The present review provides an update on endocannabinoid basic science and clinical studies and proposes a new model to describe reciprocal interactions between somatic dysfunction and the endocannabinoid system. The endocannabinoid system consists of cannabinoid receptors, endogenous ligands, and ligand-metabolizing enzymes. The system exemplifies the osteopathic principle that the body possesses self-regulatory mechanisms that are self-healing in nature. Enhancing endocannabinoid activity has broad therapeutic potential, including the treatment of patients with somatic dysfunction, chronic pain, and neurodegenerative diseases as well as inflammatory conditions, bowel dysfunctions, and psychological disorders. Blockade of the endocannabinoid system with drugs such as rimonabant and taranabant may oppose self-healing mechanisms and elicit adverse effects. Osteopathic physicians wield several tools that can augment endocannabinoid activity, including lifestyle modifications, pharmaceutical approaches, and osteopathic manipulative treatment.

The endocannabinoid system was discovered long after the endorphin system, which was indirectly detected in 1801 when morphine sulfate was isolated from opium. Morphine's mechanism of action remained a mystery until the opioid receptor was identified. That discovery begged the question: Why do humans express a receptor for an opium poppy (Papaver somniferum) plant compound? Scientists quickly identified endorphins and enkephalins, which are endogenous compounds mimicked by the plant compound.1

In 1897, Andrew Taylor Still, MD, DO,2 the founder of osteopathic medicine, famously stated, “Man should study and use the drugs compounded in his own body.” Still hypothesized that osteopathic manipulative treatment (OMT) stimulated endogenous compounds that promoted homeostasis and healing. Not long after the discovery of endogenous opioids in 1975, JAOA—The Journal of the American Osteopathic Association published a supplement dedicated to endorphins and enkephalins.3 However, the initial enthusiasm dampened after seven subsequent studies4,5 showed no effects of OMT or chiropractic manipulation on serum levels of these compounds.

Since then, research—particularly osteopathic medical research—has redirected its attention from the endorphin system to the endocannabinoid system.4-10 A search on the National Library of Medicine’s PubMed database of endorphin in the 1992 literature, the year endocannabinoids were discovered, returns 596 citations, whereas endocannabinoid yields only two citations. In a search limited to 2007, endorphin produces 122 citations, whereas endocannabinoid generates 480 citations.

The primary purpose of the current article is to review the expanding endocannabinoid literature beginning with exogenous compounds—Cannabis and plant cannabinoids—and then shift to the endogenous system, highlighting embryology and development, neuroprotection, autonemics and immunity, inflammation, apoptosis, hunger and feeding, and nociception and pain.

Because the literature is so voluminous—more than 10,000 cannabinoid citations in PubMed—the present article is not a systematic review. Review articles were considered the preferred source and are referenced throughout to enable continued education.

In addition, the present review seeks to draw parallels between the endocannabinoid system and the principles of osteopathic medicine.11 The endocannabinoid system is a homeostatic mechanism that exemplifies the key osteopathic concepts of mind-body unity11 on a molecular level. A new neuroimmunologic model describes reciprocal interactions between the endocannabinoid system and the osteopathic concept of somatic dysfunction. Finally, the current review will describe how osteopathic physicians may enhance endocannabinoid function in their patients.
Exogenous Cannabinoids

The plant Cannabis sativa, the source of cannabis (ie, marijuana, hashish), is native to central Asia. Several indigenous “traditional medicine” systems (eg, Ayurvedic medicine, Tibetan medicine, traditional Chinese medicine) evolved and make use of this substance.12

In the 1830s, a physician serving the British Crown in India conducted a series of laboratory experiments, including animal studies and clinical trials, to determine the safety and efficacy of cannabis. He subsequently introduced cannabis to England and was knighted by Queen Victoria.13

Cannabis entered The Dispensatory of the United States of America in 1854.14 Although cannabis met a variety of applications, its primary use was for the alleviation of pain and spasticity. In fact, Sir William Osler considered cannabis the “most satisfactory remedy” for migraine.15

In the late 19th and early 20th centuries, cannabis was manufactured by a number of pharmaceutical companies in the United States and was dispensed as an orally administered fluid extract. When coupled with variable product potency, unreliable sources of supply, poor storage stability, and evidence that the liquid form was erratically absorbed by the gut, fluid extracts soon fell out of favor.13 Its decline in popularity was further hastened by new and inexpensive synthetic medicines such as aspirin. Finally, after growing concern of “reefer madness,” cannabis was prohibited in 1937 despite vigorous opposition by the American Medical Association.16

In fact, many leaders in the allopathic medical profession continue to support the medicinal use of cannabis.17

Whereas morphine forms a water-soluble salt easily isolated from Papaver somniferum, the active ingredients in cannabis are lipophilic and resist crystallization. In 1964, after foiling scientists for 150 years, Raphael Mechoulam isolated Δ9-tetrahydrocannabinol (THC) and cannabidiol.12 More than 70 separate 21-carbon terpenophenols unique to cannabis, collectively called the cannabinoid, have been identified by Mechoulam,12 Pertwee,18 and others.

Animal studies of THC began immediately after its discovery. By 1975, the first phase 3 clinical trials were published.12,18 Dronabinol, a synthetic THC, was approved as a schedule II drug in 1986 and was moved to schedule III in 1999.17 Its indications include nausea and vomiting associated with cancer chemotherapy as well as appetite and weight loss in patients with AIDS.19 Nabilone, a THC analog with the same indications, was approved by the US Food and Drug Administration in 1985 but was not marketed in the United States until 2006.20

Receptors and Signal Transduction

Discovery of the µ-receptor launched a search for cannabinoid receptors. However, the search was stymied by THC because of its nonspecific (ie, indiscriminate) binding.

