (http://www.ghmedical.com/diseases-2/). This list is likely to grow, as any disorder marked by unbalanced cell division, metabolism, immune system or brain activity is potentially eligible for cannabinoid therapy.

Strikingly, the bulk of evidence for therapeutic cannabinoids is based on THC and CBD. THC, the quintessential cannabinoid, is known for stimulating appetite, blocking pain and inducing sleep and amnesia. In addition, THC can actually stop cancer cells from dividing and for instance brain cells from an Alzheimer's patient from degenerating. Interestingly, although THC usually wreaks havoc on the memory of recreational users, it can actually improve memory in demented patients. This shows an important point: the effect of cannabinoids very much depends on the individual and the situation. In short, THC is the main psychoactive cannabinoid but it has phenomenal therapeutic potential too.

CBD a sort of THC-light; the therapeutic properties of CBD are weak compared to THC, but CBD is not psychoactive. In fact, CBD can counteract the psychoactive effect of THC, prevent a patient from getting high/stoned and thus increase the therapeutic value of THC. This shows another important point that cannabinoids can be used in combination to synergistically sculpt the desired effect.

'Orphan' cannabinoids with unknown functions

Apart from THC and CBD, 30 other plant cannabinoids have been described that activate one of 42 cannabinoid receptors in the body (Figure 5, 6). Next to nothing is known about any of these cannabinoids. However, these cannabinoids are bound to have therapeutic value as cannabis extracts (arguably containing all cannabinoids in varying amounts) consistently give better clinical results than isolated individual cannabinoids (read THC and CBD). This suggests the presence of other cannabinoids with unknown functions enabling more synergy between cannabinoids (see above). The reason nothing is known about these orphan cannabinoids is simply because they are not around in sufficient quantity to conduct research or to use therapeutically. Ironically, this could be a result of selective breeding; since cannabis was banned by the United Nations in 1937 all selection criteria apart from the recreational ones became obsolete. As a result, every commercially available cannabis strain in the world is high in THC and low in most other cannabinoids.

In order to exploit the full therapeutic potential of cannabis, these 'orphan' cannabinoids should be isolated, purified and tested. GH Medical has unique access to original cannabis landraces that have not been bred to boost THC levels and are

expected to have relatively high levels of other cannabinoids.

Cannabinoid receptor classes

Just as there are more cannabinoids than just **THC**, there is more than one cannabinoid receptor. To date, we have found 42 receptors that are activated, blocked or otherwise modulated by cannabinoids. These receptors are divided over 10 classes (Figure 6).

The first class, of 'true' cannabinoid receptors consists of two members. **CB1** is most abundant in the brain but present throughout the body. Although **CB1** can mediate many functions it is best known for its negative feedback role in brain activity: Depolarization-induced Suppression of Excitation/Inhibition. In short this means that when a nerve cell is activated by another nerve cell, it will release an endocannabinoid that will reduce the chance of being activated by that cell again. As a result stronger connections get weaker and weaker connections get a chance to grow stronger. This 'democratizing' factor is the reason why cannabis users often report difficulties remembering things on the one hand and increased inspiration/ association on the other.

CB2 is most abundant on cells of the immune system but can be found throughout the body. Like **CB1, CB2** can adopt many functions but it is best known for its capacity to suppress, boost or modulate the immune system and inflammatory reactions.

Both **CB1** and **CB2** are **G** Protein Receptors. **GPRs** are a family of proteins that control a range of critical cellular functions such as cell division and metabolism. It is the potential to interfere with these processes that explains the vast therapeutic potential of cannabinoids.

The second class of 'orphan' cannabinoid receptors also consists of **GPRs**. These receptors are called orphans because their main function or classification is still under dispute. Still, **GPR18** is involved in programmed cell death and immune responses.

GPR30 is involved in breast and prostate cancer and has an interaction with CBD that needs to be further defined.

GPR55 most likely plays a role in cell division and growth.

GPR119 is involved in insulin secretion and food intake.

The third class is that of 'nuclear' receptors. Nuclear receptors are involved in the regulation of genes and are essential factors in cell differentiation and metabolism.

PPARα is involved in lipid metabolism and neuro-protection.

PPARγ regulates fat, insulin sensitivity and inflammation.

PPARβ/δ is present in brain, fat tissue and skin but other than binding them, their role regarding cannabinoids is unknown.

