REVIEW ARTICLE

Clinical endocannabinoid deficiency (CECD) revisited:

Can this concept explain the therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions?

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Submitted: 2014-04-20 Accepted: 2014-05-30 Published online: 2014-06-27

Key words: **cannabis; cannabinoids; endocannabinoids; medical marijuana; migraine; analgesia; headache; irritable bowel syndrome; fibromyalgia; causalgia; allodynia; THC; CBD**

Neuroendocrinol Lett 2014; **35**(3):198–201 **PMID:** 24977967 NEL350314R02

Abstract

OBJECTIVES: Ethan B. Russo's paper of December 1, 2003 explored the concept of a clinical endocannabinoid deficiency (CECD) underlying the pathophysiology of migraine, fibromyalgia, irritable bowel syndrome and other functional conditions alleviated by clinical cannabis.

METHODS: Available literature was reviewed, including searches via the National Library of medicine database and other sources.

RESULTS: A review of the literature indicates that significant progress has been made since Dr. Ethan B. Russo's landmark paper, just ten years ago (February 2, 2004). Investigation at that time suggested that cannabinoids can block spinal, peripheral and gastrointestional mechanisms that promote pain in headache, fibromyalgia, irritable bowel syndrome and muscle spasm.

CONCLUSION: Subsequent research has confirmed that underlying endocannabinoid deficiencies indeed play a role in migraine, fibromyalgia, irritable bowel syndrome and a growing list of other medical conditions. Clinical experience is bearing this out. Further research and especially, clinical trials will further demonstrate the usefulness of medical cannabis. As legal barriers fall and scientific bias fades this will become more apparent.

Abbreviations:

AEA	- arachidonylethanolamide, anandamide
ASD	- autism spectrum disorder
CB1	- cannabinoid 1 receptor
CB2	- cannabinoid 2 receptor
CECD	- clinical endocannabinoid deficiency
PBMC	- peripheral blood mononuclear cells
RNA	- ribonucleic acis
RSD	- reflex sympathetic dystrophy
THC	- tetrahydrocannabinol

INTRODUCTION

In 1964, thanks to the groundbreaking work of two Israeli researchers, Drs. Raphael Mechoulam and Yehiel Gaoni, the psychoactive component of marijuana was identified and synthesized at the Hebrew University in Jerusalem. The substance, named THC (tetrahydrocannabinol) turned out to be just one of an entire family of cannabinoid ("cannabis-like") compounds. However, THC is the only cannabinoid that has psychoactive properties (Mechoulam 2004).

Over the decades that followed, the role of cannabinoids in neurological function were teased-out, first by Allyn Howlett, Ph.D. and her graduate student assistant, William Devane, in 1988. They demonstrated how THC binds to receptors in the brain.

This was a breakthrough in our understanding of receptors – a biologic "signaling system" that indicated that we produce substances similar to cannabis, to act on these receptors, switching them on and off. The first two receptors identified were CB1 and CB2 – Cannabinoid #1 and #2. By 1992 the endogenous compounds that fit these receptors like a key in a lock were discovered, again at the Hebrew University. Thus began the story of cannabis' role in our bodies.

Subsequent research has shown that these receptors are scattered throughout various organs, CB1 primarily in the brain and CB2 in the GI tract, liver spleen, various endocrine glands and reproductive system. CB2 receptors are also involved in our immune system and peripheral nervous system (Di Marzo 1998). Thus, is it any surprise to find that cannabis can affect multiple bodily systems and play a role in helping our bodies deal with these systems when they go awry?

These discoveries, and those that followed, have become the scientific basis for debunking the stigmatization of cannabis that began with a vengeance in 1935. Finally, after more than three-quarters of a century, the mainstream media is finally telling the true story of cannabis and its role in fighting disease (Gupta 2013).

