2. Cannabinoids

By Kevin Baiko

The cannabinoids are the movers and shakers of the endocannabinoid (eCB) system – in other words, the compounds which activate eCB receptors, which, in turn, modulate and regulate our nervous and immune systems, and hence help maintain homeostasis (systemic balance) throughout the entire body. Several categories of compounds are worth mentioning: endocannabinoids, phytocannabinoids, cannabinoid modulators and synthetic cannabinoids.

The endocannabinoids (eCBs) are synthesized in the body itself. The two known eCBs are anandamide and 2-AG (2-aracidonylglycerol). They are produced "on demand" from arachidonic acid in cell membranes and only activate receptors near-at-hand because they are immediately metabolized (broken down). Because arachidonic acid is a common Omega-6 fatty acid, diet can influence production of eCBs. Anandamide and 2-AG seem to exert different effects on the eCB system, and whereas 2-AG is a full agonist (fully stimulates eCB receptors), anandamide is only a partial agonist. This distinction is important because partial agonists tend to cause less desensitization and down regulation of their target receptors (which is to say, less tolerance develops.)

The phytocannabinoids (usually just called cannabinoids) are a group of at least 60 compounds with similar molecular structure found exclusively in the cannabis plant. Like the eCBs, the different cannabinoids (CBs) also exert varying effects on the eCB system. The two most prominent and best studied are THC (short for delta-9-tetrahydrocannabinol) and CBD (cannabidiol). Like anandamide, THC is parital agonist on eCB receptors. Curiously, researchers have yet to locate the receptors to which CBD binds.

The medicinal effects of cannabis seem to depend primarily on its THC content. Cannabis treated to remove THC, while preserving other CBs present, has yet to demonstrate significant pharmacological effect. Alone THC is best known for its psychoactive effects, but it has also anti-emetic, antispasmodic, anti-proliferative (anti-tumoral) and appetite stimulant effects as well, but other CBs (most notably CBD) modulate and add to these effects.*

THC & CBD seem to work both in synergy and opposition. CBD enhances the expression of CB1 receptors in the brain, decreases tolerance to THC, stimulates the release of 2-AG and inhibits the breakdown of anandamide. While CBD blunts the psychoactive "high" that THC delivers, it also appears to blunt the paranoia that can accompany THC use and counteract the link (extremely weak as it is) between THC use and depression and psychosis in those predisposed to such mental illness. Even more amazing, CBD appears to magnify THC's inhibitory effect on certain forms of cancer (Christian *et al*). A host of other studies have demonstrated that CBD also adds analgesic, anti-inflammatory, anticonvulsant, antiarrhythmia, antidiabetic, antibacterial, antioxidant, neuroprotectant, and neurogenic effects.

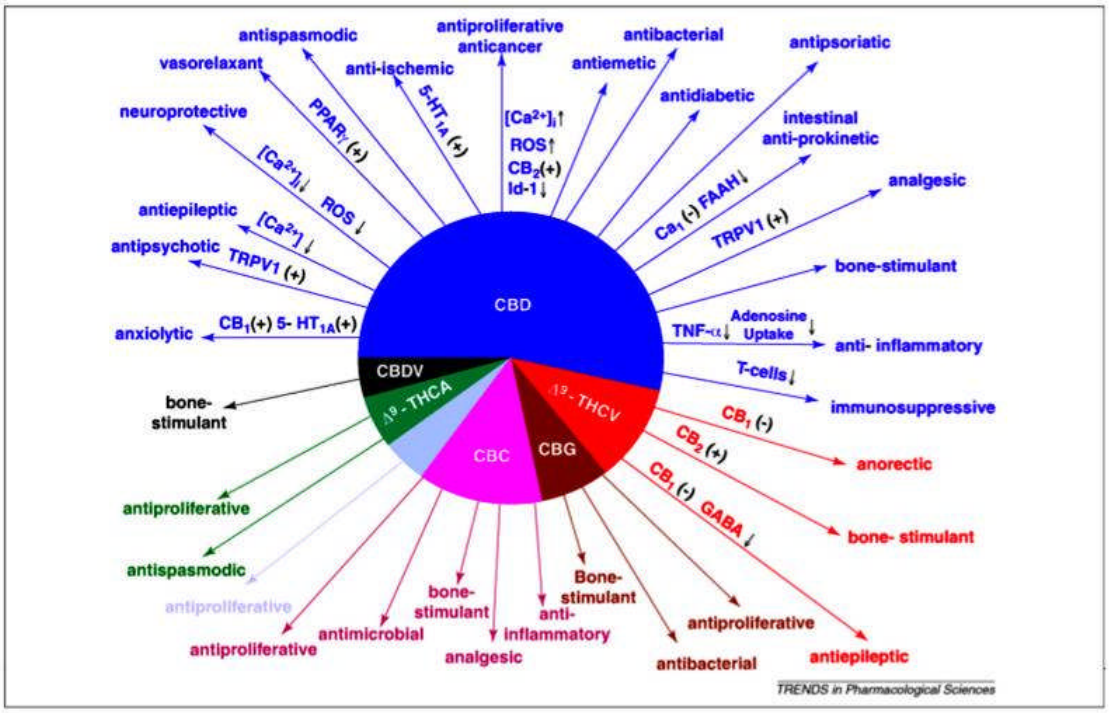

Figure 1. Pharmacological actions of non-psychotropic cannabinoids (with the indication of the proposed mechanisms of action).
Abbreviations: Δ^9-THC, Δ^9-tetrahydrocannabinol; Δ^8-THC, Δ^8-tetrahydrocannabinol; CBN, cannabinol; CBD, cannabidiol; Δ^9-THCV, Δ^9-tetrahydrocannabivarin; CBC, cannabichromene; CBG, cannabigerol; Δ^9-THCA, Δ^9-tetrahydrocannabinolic acid; CBDA, cannabidiolic acid; TRPV1, transient receptor potential vanilloid type 1; PPARγ, peroxisome proliferator-activated receptor γ; ROS, reactive oxygen species; 5-HT_{1A}, 5-hydroxytryptamine receptor subtype 1A; FAAH, fatty acid amide hydrolase. (+), direct or indirect activation; ↑, increase; ↓, decrease.