The fourth class of receptors is formed by **TRPs** for Transient Receptor Potential. **TRPs** are best known for their involvement in vision and the sensation of pain, temperature, pressure and various tastes. **TRPV1, 2, 3** and **4** are involved in body heat regulation and the detection of pain and… Vanilla. **TRPA1** is involved in the detection of pain, cold and stretch.

TRPM8 has an unspecified role in general sensory perception.

‘Orphan’ cannabinoids with unknown functions

1	CBV	10	THCA	19	8-OH-CBN
2	THCV	11	THCVA	20	CBV
3	CBC	12	11-OH-Δ9-THC	21	6,7-epoxy-CBG
4	CBG	13	11-COOH-Δ9-THC	22	5-metoxy-CBG
5	CBN	14	10-α-OH-THC	23	4-OH-5-acetoxy-CBG
6	CBDA	15	Cannabiripsol	24	Cannabichromanone B
7	CBGA	16	10-α-OH-HexaHC	25	Cannabichromanone C
8	CBDV	17	Δ8THC	26	Cannabichromanone D
9	CBGV	18	10-α-OH-Δ8THC		

Figure 5

List of receptors and ion channels that are activated, blocked or modulated by cannabinoids

True:
CB1
CB2

Ca^{2+}-channels:
L-type
N-type
P/Q-type
T-type

Na^{+}-Channels:
Nav1.1
Nav1.2
Nav1.5

Orphan:
GPR55
GPR119
GPR18
GPR30

K^{+}-Channels:
K-ATP
TASK-1
TASK-3
TREK-1
Kv1.2
Kv1.5
Kv3.1
Kv4.3

Nuclear:
PPARα
PPARβ/δ
PPARγ

Serotonin:
1a
2a
3

Opioid:
μ
δ

TRPs:
TRPV1
TRPV2
TRPV3
TRPV4
TRPA1
TRPM8

Other:
nAChRs
GlyRs
NMDARs
α2

Figure 6

For the remaining classes of cannabinoid receptors the term receptor is used liberally to cover anything that has a direct interaction with a cannabinoid, with functional consequences.

These receptors are various types of neurotransmitter receptors and ion channels that form the core machinery of the brain; calcium channels, sodium channels, potassium channels, serotonin receptors, opioid receptors and receptors for acetylcholine, glycine, glutamate and adrenalin. Because these receptors are so central to brain function their interactions with cannabinoids offer huge therapeutic potential. Already, cannabinoids were found to be promising in brain disorders ranging from epilepsy and migraine to autism, depression and psychosis. Although the results were far from equivocal, it must be noted that we have only just scratched the surface of cannabinoid research and further research is warranted.

The list of cannabinoid receptors will probably have several future updates but already a picture is emerging that cannabinoids have a wide range of receptors that regulate many critical functions in the body and thus that the therapeutic promise of cannabinoids is vast.

Smoking cannabis has limited therapeutic potential; concentrated extracts are required

The majority of medical cannabis patients prefer to smoke their cannabis. This is probably because smoking cannabis is relatively fast in onset and easy to dose. Therefore, let's see what happens when someone smokes cannabis (Figure 7). In the top panel, the red bars represent receptors that can be activated by THC. The vertical axis represents the physiological range of cannabinoid levels that can be found in the body. The transparent red box illustrates the range of THC levels that can be expected at the peak, ten minutes after starting to smoke (top of the box), after half an hour (red line) and after 2 hours (bottom of the box). When a red bar does not reach the red box (GPR55) this means that this receptor will be activated strongly and for a long time after smoking cannabis.[3]

When a red bar ends in the red box (CB1) this means the receptor will be activated as long as the cannabinoid level is higher than the bar.
When a red bar ends above the red box (TRPV3) this means the receptor is never activated by smoking cannabis. In the case of THC this means that 8 out of 18 receptors are never activated. However, the bottom panel shows that 0 out of 19 receptors are activated by CBD after smoking cannabis . This shows a very important point about cannabinoids: smoking cannabis may be effective to treat some ailments but it cannot be expected to have therapeutic potential for each of the diseases mentioned above. Therefore, to reach the full therapeutic potential of cannabinoids, stronger cannabinoid preparations or extracts are necessary. Also, smoking may not be the most effective way to deliver cannabinoids and other routes of cannabinoid application need to be explored (see figure 8).

[3] Values for receptor activation are derived from literature. For a full justification of the used values please see: http://www.ghmedical.com/endocannabinoid-system/ THC values are adopted from: Huestis, M.A. (2007). Human Cannabinoid Pharmacokinetics. Chem. Biodivers. 4, 1770–1804.
CBD values after smoking a cannabis have never been measured but are extrapolated from THC and the estimated CBD content in commercially available cannabis.