CLINICAL ENDOCANNABINOID DEFICIENCY SYNDROME (CECD) AND OTHER NEUROLOGICAL DISORDERS

In 2003 Ethan Russo, M.D. proposed the concept that a chemical endocannabinoid deficiency could explain the underlying cause of migraine, fibromyalgia, and irritable bowel syndrome (IBS) among other neurophysiological conditions (Russo 2004).

Dr. Russo understood that each neurotransmitter system can have pathological conditions caused by a deficiency: Alzheimer's dementia attributed to loss of acetylcholine activity, parkinsonism due to dopamine deficiency, depression associated with lowered levels of seratonin, etc.

Thus he reasoned, should this be any different in the endocannabinoid system, where the endocannabinoid receptors are especially dense? Could an endocannabinoid deficiency – either congenital or acquired – explain the pathophysioloogy of these elusive conditions?

MIGRAINE, FIBROMYALGIA AND IRRITABLE BOWEL SYNDROME

In migraine, pathways involving seratonin are integral to the condition. THC (tetrahydrocannabinol) inhibits seratonin release from the blood platelets of humans with migraine headaches (Volfe *et al.* 1985). Through a series of reactions involving "amandamide" (AEA – the common name for arachidonylethanolamide – with behavioral activity similar to THC) both of these substances partially oppose CB1 receptors which are especially prevalent in the periaquaductal gray matter, the cerebral origin of most migraine headaches (Russo 2008). These and other observations suggest the probable efficacy of therapeutic cannabinoid in the treatment of migraine.

Myofascial pain syndrome – fibromyalgia – is characterized by tender muscle points which tend to cluster in similar anatomical locations from patient-to-patient. Although the veracity of the condition has been questioned by neurologists, studies by

J.D. Richardson, *et al.* support a relationship of fibromyalgia to a clinical endocannabinoid deficiency, suggesting that the endocannabinoid system regulates pain thresholds and its absence may underlie the hyperalgesic tender muscle points of this condition (Bohr 1996; Richardson *et al.* 1997). These and subsequent studies have suggested that cannabinoid agonists would be useful in the treatment of chronic pain conditions such as myofascial pain syndrome, temporomandibular joint pain (TMJ) and reflex sympathetic dystrophy (RSD), a condition which can follow minor trauma, usually to an extremity, and is often described as being worse than the original injury.

Irritable bowel syndrome (IBS) can be a recurring nightmare for patients and their physicians. It involves recurrent constipation and/or diarrhea, often associated with painful abdominal spasms and distention. Infection, diet and emotional stress can trigger an attack, and the condition represents the most common causes of referral to a gastroenterologist. All of the current treatments are only partially effective.

We have previously noted that CB2 receptors are commonly found in the gut, and 2-arachidonylglycerol (2-AG) has been identified in dog intestine by Dr. Mechoulam and her associates to bind to these cannabinoid receptors (Mechoulam *et al.* 1995).

Pertwee, who has exhaustively studied the relationship of cannabinoids in gastrointestinal function, has demonstrated that mammal's enteric nervous systems contain CB1 and stimulation depresses GI motility (Pertwee 2001). These stimuli include delayed gastric emptying, decrease peptic acid production, and slowed peristalsis. Furthermore, these effects are also mediated in the brain, confirming the old adage "the brain and gut speak the same language." Confirming this, it has been shown that chronic intestinal inflammation results in the sensitization of cannabinoid receptors, to the extent that Izzo and DiCarlo suggested the use of cannabinoid drugs to treat IBS (Izzo *et al.* 2001; Di Carlo & Izzo 2003).

Given the above, it is not surprising that co-morbidities of these conditions should exist. Indeed, a high lifetime prevalence of migraine, IBS, depression and panic disorder were found among 33 women meeting

the American College of Rheumatology criteria for figromyalgia (Hudson *et al.* 1992).

AUTISM SPECTRUM DISORDER

The interaction of gastric and environmental factors appear to play a role in the genesis of the constellation of clinical entities known as Autism Spectrum Disorder (ASD). They are recognized by delayed and disordered social and communication skills and frequently with repetitive speech and behavior.