In 1988, Howlett et al developed synthetic, water-soluble THC analogs showing that a radiolabelled cannabinoid receptor agonist ([3H]CP55,940) bound specifically to a receptor located in neuron cell membranes.21 Two years later, Matsuda and Bonner cloned the gene for the receptor, which translated into a chain of 472 amino acids that weave back and forth across the cell membrane seven times.21 This weaving structure is the same as those of G protein–coupled receptors (GPCRs), which are named for their G (guanine nucleotide binding) proteins and function as intracellular “molecular switches.” Well-known GPCRs include opioid, dopamine, serotonin, and β-adrenergic receptors.

Each GPCR possesses a unique binding pocket with an affinity for specific ligands, like a lock-and-key mechanism. When a ligand docks in the binding pocket, it may initiate any of the following changes, depending on the agonist:

- **Full agonists**—These agonists, such as morphine and β-endorphin, maximally activate receptors.
- **Partial agonists**—These agonists submaximally activate receptors, often less than an endogenous ligand. For example, the β-blocker pindolol occupies the norepinephrine binding site but exerts much less activity.
- **Neutral antagonists**—Agonists in this category, such as naloxone hydrochloride and alpranolol, dock at receptors but do not activate them.
- **Inverse agonists**—These agonists, such as metoprolol succinate, metoprolol tartrate, prazosin hydrochloride, cimetidine and haloperidol deactivate receptors by suppressing their spontaneous activity.

A ligand docking in a GPCR distorts the shape of the GPCR’s transmembrane weave of amino acids (a “conformational change”), thereby altering the intracellular side of the receptor and its interface with the G protein. If the ligand is an agonist, the G protein decouples from the receptor and couples to an ion channel (eg, K+, Ca2+) or enzymes (eg, adenylate cyclase), causing a “signal cascade” that governs cell behavior.21

The cannabinoid receptor can activate different G protein subtypes. For example, subtype Gαi, couples to ion channels, Gi inhibits adenylate cyclase, and Gs stimulates adenylate cyclase.21 The deciding factor is the agonist because various agonists preferentially direct the receptor toward the different G protein subtypes.21 This “agonist trafficking” may explain why different strains of cannabis produce different psychoactive effects.22 Agonist trafficking alters the traditional lock-and-key metaphor. In this setting, an assortment of keys unlock the same lock, but the door opens into different rooms.

Cannabinoid receptors are the most common GPCRs in the brain, but they are unevenly distributed. High densities are found in the basal ganglia, which is composed of the globus pallidus, substantia nigra, and striatum (comprising the caudate nucleus and putamen); hippocampus; cerebral cortex; cerebellum; and amygdaloid nucleus.23 Receptor distribution accounts for the well-known effects of cannabis on short-term memory, cognition, mood and emotion, motor function, and...
nociception. Unlike μ-receptors, cannabinoid receptors are virtually absent in brainstem cardiorespiratory centers, which probably account for the lack of lethal effects from cannabis overdose.23

Cannabinoid receptors are downregulated and desensitized when exposed to high doses of THC. This effect results in “drug tolerance,” which occurs at varying rates and magnitudes in different brain regions. For example, it occurs faster and greater in the hippocampus, which regulates memory, compared with the basal ganglia, which mediates euphoric effect.24 This difference may explain why memory loss decreases among frequent cannabis users, but its euphoric effects remain.25

Curiously, cannabinoid receptors may activate G proteins in the absence of THC or endogenous cannabinoid compounds.2 This “constitutive activity” is difficult to separate from “endogenous tone” experimentally, where tonic release of endocannabinoids activates the receptors. Constitutive activity has also been measured in other GPCRs, such as the angiotensin receptor, which is stretched into an active conformation by hydrostatic pressure in blood vessels.26

A second cannabinoid receptor, CB2, was discovered in 1993. While the first receptor, CB1, is principally located in the nervous system, CB2 is primarily associated with cells governing immune function: leukocytes, splenocytes, and microglia.21 The genes for CB1 and CB2 are paralogs (ie, genes separated by a gene-duplication event), with orthologs (ie, genes separated by speciation events) in all vertebrate species investigated to date.27

In fact, orthologs of cannabinoid receptors have been identified in primitive organisms, such as nematodes and sea squirts, which suggests cannabinoid receptors evolved 600 million years ago.28 Therefore, from an evolutionary perspective, human CB1 is under strong purifying selection, whereas CB2 is under reduced functional restraint. In fact, the mutation rate of CB2 is four times higher than CB1.29

**Endogenous Cannabinoids**

Humans likely did not evolve receptors for a Cannabis compound. Indeed, the cannabinoid receptor evolved long before cannabis, which is not more than 34 million years old.22 The first endogenous cannabinoid, anandamide (AEA), was discovered by Mechoulam in 1992—nearly 30 years after he discovered THC. The discovery of 2-arachidonoylglycerol (2-AG) occurred shortly thereafter.

Both the AEA and 2-AG endocannabinoids are metabolites of arachidonic acid. They do not resemble THC but nonetheless fit the CB1 and CB2 binding pockets. Therefore, the effects of THC, AEA, and 2-AG substantially overlap, activating the same receptors.30 However, THC is a partial agonist and may block 2-AG’s full agonist activity in some situations.31-33

Unlike classic neurotransmitters, AEA and 2-AG are not stored in vesicles. Instead, they are synthesized and released “on demand” from precursor phospholipids within the cell membrane. The AEA endocannabinoid is cleaved from its precursor phospholipid by the enzymes N-acyl phosphatidylethanolamine phospholipase D and alpha-beta hydrolase 4, while 2-AG is cleaved from its precursor diacylglycerol (DAG) by two DAG lipase enzymes, DAGLα and DAGLB. After release into the synapse, AEA and 2-AG activate CB1. Thereafter, several other catalytic enzymes break down AEA and 2-AG.18,34 Several agents that block catalytic enzymes—specifically fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL)—have been described, which prolong AEA and 2-AG synaptic activity, analogous to a serotonin uptake inhibitor. Pharmacologists are searching for inhibitors of the other endocannabinoid enzymes as well.35 Although few endogenous inverse agonists are known for any receptors, one inverse agonist called hemopressin was discovered for CB1 and has exhibited surprising analgesic properties.35