Smoking cannabis does not activate all receptors

Stronger extracts are needed!

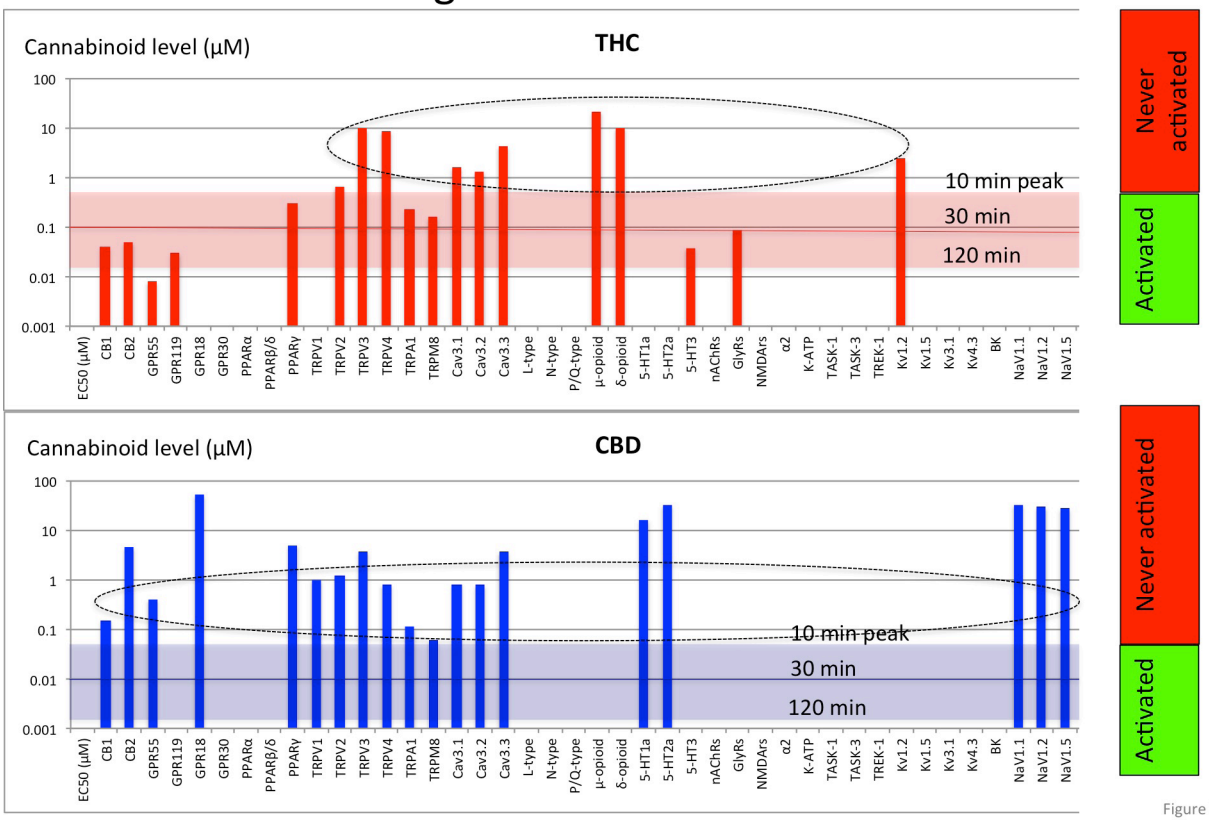
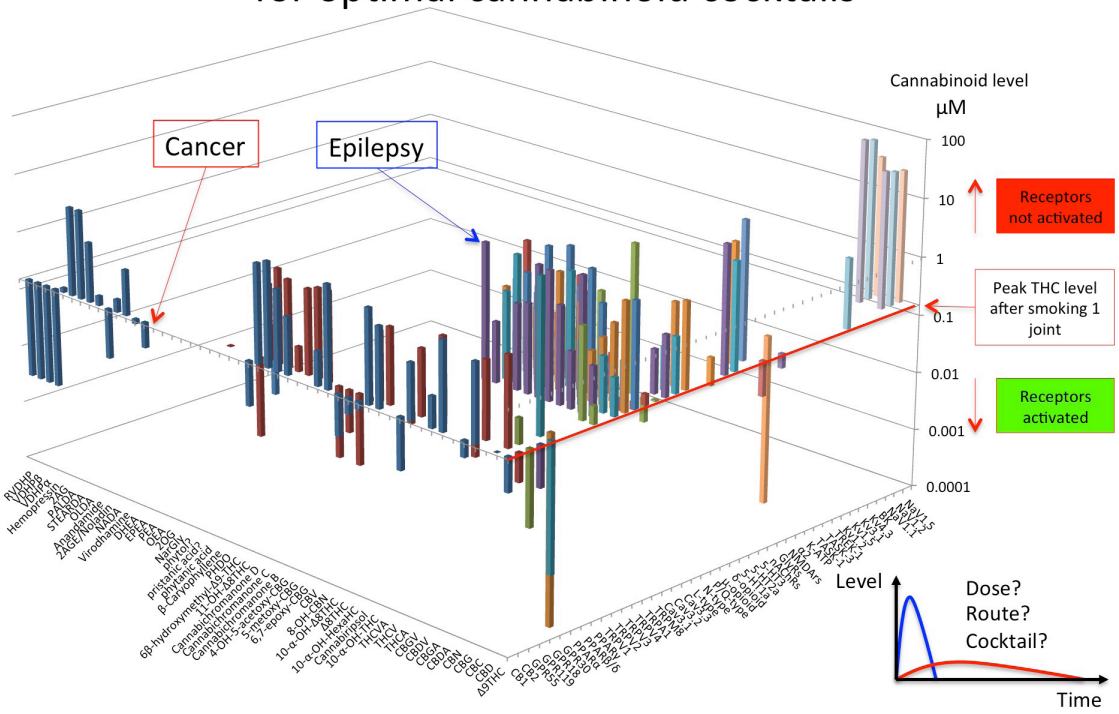