Success in treating ASD has been slow due to our poor understanding of its causes. This has resulted in the lack of a single standard approach to treatment. However, in 2008 Agudelo, Newton and associates discovered an immune system dysregulation in autistic children revealing an altered immune response in peripheral blood mononuclear cells (PBMC's) (Agudelo *et al.* 2008).

As noted above, there are two known cannabinoid receptor subtypes: CB1, expressed primarily (but not exclusively) in the brain and CB2, found primarily in peripheral somatic tissue and to a lesser extent, in the brain. The next exciting revelation came in April, 2013, when Dr. Dario Siniscalo and his co-workers discovered that CB2 was significantly increased in the peripheral blood mononuclear cells (PBMCs) of autistic children compared to their age-related normal controls. Variations in cellular biochemical events in ASD have been identified, such as mitochondrial disfunction, intestinal disfunction and immune dysregulation (Ashwood *et al.* 2006). Other immunological dysfunction in ASD demonstrated that PMBCs show increased levels of pro-inflammatory cytokines and interleukins that result in long-term immune system alterations (Molly *et al.* 2006).

Recently Siniscalo and co-workers demonstrated that PBMCs in ASD children show altered pleiomorphic enzymes (caspases) that regulate apoptosis and inflammatory signaling pathways. Caspases are pleiomorphic enzymes that function in cell proliferation and differentiation, as well as cellular activation and nuclear re-programming (Siniscalo *et al.* 2012; Algeciras-Schimnich *et al.* 2002).

THE FUTURE OF ENDOCANNABINOIDS

Endocannabinoids consist of arachidonic acid-derived compounds and their receptors, representing a complex network of lipid signaling pathways. A growing body of evidence is accumulating that pinpoints the endocannabinoid system plays a role in such psychiatric disorders as anxiety, major depression, bipolar disorder and schizophrenia as well as developmental disorders, including the elusive autism spectrum disorder (Barna & Zelena 2012; Schneider & Koch 2005; Ishiguro *et al.* 2010; Robinson *et al.* 2010; Garcia-Gutierrez & Manzanares 2011). We can expect that in the near future, our understanding of the role of the endocannabinoid system will grow exponentially.

A study of 17 children with autism was reported in 2013 by Dr's Dario Siniscalo, Anne Sapone and associates (Siniscalo *et al.* 2012). The study children were compared with 22 age and sex matched healthy children devoid of any neurological or psychiatric disorder. Fresh peripheral blood samples were obtained from each subject and their peripheral blood mononuclear cells (PMBCs) were isolated and the ribonucleic acid (RNA) was extracted.

From these samples the endocannabinoid system gene expression was determined (Siniscalo *et al.* 2012). Compared to the controls, the PMBC-extracted RNA levels showed an increase in the CB2 receptor genes of the ASD children. CB2 protein levels are increased in the polymorphonuclear blood cells of ADS children. No differences were noted in the CB1 receptor regulation.

CB2 receptor activation triggers immune suppression (Hyde *et al.* 2010) and after inflammation or tissue injury, there is a local rapid increase in endocannabinoid levels. This appears to mediate immune response through down-regulation of cytokine expression (Jean-Gilles *et al.* 2010). Furthermore, Basu and Dittel demonstrated that CB2 receptors are able to modulate the development, migration, proliferation and effector function of immune cells (Basu & Dittel 2011).

Combining these observations with our current understanding suggest that CB2 receptor up-regulation in PMBCs may be related to ASD-immune dysregulation. The CB2 receptor changes, but not CB1 or anandamide enzyme(s). This would indicate that the main function of CB2 endocannabinoids in these cells is to regulate inflammation and immune responses. CB1 receptors do not appear to be involved.