THC & CBD are actually members of several subclasses of cannabinoids which have been identified. The THC type includes 9 cannabinoids with similar chemical structure and properties, though delta-9 tetrahydrocannabinol is considered the most psychoactive (whereas its acid precursor is not.) The CBD type includes 7 cannabinoids with similar structure, cannabidiol being the most prevalent. The CBG (cannabigerol) type, which includes 5 related compounds, and the CBC (cannabichromene) type, which includes 5, have been shown to have anti-proliferative, anti-inflammatory, analgesic, bone stimulant, antimicrobial effects. There are also delta-8 THC types, cannabinol types and cannabinodial types.*

Also present in the cannabis plant are compounds which, though not cannabinoids by chemical classification, contribute synergistic healing effects and may also modulate cannabinoid activity. These include terpenoids and flavenoids. The terpenoids, numbering over 100 in cannabis, but also found in citrus, pine and hops, give each strain its unique smell, and some have shown to have anti-cancer activity. The flavonoids, widespread throughout the plant kingdom, number around 20 in cannabis, and have been shown to have anti-inflammatory, anti-oxidant and anxiolytic effects. In addition, terpenoids and flavonoids may increase cerebral blood flow, enhance brain function and kill respiratory pathogens.* Several plants produce compounds that modulate the immune system by selectively binding to CB2 receptors. For example, alkamides in Echinacea species directly bind to CB2, and alkamides also inhibit the breakdown of anandamide (Raduner *et al*). And Beta-caryophyllene in black pepper (also in cannabis) binds to CB2, demonstrating anti-inflammatory effects (Gertsch *et al*).

Without general awareness, many have been modulating their endocannabinoid system with pharmaceuticals also. One of metabolites of acetaminophen (tylenol) activates CB1 receptors and inhibits anandamide reuptake and breakdown (Hogestatt *et al*). NSAID drugs like ibuprofen inhibit the enzyme which breaks down 2-AG (Fowler *et a*l) and enhance anandamide activity (Guindon *et al*). Given the evidence that the eCB system modulates pain, it is probable that such medications alleviate pain in part because of their effect on the eCB system. Several classes of psychiatric medications increase and/or decrease expression of CB1 receptors in the brain. (Hill, Secher, Anderson, *et al*). No doubt, many more medications will prove to influence the endocannabinoid system, for better or worse.

If one truth can be weaned from this summary so far, it is that the many naturally occurring compounds found in the cannabis plant work synergistically with one another. This fact challenges the mainstream pharmaceutical model, which generally demands that medicinal compounds be isolated, concentrated, and quantified into specific doses. I daresay, cannabis does not so much fail this model as federal regulators and allopathic dogmatists tend to argue, but rather it is this pharmaceutical model which fails those doctors and patients who would chose to use cannabis in its natural state simply because it works. This failure has been exemplified by several attempts to deliver single synthetic cannabinoids.

Synthetic cannabinoids are, of course, man made. The prime example is dronabinol (called marinol when encapsulated with sesame oil), which is a synthetic isomer of THC. While it is effective in treating many of the same conditions cannabis treats, research and anecdotal evidence proves it less effective than the herbal form. Making things worse, while no death has ever been directly associated from cannabis use, a few deaths have been attributed to the dronabinol. Also of concern are the many emerging synthetic cannabinoids being sprayed on herbs and sold for recreational use under names like “Spice”. Severe adverse effects (far in excess of any associated with cannabis use) and possibly even a few deaths have been linked to use of these compounds. One such synthetic cannabinoid, HU-210, acts as a super agonist, producing a greater than maximum response than eCBs are capable of producing (Luk *et al*). Here (and elsewhere as any responsible naturopath would note) it becomes obvious that a stronger medicine isn’t necessarily a better medicine. Exceeding nature is a risky business indeed, particularly in the unregulated world of synthetic recreational drugs.

While the pharmaceutical-industrial complex seems hell-bent on banning the cannabis plant (competition) while patenting synthetic analogs to cannabinoids readily available to every gardener capable of its cultivatation, the nutriceutical industry has offered another option: whole plant extracts. One such whole plant extract on the market is Sativex, which boasts a 1:1 THC/CBD ratio without the euphoric (so-called) side effect. Taken sublingually, it is unfortunately not yet available in the United States. Time will tell how well cannabis based nutriceuticals hold up to the tried and tested approaches of cannabis use.

One thing is sure: we will be hearing lots more about cannabinoids - especially CBD - in the years to come. Cannabis cultivators the world over are already developing CBD rich

strains (4% or greater), and patients are lining up to buy/grow these strains. In the end, consumer demand, whether in its black market form or in its freer versions is the engine driving medical cannabis research.

(*Much of this information sourced from Cannabis and Cannabinoids: Pharmacology, Toxicology and Therapeutic Potential by Grotenhermen and Russo, Haworth Integrative Healing Press, 2002.)

Doctor Kevin Baiko is a Board Certified Diplomat of the American Academy of Cannabinoid Medicine.