Figure 7

Figure 7



18 endocannabinoids + 32 plant cannabinoids x 42 cannabinoid receptors = 1000s of solutions

Figure 8

Cannabinoid – Receptor Activation Matrix for optimal cannabinoid cocktails

When we make a similar receptor activation profile for all cannabinoid receptors, we end up with the Cannabinoid-Receptor Activation Matrix (Figure 8).[4]
The X-axis, going from the front to the left contains all plant cannabinoids (THC, CBD etc.) and all endocannabinoids (NarGly, 2OG etc.) that are known to bind, activate, inhibit or otherwise modulate the function of any of the known cannabinoid receptors.

The Y-axis, going from the front to the right contains all cannabinoid receptors known to be bound, activated, inhibited or otherwise modulated by any of the known cannabinoids.

The vertical Z-axis, going from 0.0001 to 100 µM (micromolar) covers the physiological range of cannabinoid concentrations at which they operate (bind receptors).

The red line on the Y-axis indicates the peak THC level after smoking one joint (corresponding to the top of the red bar in figure 7). If we draw a virtual plane through the graph at the level of the red line any bar pointing up represents a receptor that is not activated by that particular cannabinoid at that concentration. Any bar pointing down represents a receptor that is activated.
What we see is that at this particular level (peak THC level after smoking one cannabis cigarette) most receptors are not activated by most cannabinoids. It should be realized though that most cannabis is very high in THC and very low in all other cannabinoids and realistic cannabinoid levels are easily 10 to 100 times lower than that of THC. If we were to draw a plane around the 0.01 or 0.001 we would see that almost no receptors are activated. This means that smoking a joint may activate a few receptors by THC but the vast majority of cannabinoid-receptor interactions require far higher cannabinoid levels and thus different methods of application.

The Cannabinoid-Receptor Activation Matrix shows that different cannabinoid receptors are differentially activated by different cannabinoids at different levels. We also know that different receptors are relevant to different bodily functions. Thus, to combat cancer an entirely different cocktail of cannabinoid is required than for instance to treat epilepsy.

The data used in this graph is derived from many different studies using different methodologies making interpretation of this matrix difficult.
In addition, many of the possible cannabinoid-receptor interactions are still blank. This could be because the interaction does not exist or because it has not been tested yet.

As a first step towards discovering the full therapeutic potential of cannabinoids, the Cannabinoid-Receptor Activation Matrix should be remade using standardized methods. This matrix can then be used to formulate optimal cannabinoid cocktails for each eligible disease.

[4] The Cannabinoid-Receptor Activation Matrix is derived from a meta-analysis of values reported in many different studies. Since not all studies used the same methodology and criteria one should be careful interpreting this graph. However, one conclusion that can be safely drawn from this graph is that most cannabinoid receptors are activated by different cannabinoid at different levels and thus that cannabinoid cocktails of different compositions can be used to achieve any particular effect.