Within the central nervous system, the endocannabinoid system acts as a negative feedback mechanism to dampen synaptic release of classic neurotransmitters. A simplified example is presented in Figure 1. Persistent activation of a nerve—in this case, a sensory C-fiber nociceptor—causes excessive release of glutamate from its central terminal, which synthesizes in the dorsal horn. Excessive glutamate causes an upregulation of glutamate receptors in the postsynaptic cell (in this case, a wide dynamic range neuron). Persistent nociception and upregulated glutamate receptors lead to a form of neural plasticity known as central sensitization.36,37 Neural plasticity is characterized by the sprouting and pruning of synapses, changes in dendritic spine density, and changes in neurotransmitter pathways. It gives rise to all types of adaptive learning, including the subcortical events leading to a facilitated spinal segment as well as the conscious act of gaining a new skill or the unconscious acquisition of a new emotional response.38

Central sensitization elicits a homeostatic response by the endocannabinoid system: upregulated glutamate receptors in the postsynaptic cell lead to an influx of Ca^2+ (Figure 1A), which causes DAGLα enzymes in the postsynaptic cell to synthesize 2-AG (Figure 1B). The 2-AG endocannabinoid moves retrograde (ie, opposite the direction of glutamate) across the synapse to CB1 located on the presynaptic neuron. The activated CB1 closes presynaptic Ca^2+ channels, which then halts glutamate vesicle release.31 This “retrograde signaling” mechanism is termed depolarization-induced suppression of excitation (DSE) and enables the postsynaptic cell to control its own incoming synaptic traffic.

Alternatively, if endocannabinoids transiently attenuate the release of an inhibitory neurotransmitter such as γ-aminobutyric acid, the mechanism is termed depolarization-induced suppression of inhibition (DSI).31 As a ubiquitous phenomenon, DSI modulates neurotransmission in the hippocampus, cerebellum, basal ganglia, cerebral cortex, and amygdaloid nucleus.31
Although DSE is less common and the data suggest CB₁ occurs both pre- and postsynaptically in the dorsal horn,⁶⁶ evidence indicates that DSE dampens nociception at the spinal level.³⁹ The endocannabinoid system also controls other forms of neural plasticity such as long-term depression, which is caused by a sustained decrease in glutamate release from presynaptic cells.⁴⁰

**Embryology and Development**

For endocannabinoid receptors to survive 600 million years, they must serve evolutionarily important functions. The CB₁ receptors have been detected in mouse embryos as early as the second day of gestation.⁴¹ Blastocysts express CB₁, CB₂, and FAAH, and blastocyst implantation into the endometrium requires suitable levels of AEA.⁴¹ In fact, the endocannabinoid system organizes a broad array of developmental processes in the embryonic brain. Proliferation and differentiation of neural stem cells are shaped by extracellular cues provided by endocannabinoids.⁴² Indeed, once stem cells commit to neuronogenesis, endocannabinoids regulate neuronal migration and synaptogenesis. Lastly, axon guidance is shaped by axon growth cones, and endocannabinoids are part of the molecular “soup” that guides growth cones to their destinations.⁴³

Adult neurogenesis is regulated by many of these “embryonic” mechanisms and primarily arises in neural stem cells within the subependymal layer lining the cerebral ventricles and the dentate gyrus of the hippocampus. Neural stem cells in both of these brain regions express CB₁,⁴⁴ and neurogenesis by these cells is driven by the endocannabinoid system.⁴⁵

Considering the prominence of the endocannabinoid system in embryogenesis, its equal importance in adult neurogenesis brings to mind a quote by James Jealous, DO:

> The formative and regenerative forces that organize embryological development are present throughout our life span [...]. In other words, the forces of *embryogenesis* become the forces of *healing* after birth.⁴⁶

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**Figure 1. Retrograde transmission at the dorsal horn.** Nociceptor action potentials open calcium (Ca²⁺) channels in the presynaptic axon terminal, which cause vesicles of glutamate to release into the synaptic cleft. (A) Excessive glutamate release causes upregulation of glutamate receptors in the postsynaptic cell, which open Ca²⁺ channels. (B) Postsynaptic calcium influx stimulates diacylglycerol lipase enzymes to synthesize 2-AG, which diffuses across the synapse to the presynaptic cell and activates CB₁, which closes presynaptic Ca²⁺ channels, arresting the release of glutamate vesicles. Abbreviations: AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; eCBS, endocannabinoid system; mGLU, metabotropic glutamate receptor; NMDA, N-methyl-D-aspartic acid receptor. Reprinted with permission from the Journal of Bodywork and Movement Therapies.¹⁰ Copyright Elsevier, 2008.
Neuroprotection

The anti-inflammatory, antioxidant, and antispasmodic properties of THC and cannabidiol in cannabis reduce the symptoms and slow the progression of multiple sclerosis. These properties also benefit patients with Huntington disease and amyotrophic lateral sclerosis.47 Dampening of glutamate excitotoxicity prevents epileptic attacks and limits infarct size post-stroke. Both AEA and 2-AG thwart Alzheimer disease by blocking microglial activation and β-amyloid plaque formation. They also prevent Parkinson disease symptoms by rebalancing neural activity in the striatum.47

Although controversial, the endocannabinoid system has been associated with psychotic disorders. Individuals with schizophrenia have elevated levels of AEA in their cerebrospinal fluid, but the elevated levels are negatively correlated with psychotic symptoms.48 This association suggests that abnormal activation of postsynaptic D2 receptors trigger the release of AEA and retrograde signaling via CB1, thus homeostatically attenuating dopamine release. High doses of THC may therefore provoke psychiatric illness in susceptible individuals by desensitizing CB1 receptors and diminishing retrograde signaling.49 Alternatively, cannabidiol, which is not psychoactive, shows promise as an antipsychotic agent.49

