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From “Azalla” to Anandamide: Distilling the Therapeutic Potential of Cannabinoids

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Root of caper which is on a grave, root of acacia...[and] azalla (cannabis); these seven drugs are a cataplasm for the Hand of a Ghost, with which to bind his temples.

—Assyrian prescription for treating bruises or swellings,
Assyrian Medical Tablet K2615

Cannabis has held a unique place in the hearts and minds of people since time immemorial: some have exalted its properties and considered it to be sacred; others have reviled it, considering it a root cause of social evil. The Assyrians, who lived about 3000 years ago, documented the effects of cannabis on clay tablets. They referred to the plant according to its various uses: as “azalla,” when used as a medical agent; as hemp; and as “gan-zi-gun-nu” —“the drug that takes away the mind” (1). These seemingly contradictory properties—a substance that can be both a therapeutic agent and a corrupting psychoactive drug—have continued to puzzle us over the ensuing centuries. As early as the 11th century, excessive cannabis use was suggested to be a cause of “moral degeneracy.” This was exemplified by the story of Hassan-i-Sabbah and his fanatical, murderous followers. The group was renowned for smoking hashish (cannabis resin) excessively and therefore came to be known as Hashishin—the term from which the English word assassin is derived (2). On the other hand, the ostensible therapeutic value of cannabis was documented extensively in the early 19th century by Sir William B. O’Shaughnessy, an Irish physician working in Calcutta, India (3).

Despite the great interest from both sides of the debate in understanding the properties of the cannabis plant, it was not until the 1960s that the main chemical constituents, Δ^9 -tetrahydrocannabinol and cannabidiol, were first isolated by Mechoulam and Gaoni [reviewed in (4)]. Even after this initial discovery, the mechanism by which these so-called cannabinoids (i.e., chemical constituents of the cannabis plant) acted remained a mystery (they were originally thought, based on their high lipophilicity, to act via an effect on the plasma lipid membrane). It was another 20 years before cannabinoid receptor 1 (CB₁R) was finally identified (4). The discovery of this receptor prompted the even more intriguing question: Why did the human brain contain a receptor for a compound found in a plant? (A

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joke made at the time was that the receptor existed in the human brain solely so that man may enjoy smoking cannabis.) The actual answer emerged a few years later when Mechoulam *et al.* (5) discovered two endogenous ligands that activated CB₁R: anandamide (derived from the Sanskrit word “ananda” [bliss]) and 2-arachidonyl glycerol (2-AG). Together, these ligands came to be known as endocannabinoids—in contrast to the range of plant-based (phytocannabinoids) and other exocannabinoids (e.g., synthetic molecules like dronabinol and spice/K2). [It is worth noting that the cannabis plant contains more than 200 chemical compounds, including 120 different phytocannabinoids, in addition to other constituents, such as terpenoids and flavonoids (2).]

What has emerged from these initial discoveries is one of the most fascinating stories in modern neuroscience: as it turns out, the endocannabinoid system is a unique regulatory neurotransmitter system, defying many properties of conventional neurotransmitters (6). First, unlike other neurotransmitters (e.g., serotonin, dopamine, acetylcholine), endocannabinoids are not stored in vesicles—rather, they are synthesized on demand. A second fascinating detail is that they are produced and released from the postsynaptic terminal (generally in response to the activation of other receptors, such as metabotropic glutamate receptor 1 or metabotropic glutamate receptor 5). Once released, they then diffuse into the synaptic cleft and act on the cannabinoid receptor on the presynaptic terminal to inhibit the further release of neurotransmitters (Figure 1). This process is known as retrograde signaling: a signal sent from the postsynaptic terminal to the presynaptic terminal, in this case acting as an inhibitory “brake” on the action of the neurotransmitter. Retrograde signaling has been noted for only a few other neurotransmitters (e.g., nitric oxide and dynorphin). A third unique aspect of endocannabinoids is that they exhibit a property known as the entourage effect: their activity can be enhanced by structurally related, but otherwise biologically inactive, endogenous constituents [a property shared by other lipid mediators (7)]. A final property of the endocannabinoid system that is worth highlighting is that activation of the CB₁R can have biphasic effects, which is to say that different levels of stimulation can lead to opposite types of outcomes. For example, low-dose stimulation of CB₁R can have an anxiolytic effect, whereas high-dose stimulation may be ineffective or even anxiogenic.