Route of application

Apart from finding the right cannabinoid cocktail, the route of application is equally relevant to devise optimal treatment for any particular disorder (Figure 9).

Smoking

As discussed above, smoking cannabis may be suited to treat some diseases or discomforts but leaves many receptors un-activated and is therefore not an option for each possible disease. In addition, smoking incinerates about 30% of the available cannabinoids. Also the effect peaks quickly and lasts shortly.

Eating

When eating cannabinoids, the effect takes a lot longer to start, peak and taper off. However, ingested cannabinoids are bathed in stomach acid first and then partially metabolized the liver, severely limiting cannabinoid bioavailability.[5]

Sublingual

Applying cannabinoids to the mucous membranes in the mouth (tongue, cheek, pallet or gums) rather than ingesting them doubles bioavailability and dramatically reduces the 'time-to-effect'.

Topical

Application to the skin takes hours to take effect but the effect can last up to days. Similar but distinct effects are reached by rectal or vaginal application. Topical application is slow in onset, long in duration and, importantly, does not produce psychoactive side-effects.

Nasal

Alternatively cannabinoids delivered by nasal spray can take effect in seconds.
Thus, depending on the desired effect different routes of application might be preferred.

Clinical trials

Once the optimal cannabinoid cocktail and route of application to treat any particular disease has been formulated, these cocktails can be tested in clinical trials. Until then, the only option is whether or not the cocktail is psychoactive (makes a patient high or stoned); THC is the main psychoactive ingredient in cannabis, but it is (currently) also the cannabinoid with most therapeutic value attributed to it. Therefore, a cannabis extract that is high in THC can be used therapeutically but it comes with the risk of getting high.

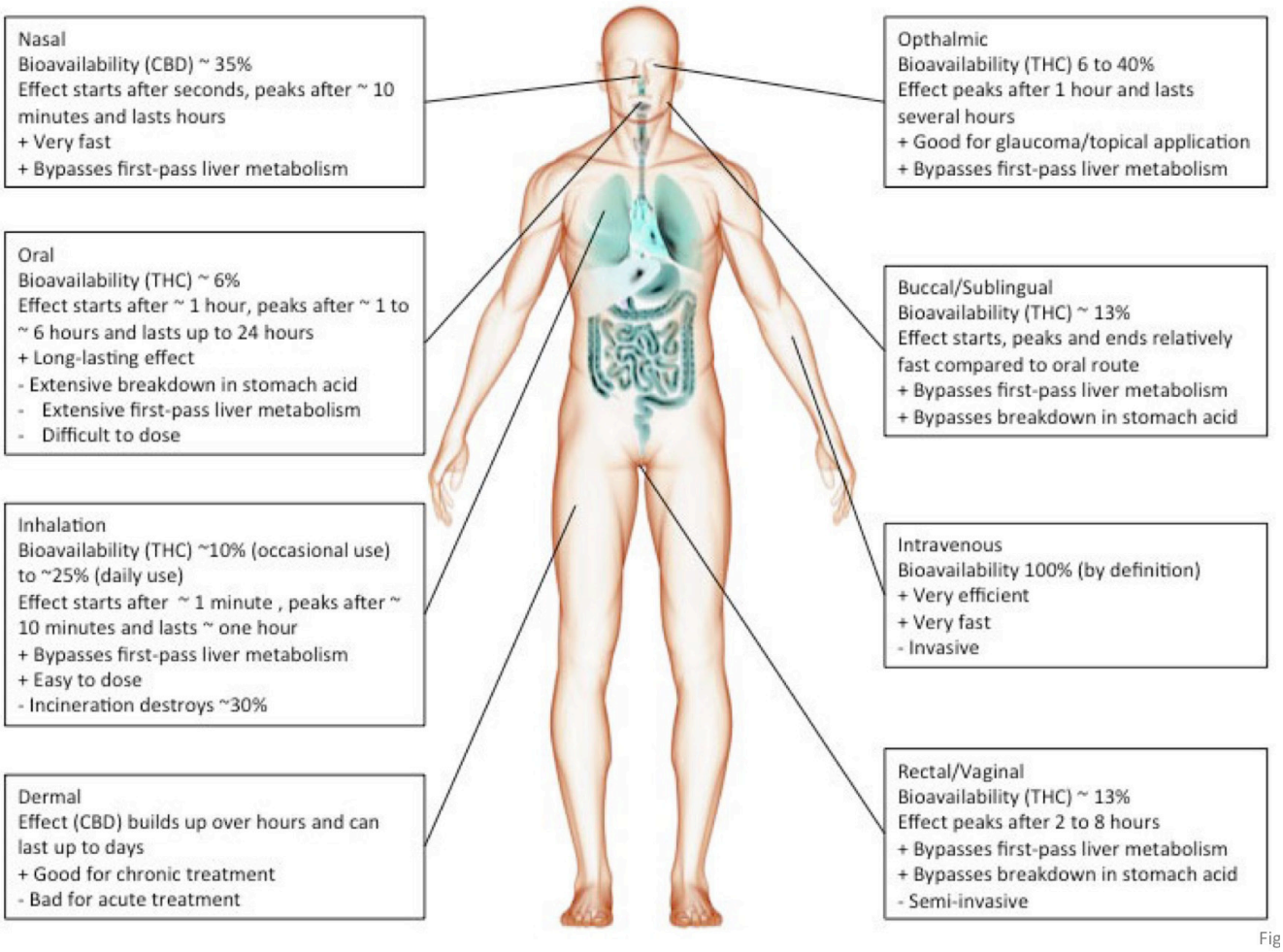
A patient that only wants the therapeutic effects of cannabinoids without getting high can opt to have extra CBD added to neutralize the psychoactive effects of THC without interfering with the therapeutic benefits.