Autonomic Function and Immunity

Endocannabinoids and THC affect autonomic outflow through the peripheral and central nervous systems. The endocannabinoid system reduces elevated parasympathetic activity, providing the antiemetic effects of cannabinoids.18

In rodent studies, activation of myocardial CB1 caused vagally mediated biphasic effects in heart rate and cardiac contractility, while activation of CB1 in vascular tissues leads to vasodilation.50

Cannabinoids provide antihypertensive benefits in humans and a protective role in myocardial ischemia has been suggested in rodent studies.50 However, human in vitro studies have implicated the autonomic effects of THC and endocannabinoids in hypotension associated with hemorrhagic and endotoxic shock. The autonomic effects have also been described in human clinical studies on advanced liver cirrhosis.50

Sympathetic nerve terminals contain CB1, and activation of these receptors has been shown to inhibit norepinephrine release and dampen sympathetically mediated pain.50 The endocannabinoid system modulates the sympathetically driven hypothalamic-pituitary-adrenocortical (HPA) axis as well as the hypothalamic-locus coeruleus-norepinephrine (HLN) axis. Psychologic stress induces the secretion of corticotropin-releasing hormone, which activates the HPA and HLN axes and results in corticosteroid and norepinephrine release, respectively. The endocannabinoid system blocks HPA and HLN axis activation, though doses of THC may cause the reverse response and increase corticotropin-releasing hormone and anxiety.50

In addition, HPA axis activation hinders the immune response. Cannabinoids are immunomodulators—not simply immunosuppressors, as they were characterized in the 1970s.51,52 Cannabinoids suppress production of T-helper 1 (TH1) cytokines such as interleukin (IL) 2, immune interferon (INF-γ), and tumor necrosis factor α (TNF-α). On the other hand, cannabinoids increase secretion of TH2 cytokines (eg, IL-4, IL-5, IL-10). Other subsets of lymphocytes, including B cells (eg, MZ, B1a) and natural killer cells, require endocannabinoids and CB2 to function properly.51,52

Inflammation and Connective Tissues

More than 4000 years ago, the Chinese physician Shen Nung recommended cannabis for rheumatic pains.13 More recently, patients with myofascial pain and arthritis are among those who most often use cannabis medicinally.13 Activation of CB2 suppresses proinflammatory cytokines such as IL-1β and TNF-α while increasing anti-inflammatory cytokines such as IL-4 and IL-10.51,52 Although THC has well-known anti-inflammatory properties, cannabidiol also provides clinical improvement in arthritis via a cannabinoid receptor-independent mechanism.18 Many connective tissue–related cells express CB1, CB2, and endocannabinoid-metabolizing enzymes such as fibroblasts, myofibroblasts, chondrocytes, and synoviocytes.10

The endocannabinoid system alters fibroblast “focal adhesions,” by which fibroblasts link the extracellular collagen matrix to their intracellular cytoskeleton—the mechanism of fascial remodeling. Cannabinoids prevent cartilage destruction such as proteoglycan degradation and collagen breakdown by inhibiting chondrocyte expression of cytokines and metalloproteinase enzymes.10 In addition, the tonic release of endocannabinoids is upregulated in rats that have experimentally induced osteoarthritis, thereby providing endogenous pain relief.55

The endocannabinoid system has been shown to attenuate allergic contact dermatitis in rodent studies—THC decreases allergic inflammation whereas CB1-blocking agents exacerbate the condition.36 The endocannabinoid system likewise protects against Crohn disease—a TH1-mediated inflammatory bowel condition—and also perhaps ulcerative colitis.63,52 The endocannabinoid system dampens the inflammatory component of atherosclerosis in animal studies via CB2 receptors expressed by macrophages within atherosclerotic plaques.18

Lastly, the endocannabinoid system is essential for the maintenance of normal bone mass: CB2 agonists enhance osteoblast activity and inhibit osteoclast activity, therefore offering a potential treatment option for osteoporosis.57
**Apoptosis**

With the exception of cannabis smoke, cannabinoids are anticarcinogenic. They have been found to induce apoptosis in cancer cells via a CB1-mediated ceramide-caspase pathway, thereby inhibiting tumor growth in breast, prostate, and lung carcinomas as well as gliomas, melanomas, lymphomas, and other cancers. In normal, nontransformed cells, endocannabinoids actually promote cell survival via the extracellular signal-regulated kinase (ERK) pathway.

Reducing apoptosis in normal cells is one mechanism by which cannabinoids act as neuroprotectants. Cannabinoids also suppress tumor angiogenesis. However, one contrary study reported that the CB2 gene serves as a retrovirus insertion site (ie, a proto-oncogene) involved in leukemic transformation.

**Nociception and Pain**

Research on the effects of endocannabinoids on nociception has focused on the following four areas:

- peripheral terminals of nociceptors
- the dorsal horn
- the descending pain inhibitory pathway
- supratentorial sites

Peripheral terminals of C-fiber nociceptors contain receptors for “activators” and “sensitizers” (Figure 2). Activators trigger an action potential in the nerve while sensitizers decrease the nerve’s activation threshold, so it fires with less activation.

Activators and sensitizers are released from damaged tissue (eg, K+ and H+ ions, bradykinins, adenosine triphosphates), leukocytes (eg, histamines, prostaglandins, leukotrienes, proinflammatory cytokines), leukocyte-activated platelets (eg, 5-hydroxytryptamine), neighboring autonomic nerves (eg, norepinephrine), and the nociceptor itself (ie, substance P and calcitonin gene-related peptide). Activators and sensitizers cause peripheral sensitization, including hyperalgesia and allodynia. Peripheral sensitization elicits a homeostatic response by the endocannabinoid system: CB1 signaling decreases the release of activators and sensitizers around the site of tissue injury and opens K+ channels in the nociceptor cell membrane, so the nerve becomes hyperpolarized and less likely to fire.