The role of endocannabinoids is thus to maintain an exquisite balance of neurotransmitter levels, on one hand preventing excessive release and potential excitotoxicity while on the other hand ensuring adequate levels for optimal signaling. Effectively, they help keep neurotransmitter levels in the synapse in the so-called Goldilocks zone where the balance is “just right.” It is therefore not surprising that the endocannabinoid system is emerging as a significant player in the modulation of many physiological processes, ranging from pain sensation and autonomic system tone to the regulation of intrauterine development, appetite, mood, cognition, and anxiety. Given this wide role across physiological functions, it is not surprising that therapeutic uses have begun emerging for a range of medical conditions. The synthetic cannabinoid dronabinol is approved by the U.S. Food and Drug Administration for the treatment of anorexia associated with weight loss in patients with acquired immunodeficiency syndrome. It is also approved for treating nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments. In addition, a fixed-drug combination of D-9-tetrahydrocannabinol

and cannabidiol is approved in the United Kingdom and Canada for the treatment of neuropathic pain and for spasticity in multiple sclerosis.

Within psychiatry, the therapeutic role of cannabinoids is less clear. One major question is whether cannabinoids may be useful for the treatment of anxiety disorders. In the October 2017 issue of *Biological Psychiatry*, Bedse *et al.* (8) followed up on a fascinating aspect of the endocannabinoid system to explore this question. As described above, two key endogenous activators of the CB₁R receptor are 2-AG and anandamide. Historically, most of the published literature has suggested that increasing anandamide levels leads to decreased anxiety; a smaller body of literature has suggested that 2-AG may also play a role in decreasing anxiety. It seems that one difference between the two molecules is how they affect presynaptic neurotransmitter release: 2-AG appears to mediate short-term suppression, whereas anandamide appears to mediate long-term suppression. However, a key aspect that has not been well understood is how these two pathways interact with each other. Bedse *et al.* (8), consistent with previous work, show that 2-AG plays a key role in regulating anxiety: increasing 2-AG led to decreased anxiety whereas depleting 2-AG led to increased anxiety-like behaviors. Interestingly, the increase in anxiety with 2-AG depletion could be normalized by selectively increasing anandamide levels (which was also shown to be acting on the CB₁ receptors). These findings suggest that there is a “functional redundancy” in the system. This is a tantalizing finding: does it mean that nature has crafted the endocannabinoid system to have two levels of fail-safe protection, one via 2-AG and the other via anandamide (akin to a bicycle with both a hand brake and a brake pedal)? Or does it speak to a complexity of the endocannabinoid system that we do not fully understand?

Given the critical role of the endocannabinoid system in modulating anxiety, it is clear that compounds that can modulate this system offer great promise as therapeutic agents for psychiatric disorders. It is therefore not surprising that the concept of medical marijuana is compelling to laypersons, clinicians, and researchers alike. While there is not yet a robust body of literature supporting any specific psychiatric indication (despite the regulatory approval in some states of medical marijuana for specific psychiatric disorders), active lines of investigation of therapeutic targets within the endocannabinoid system offer hope for better treatment options. Preliminary studies using partial allosteric modulators of the CB₁R (9) and inhibitors of the endocannabinoid degradation enzymes fatty acid amide hydrolase and monoacylglycerol lipase (10) have been promising. Furthermore, if the finding of Bedse *et al.* (8) is in fact true—i.e., if the system can be effectively modulated by either 2-AG or anandamide—this further expands the number of potential therapeutic targets. However, while there is great optimism that these compounds can provide new treatments, the yet unknown effects on intrauterine development, cognition, and mood remind us to be cautious. The evidence at present suggests that the question of whether cannabinoids are good or bad is not dichotomous—it is likely both good and bad depending on the context of use, including dose, duration of exposure, and an individual’s genetic vulnerabilities. Therefore, the challenge that remains is to distill the good therapeutic effects of cannabinoids and thus weed out “gan-zi-gun-nu” from “azalla.”

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Figure 1.

Endocannabinoid synthesis and signaling. (1) Endocannabinoids (anandamide and 2-arachidonyl glycerol [2-AG]) are synthesized in the postsynaptic terminal in response to the activation of metabotropic glutamate receptor 1 and 5 (mGluR1/5) receptors. (2) Anandamide and 2-AG diffuse out of the postsynaptic terminal back into the synaptic cleft. (3) Anandamide and 2-AG bind to cannabinoid receptor 1 (CB₁R) on the presynaptic terminal (“retrograde signaling”). (4) The activation of CB₁R suppresses further release of the neurotransmitter. AMPAR, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptor; Na, sodium.