Alternatively, one could choose to leave psychoactive cannabinoids out of the cocktail altogether although it should be noted that non-psychoactive cannabinoids so far have shown far less therapeutic effect than THC and therefore these cocktails will be less effective in many diseases.

Still the best therapeutic effect can be expected once we start formulating cannabinoid cocktails specific to particular diseases but this requires time, money and a political climate that will allow us to do this life-saving research.

[5] Bioavailability is a measure for the percentage of a biologically active substance that is available for a reaction. By definition injected compounds have a 100% bioavailability and every other route of application is compared to that.

Route of application



Fig

Figure 9

Perspective

Cannabinoids are revolutionary even from a biological perspective: The general evolutionary dogma in life is to be energy efficient, kill anything foreign to the body and maximize brain function/ memory.

Energy efficiency causes us to store excess food, making us fat.

Energy efficiency also causes genetic control over cell division to decline with age, causing cancer, Alzheimer's etc.

A rigorous immune system killing anything it does not recognize causes collateral damage such as multiple sclerosis, irritable bowel syndrome and inflammation.

Lastly, our immensely developed and efficient brains have developed sophisticated bugs like autism, epilepsy, depression and psychosis. Cannabinoids loosen the reigns of efficiency on our metabolism, immune system and brain a bit. Cannabinoids (and our endocannabinoid system) seem to shift the focus of our metabolism from fuel-efficiency (read optimal growth) to optimal body maintenance at the expense of fuel-efficiency. Such an adaptation would normally not be viable from an evolutionary perspective but is actually perfect for modern Western societies where food is around in ample supply and we tend to die of obesity or related conditions.

It would be tantalizing to think that the excess energy obtained by blocking fat storage is used to increase cellular maintenance/turnover. This, in turn, could release the strain on the brain and immune system to make us healthier of mind and body. As a first step to such a paradigm we need to do more research to update the Cannabinoid-Receptor-Activation-Matrix and determine which cannabinoid does what in each relevant cell type.

Only then can we begin to develop cannabinoid cocktails that can push our mental and physical state to where we want it to be.

About the author:

Dr. Joost Heeroma is a biomedical researcher with an MSc in Medical Physiology and Neurobiology and a PhD in Functional Genomics. Joost specializes in homeostasis; a collection of biological feedback mechanisms that keep the body in balance and free from disease. For his MSc thesis, Joost studied the genetic network that controls cell division and thereby protects the body from degeneration on the one hand and cancer on the other. For his PhD thesis, Joost studied how brain activity regulates itself via feedback control over brain structure (Heeroma et al., 2003, 2004; Verhage et al., 2000). As a postdoctoral researcher, Joost studied how the brain employs feed forward and feedback rules to encode memories and how mutations that disrupt negative feedback on brain activity cause diseases such as epilepsy (Heeroma et al., 2009; Lamsa et al., 2005, 2007). He later employed this principle to develop genetic therapy for epilepsy (Walker et al., 2013; Wykes et al., 2012). Now Joost studies what is possibly the greatest group of feedback regulators of all: cannabinoids. Joost is currently owner of Heeroma Biotechnology Consultancy and Director of Science at GH Medical.

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