In addition, CB2 signaling decreases the release of activators and sensitizers from neighboring mast cells and macrophages (Figure 2). Functioning of the endocannabinoid system at the peripheral terminal of the nociceptor provides the “first line of defense against pain.”

In the dorsal horn, the nociceptor synapses with a nociceptive-specific neuron or a wide dynamic range neuron. Normally, the nociceptor action potential arrives at the dorsal horn and releases glutamate and substance P into the synaptic cleft. These neurotransmitters bind to their respective receptors in the postsynaptic cell. Cell activation initiates another action potential that ascends to the brain. Abnormal persistent release of glutamate upregulates glutamate receptors in the postsynaptic cell, as illustrated in Figure 1. As previously described, this causes an influx of Ca2+ in the postsynaptic cell and leads to central sensitization, “wind-up,” or “dorsal horn memory.”

However, Ca2+ influx elicits endocannabinoid synthesis, followed by retrograde signaling, and quickly shuts down presynaptic glutamate release. In other words, the endocannabinoid system induces “dorsal horn memory loss” and...
The endocannabinoid system modulates cell metabolism via ghrelin, leptin, orexin, and adiponectin signaling pathways. Obesity leads to excessive production of endocannabinoids by adipocytes, which drives CB1 into a feed-forward dysfunction, contributing to metabolic syndrome.

A pharmaceutical corporation recently sought approval of rimonabant for the treatment of obesity. However, the US Food and Drug Administration rejected it, in part, because 26% of subjects who took rimonabant in clinical studies reported depressed mood, irritability, agitation, anxiety, insomnia, headache, or other adverse psychiatric effects. Given the many beneficial roles of the endocannabinoid system, it should be no surprise that rimonabant unmasked previously silent multiple sclerosis and seizure disorders and doubled the risk for suicidality.

Mood disorders call into question the external validity (or generalizability) of rimonabant clinical trials because patients with depression were excluded from the studies, yet psychiatric illness was the leading reason subjects dropped out of the studies. In standard clinical practice, approximately 50% of patients seeking treatment for obesity also suffer from depression.

Complete blockade of CB1 might approximate the phenotype expressed by genetically engineered “CB1 knockout mice.” Mice lacking CB1 have increased morbidity, premature mortality, age-related neuron loss, and show greater, epilepsy, and anhedonia. They also exhibit aggressive, anxiogenic-like, and depressive-like behavior, as well as a fear of newness.

Compared with mice, humans have a higher “endocannabinoid tone.” Rimonabant blocks endocannabinoid tone at CB1, and spontaneous CB1 constitutional activity because it works as a full inverse agonist. As suggested in one study, sustaining a baseline endocannabinoid “hedonic tone” in the mesolimbic system may enable humans to maintain personal optimism and productivity in the face of chronic societal stress and an ultimately unrewarding consumer culture. Thus, systemic CB1 blockade may not help a psychologically stressed obese patient who does not exercise and whose diet is high in refined sugars, white flour, and trans fatty acids, and lacks fiber, vegetables, and omega-3 fatty acids.

Rimonabant is currently approved in Europe, and similar drugs, including taranabant, surinabant, CP-945598, and SLV-319, are in development (see www.clinicaltrials.gov). Although the risk-benefit profile of systemic CB1 full inverse agonists may prohibit their use for chronic conditions such as obesity and drug or alcohol dependence, they could serve in the treatment of acute endocannabinoid dysregulation, such as hepatic cirrhosis, hemorrhagic or endotoxic shock, cardiac reperfusion injury, and doxorubicin-induced cardiotoxicity.

The use of a CB1 partial agonist may prevent adverse psychiatric effects while simultaneously acting as a partial antagonist by blocking the binding of endocannabinoids at CB1. Partial agonists serve best as partial antagonists when
levels of endogenous agonists are elevated—the exact scenario seen with endocannabinoids and obesity.\(^{70}\) Partial agonists are currently used in cardiology (eg, pindolol) and psychiatry (eg, aripiprazole, buspirone hydrochloride), with fewer adverse effects than antagonists or inverse agonists and without compromising clinical efficacy. In animal studies, two partial agonists have been shown to reverse obesity: the 5-HT\(_6\) ligand E-683777 and a Chinese herbal formula with an “undisclosed herb” that acts as CB\(_1\).\(^{78}\)

Partial agonists often act as pleiotropic drugs, also known as “selectively nonselective drugs.” These “magic shotguns” interact with several molecular targets and provide superior therapeutic effects and adverse effect profiles compared with antagonists or inverse agonists and without compromising clinical efficacy. In animal studies, two partial agonists have been shown to reverse obesity: the 5-HT\(_6\) ligand E-683777 and a Chinese herbal formula with an “undisclosed herb” that acts as CB\(_1\).\(^{78}\)

**Biological Oscillators**

The endocannabinoid system alters every biological oscillator or pacemaker cell investigated to date, beginning with somite formation in the embryo. The segmentation clock converts oscillating Hox genes into spatial somite patterns.\(^{81}\) Fibroblast growth factor regulates the Hox clock,\(^{81}\) and evidence suggests that it uses endocannabinoid signaling.\(^{80,82,83}\) Many endocannabinoid-altered oscillators change the rhythms of tissue movement, such as:

- **Cardiac pulse rate and contractility**—Endocannabinoids have been reported to cause dose-related biphasic effects in rodents and humans.\(^{50}\)
- **Thoracic respiration**—Endocannabinoids cause little change in thoracic respiration, though intravascular injection of high-dose synthetic CB\(_1\) agonists in urethane-anaesthetized rats decreased the respiration rate.\(^{50}\)
- **Gastrointestinal motility and peristalsis**—Slowing of rate and rhythm and gastrointestinal secretions in rodents and humans.\(^{50}\)

Human consciousness represents the rhythmic entrainment of synchronously firing neurons.\(^{84}\) In five regions of the human brain,\(^{23}\) such neurons are particularly enriched with CB\(_1\):

- The **hippocampus** is a source of theta and gamma band oscillations and is the neural substrate responsible for declarative memory.\(^{85}\)
- **Striatal tissues** contribute to the “beat frequency” model of time perception.\(^{86}\)
- The **cerebellum** plays a role in rhythm production and self-paced-behaviors, and cannabis accelerates the cerebellar clock.\(^{87}\)
- The **suprachiasmatic nucleus** is responsible for controlling circadian rhythms.\(^{88,89}\)
- The **pineal gland** produces melatonin and 2-AG in a circadian rhythm driven by the suprachiasmatic nucleus and regulated in part by CB\(_2\) in animal studies.\(^{90}\)

**Role of Osteopathic Medicine**

Osteopathic principles and practice (OPP) were established by Still in the late 19th century. The endocannabinoid system may reflect OPP on a molecular level. Leaders in the osteopathic medical profession proposed four tenets of OPP,\(^{11}\) which are presented below, accompanied by a description of their relationship to the endocannabinoid system.

1. **A person is the product of dynamic interaction between body, mind, and spirit**—This holistic principle is exemplified by cannabinoid receptors, which span the field of psychoneuroimmunology. Taken together, CB\(_1\), CB\(_2\), and their endocannabinoid ligands represent a microcosm of mind-body medicine.

2. **An inherent property of this dynamic interaction is the capacity of the individual for the maintenance of health and recovery from disease**—This self-regulatory capacity can be rephrased as the maintenance of homeostasis. The endocannabinoid system’s capacity to maintain homeostasis has been cited many times in this review, and dozens of additional citations can be found in the exhaustive review by Pacher et al.\(^{30}\)

The endocannabinoid literature rarely mentions allostasis, a process by which homeostasis adapts to environmental stress. However, it appears in osteopathic medical literature and may become costly in the scenario of chronic stress (“allostatic load”). Many studies cited in the present review, especially concerning HPA axis activation and the immune response, indicate that the endocannabinoid system promotes allostasis as well as homeostasis.

3. **Many forces, both intrinsic and extrinsic to the person, can challenge this inherent capacity and contribute to the onset of illness**—Correspondingly, the endocannabinoid system is challenged by intrinsic forces (changes in its structure and genetic expression) and extrinsic forces (changes in its function by unhealthy lifestyles). A corollary to this tenet is the principle that structure and function are interrelated at all levels. Because CB\(_1\) and CB\(_2\) express different molecular structures, they exert different molecular functions.

4. **The musculoskeletal system significantly influences the individual’s ability to restore this inherent capacity and therefore to resist disease processes**—The endocannabinoid system is expressed by the musculoskeletal system.\(^{10,70}\) Harnessing it has broad therapeutic potential for treating degenerative and inflammatory conditions of the musculoskeletal system. The fact that insulin resistance resides in skeletal muscles also implicates the endocannabinoid system in its relationship to cardiometabolic risk.\(^{70}\)

**Reciprocal Interactions**

A focus on somatic dysfunction, formerly referred to as the “osteopathic lesion,” dates to the founding of osteopathic medicine. Somatic dysfunction is defined as “impaired or altered function of related components of the somatic system:
skeletal, arthrodial, and myofascial structures and related vascular, lymphatic, and neural elements. A new model hypothesizing reciprocal interactions between somatic dysfunctions and the endocannabinoid system is presented in the following paragraphs.

In 1910, Still wrote that somatic dysfunction in peripheral tissues “produce[s] pressure and obstruct[s] the normal discharge of nerve and blood supply. Sometimes we find them squeezed so closely as to produce adhesive inflammation.” The inflammatory basis of somatic dysfunction was demonstrated experimentally by Burns 100 years ago and was subsequently confirmed in humans by Denslow. Inflammation arises from three sources: (1) the release of inflammatory mediators by injured tissue, (2) cytokines released by leukocytes that migrate into the area, and (3) inflammatory neuropeptides ( substance P and calcitonin gene-related peptide) released from the peripheral terminals of nociceptors. All three sources are diminished by the endocannabinoid system, as discussed previously and as illustrated in Figure 2. However, the endocannabinoid system requires the presence of CB1 in the peripheral terminal of the nociceptor because CB1 receptors are synthesized in the dorsal root ganglion of nociceptors and are carried by axoplasmic flow to peripheral sites. By obstructing axoplasmic flow and cellular trafficking of CB1, the pathophysiology of somatic dysfunction perpetuates itself.

Still further alluded to axoplasmic flow and attributed the cause of dysfunction to “partial or complete failure of the nerves to properly conduct the fluids of life.” demonstrated mechanical derangement of axoplasmic flow in rabbits and noted the following:

“Deformations of nerves and roots, such as compression, stretching, angulation, and torsion, that are known to occur all too commonly in the human being […] are subject to manipulative amelioration and correction.

A rat study demonstrated that a suture loop ligated around the sciatic nerve caused damming of CB1 proximal to the suture loop (Figure 2). The suture loop may be analogous to myofascial barriers that restrict axoplasmic flow, such as in piriformis contracture, carpal tunnel syndrome, or thoracic outlet restriction. Osteopathic physicians frequently use OMT to treat nerves restricted by mechanical compression and conceivably restore the axoplasmic transport of CB1.

Central neural mechanisms also perpetuate somatic dysfunction. Presciently focused on the dorsal horn, stating “the lesion is a sclerosis of the posterior root-zones of the spinal cord.” Denslow described the “facilitated segment” as a sustained neural reflex with motor and autonomic components, whose sensory element was proprioceptive or nociceptive.

Willard updated and extended the nociceptive model by describing segmental facilitation as a form of central sensitization driven by excessive glutamate release. The endocannabinoid system again comes into play here by reducing central sensitization, as previously discussed, and by dampening sympathetically mediated pain—thereby thwarting the primary “organizers” of somatic dysfunction.

Chiropractic researchers implicated glutamate release from nociceptors as the source of long-term potentiation in spinal cord neurons. They noted that long-term potentiation can be reversed by long-term depression and that spinal manipulation imparts long-term depression by an uncertain mechanism. However, these researchers did not mention that the endocannabinoid system induces long-term depression, which is caused by a sustained decrease in glutamate release from presynaptic cells. It has been proposed that high levels of CB1 expressed in the dorsolateral funiculus of the spinal cord are positioned to influence viscerosomatic reflexes as well.

Central sensitization is analogous to the upregulation of acetylcholine (ACh) transmission at the motor endplate (ie, the neuromuscular junction), which may be the pathologic process underlying myofascial trigger points. As my colleague David G. Simmons, MD, and I previously hypothesized, CB1 in motor end plates dampen ACh release and perhaps play a role in preventing or treating myofascial trigger points. Our hypothesis has been supported by two new animal studies showing that CB1 activation in motor end plates dampens ACh release.

It is important to note that cannabinoids suppress pain responses rather than all somatosensory input because cannabinoids scarcely alter nonnociceptive neurons in the spinal cord and thalamus. To wit, the endocannabinoid system inhibits persistent nociception (ie, inflammatory pain, neurogenic pain, chronic pain) more efficiently than acutely evoked nociception. This difference may explain the anecdotal observation that cannabis provides little relief at the dentist’s office.

Beginning with William Garner Sutherland, DO, in 1899, many researchers have made hypotheses regarding the primary respiratory mechanism, known to osteopathic physicians and other clinicians as the cranial rhythmic impulse (CRI). The CRI is an oscillatory phenomenon that remains poorly understood and is somewhat difficult to relate. Acupuncturists face a similar situation when asked to describe “chi.” The CRI is usually attributed to the well-documented oscillatory secretion of cerebrospinal fluid (CSF) by ependymal cells that line the choroid plexus and cerebral ventricles. Alternatively, the CRI may represent a palpable harmonic frequency, a summation of several biological oscillations, including CSF pulsations, Traube-Hering waves, cardiac pulse, and diaphragmatic respiration.

Given the impact of the endocannabinoid system on many biological oscillators, it is easy to speculate that the endocannabinoid system modulates the CRI. Human CSF is awash with endocannabinoids. Cells lining the rodent and human ventricular system express CB1 and endocannabinoid...
enzymes, which modulate the rhythmic production of CSF in rodents, and control endocannabinoid levels in rodent CSF, and even provide restraint of suture ossification.

An osteopathic procedure that alters the CRL, known as the compression of the fourth cerebral ventricle (CV-4), may transiently increase hydrostatic pressure in the cerebral ventricular system in humans and cats. Conceivably, the increased hydrostatic pressure could trigger CB1-constitutive activity. As described in a previous study, the angiotensin receptor is stretched into constitutive activity by hydrostatic pressure in a Flexercell apparatus (Flexcell International Corp, Hillsborough, NC).

Correspondingly, equiaxial stretching of fibroblasts in an identical apparatus caused a doubling of CB1 expression. The Flexercell management of fibroblasts has provided an in vitro model of osteopathic manipulation. Activation of CB1 may explain many CV-4 effects, such as relaxation and drowsiness, decreased sleep latency, and decreased sympathetic nerve activity.

Lastly, it should be noted that enhancing the endocannabinoid system improves cardiovascular circulation. This may be one mechanism by which OMT improves health—"the rule of the artery is supreme."

Enhancing the Endocannabinoid System

New research with endocannabinoid enzyme inhibitors provides a proof-of-principle for the concept that enhancing endocannabinoid signaling is a beneficial therapeutic strategy. Inhibitors of FAAH, an enzyme that breaks down AEA, and MAGL, an enzyme that breaks down 2-AG, are anxiolytic and antidepressant and block nociception, yet the inhibitors do not impart psychoactive effects characteristic of direct CB1 agonists such as THC.

The remainder of this review focuses on three ways to enhance endocannabinoid function: (1) lifestyle modifications, (2) pharmaceutical approaches, and (3) OMT. An increasing number of conditions have been characterized as "endocannabinoid deficiency syndromes," including posttraumatic stress disorder, chronic anxiety, migraine, Parkinson syndrome, and irritable bowel syndrome. Fibromyalgia may also involve endocannabinoid deficiency. During a normal menstrual cycle, AEA decreases during the luteal phase (circa day 21) as a result of the progesterone-induced upregulation of FAAH. In a study of healthy women with normal menstrual cycles, the luteal phase corresponded with hypersensitivity to algometer-induced pressure at fibromyalgia tender points. Several subjects "changed" fibromyalgia diagnosis during the course of a menstrual cycle, fulfilling the tender point criterion—defined as tenderness elicited by 4 kg of pressure at 11 of 18 pressure points—during the AEA-deficient luteal phase or menstrual phase, but never during the AEA-rich follicular phase. Studies suggest endocannabinoid deficiency may be rectified by lifestyle modifications, including exercise, stress reduction, dietary supplements, and drug and alcohol restraint. Exercising on a treadmill or a stationary bike increased AEA levels circulating in the bloodstream. Chronic stress downregulated CB1 expression in rodents, so stress-reduction programs may offer a potential enhancement of the endocannabinoid system.

Dietary inclusion of fish oils with DHA (docosahexaenoate 22:6 ω-3) and other polyunsaturated fatty acids increased AEA and 2-AG levels in the brain. Oral administration of Lactobacillus upregulated CB2 in intestinal epithelial cells and relieved irritable bowel syndrome. Acute ethanol ingestion decreased AEA and 2-AG in most regions of the brain, and chronic ethanol abuse downregulated CB1 expression.

A study of isopropyl dodecylfluorophosphonate, a homolog of organophosphate pesticides, showed that it inhibited both FAAH and MAGL. The inhibition caused 10-fold elevations in AEA and 2-AG in mice, leading to cannabimimetic behavioral effects. However, when incautious adolescents sprayed cannabis with organophosphate pesticides, the adulteration did not enhance cannabimimetic effects. Instead, it overwhelmed the patients with cholinergic adverse effects.

Preclinical studies (animal models and human in vitro assays) indicate that indomethacin, ibuprofen, and other non-steroidal anti-inflammatory drugs (NSAIDs) inhibit the endocannabinoid catalytic enzymes COX2 and FAAH, so NSAIDs prolong the activity of 2-AG and AEA. In animal models, coadministration of NSAIDs with endocannabinoids had a synergistic effect. This may explain why NSAIDs sometimes cause sedation and other unexpected psychotropic effects in patients. Acetaminophen is deacetylated and conjugated with arachidonic acid into N-arachidonoylphenolamine, a compound that activates CB1.

Dexamethasone potently upregulates CB1 in rodents. The tricyclic antidepressant desipramine increases CB1 densities in the brain of rodents while fluoxetine decreases CB1 expression in rodents. Diazepam and endocannabinoids produce synergistic anxiolytic effects in mice, leading researchers to propose that enhancement of endocannabinoid function increases the effectiveness of diazepam. Valproate sodium, an anticonvulsant and mood-stabilizing drug, upregulates CB1 in rodents—a newly discovered mechanism of action.

Cannabidiol and THC may widen their own therapeutic windows by increasing AEA levels. Low, subtherapeutic doses of THC markedly potentiate the antinociception imparted by endogenous cannabinoids. Surprisingly, THC upregulates CB1 expression when administered acutely. It may also cause post-translational modifications in CB1 that stabilize the receptor in a constitutively active conformation. Hypothetically, CB1 may remain constitutively active long after THC has been metabolized and excreted. Similar adaptions arise in μ-receptors after chronic exposure to plant opiates.
This discussion brings us back to the medicinal uses of cannabis. Oral administration of cannabis shares drawbacks with dronabinol capsules—erratic gut bioavailability, poor dose titration, and THC taken by mouth is converted to an 11-hydroxy-THC metabolite with two to five times more psychoactivity. Oral administration is difficult in patients who are nauseated or vomiting. Smoking cannabis is a health hazard due to polyaromatic hydrocarbons formed during combustion. Vaporization of cannabis provides an alternative to smoking, recently described in the New England Journal of Medicine. Because THC vaporizes at a temperature below the ignition point of combustible plant material, few polyaromatic hydrocarbons appear in the vapor.

Cannabis, of course, is more than THC. Other ingredients provide additional benefits and mitigate the adverse effects of THC. For this reason, many patients prefer cannabis to dronabinol. Cannabidiol, for example, reduces dysphoria and depersonalization provoked by THC while contributing its own anxiolytic, antipsychotic, analgesic, antiemetic, anti-inflammatory, antioxidant, and neuroprotective effects. Indeed, the risk posed by new high-potency cannabis may be the lack of cannabidiol in current strains of cannabis rather than the increase in THC levels. Median THC levels have only increased five fold since the 1970s, analogous to the five fold difference in caffeine between green tea and percolated coffee.

Sativex, a botanical extract standardized to contain a 50:50 mix of THC and cannabidiol, has been approved for phase 3 trials in the United States. It is currently licensed in Europe and Canada for multiple sclerosis, neuropathic pain, and cancer-related pain. The product is sprayed under the tongue, where it is absorbed into the bloodstream. Extension studies have shown that Sativex retains efficacy for at least 4 years, without evidence of drug tolerance or dose escalation and with no evidence of dependency or abuse.

Many patients have reported that OMT induces anxiolyis, eases suffering, increases sense of well-being, and even induces euphoria—psychotropic changes that can be described as cannabimimetic. Osteopathic manipulative treatment may induce such effects by boosting endocannabinoid levels.

A blinded, randomized controlled trial of 31 healthy subjects measured AEA levels pre- and post-OMT. The OMT intervention consisted of myofascial release and muscle energy and thrust techniques. The control intervention consisted of a sham cranial method. In subjects receiving OMT, serum levels of AEA obtained after OMT more than doubled the pre-OMT levels. No change was seen in control subjects. However, the doubling of AEA was not statistically significant because of a large degree of response variability.

A smaller OMT trial reported little change in AEA levels pre- and post-OMT but showed significant post-OMT augmentation of N-palmitoylethanolamine. In rodent studies, N-palmitoylethanolamine increased the antinociceptive effects of AEA via an “entourage effect.”

Speculatively, OMT may work “skin deep,” causing endocannabinoid release from keratinocytes. Epidermal endocannabinoids activate CB1 expressed on the peripheral terminals of nociceptors and provide the “first line of defense against pain.” A similar mechanism, epidermal “pounding of the pavement” by distance runners, was proposed as the source of endocannabinoid-induced “runner’s high.”

Conclusion

The endocannabinoid system has emerged as an important regulator of psychoneuroimmunologic function. Modulating CB1, CB2, and endocannabinoids present new approaches for treating a variety of functional disorders, such as supplementing receptors with exogenous agonists (eg, dronabinol).

Strategies that augment endocannabinoids offer the advantage of enhancing endocannabinoid function at localized sites of pathology already targeted by homeostatic mechanisms. For example, chronic pain syndromes lead to elevated expression of CB1 in two localized sites: the PAG and the dorsal horn. In rodent studies, augmenting endocannabinoids at these receptors relieved nociception at doses that did not elicit supratentorial effects.

This strategy echoes the osteopathic concept that the body possesses self-regulatory mechanisms that are self-healing in nature. Neuroscience investigations regarding the endocannabinoid system may continue to reveal many of the mind-body underpinnings of osteopathic medicine.

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