It has been fifty years since Drs. Mechoulam and Gaoni first isolated and named tetrahydrocannabinol. Dr. Russo found that a chemical endocannabinoid *deficiency* might explain the source of such diverse conditions as migraine and irritable bowel syndrome, Now, the pace of research is accelerating with enticing evidence that autism spectrum disorder may be related to an immune dysregulation in autism spectrum disorder and other treatment resistant conditions.

Conflicts of Interest: *Mark S. Wagner, MD holds the uncompensated, honorary position as Medical Director for C3, a patient's advocacy group for medical cannabis.*

REFERENCES

1 Agudelo M, Newton C, Widen R, Sherwood T, Nong L, Friedman H, Klein TW (2008). Cannibinoid receptor 2 (CB2) mediates immunoglobulin class switching from IgM to IgE in cultures of murine-purified beta lymphocytes. J Neuro-Immune Pharmacology. **3**(1): 35–42.

2 Algeciras-Schimnich A, Barnhart BC, Peter ME (2002). Apoptosis Independent Functions of Killer Caspases. Current Opinion of Cell Biology. **14**: 721–726.
3 Ashwood P, Wills S, Van de Water J. (2006). The Immune Response in Autism: A New Frontier in Autism Research. J of Leukocyte Biology. **80**(1): 1–15.
4 Barna I, Zelena D (2012). The Biochemical Complexity of the Endocannabinoid System: a Mini-review. Endocrine Regulations. **46**(2): 107–124.
5 Basu S, Dittel BH (2011). Unraveling the complexities of cannabinoid receptor 2 (CB2) immune regulation in health and disease. Immunologic Research. **51**(1): 26–38.
6 Bohr T (1996). Problems with myofascial pain syndrome and fibromyalgia syndrome. Neurology. **46**(3): 593–597.
7 Di Carlo G, Izzo AA (2003). Cannabinoids for gastrointestinal diseases: potential therapeutic applications. Expert Opin Investig Drugs. **12**(1): 39–49.
8 Di Marzo V (1998). 'Endocannabinoids' and other fatty acid derivatives with cannabimimetic properties: biochemistry and possible physiopathological relevance. Biochem Biophys Acta. **1392**(2–3): 153–175.
9 Garcia-Gutierrez MS, Manzanares J (2011). Overexpression of CB2 cannabinoid receptors decreased vulnerability to anxiety and impaired anxiolytic action of alprazolam in mice. J Psychopharmacology. **25**(1): 111–120.
10 Gupta S (2013). CNN Chief Medical Correspondent. CBS Special Report: "Weed", available at www.cnn.com/2014/03/05/health/gupta-medical-marijuana.
11 Hyde VL, Nagarkatti M, Nagarkatti PS. (2010). Cannabinoid receptor activation leads to massive mobilization of myeloid-derived suppressor cells with potent immunosuppressive properties. Eu J Immunology. **40**(12): 3358–3371.
12 Hudson JI, Goldenberg DL, Pope HG Jr, Keck PE Jr, Schlesinger L. (1992). Co-morbidity of fibromyalgia with medical and psychiatric disorders. Am J Med. **92**(4): 363–367.
13 Ishiguro H1, Horiuchi Y, Ishikawa M, Koga M, Imai K, Suzuki Y, et al (2010). Brain Cannabinoid CB2 Receptor in Schizophrenia. Biol Psychiatry. **67**(10): 974–82.
14 Izzo AA, Fezza F, Capasso R, Bisogno T, Pinto L, Iuvone T, Esposito G, Mascolo N, Di Marzo V, Capasso F (2001). Cannabinoid CB1-receptor mediated regulation of gastrointestinal inflammation. Br J Pharmacol. **134**(3): 563–570.
15 Jean-Gilles L, Gran B, Constantinescu CS (2010). Interaction between cytokines, cannabinoids and the nervous system. Immunology. **215(**8): 606–610.
16 Mechoulam R, Ben-Shabat S, Hanus L, Ligumsky M, Kaminski NE, Schatz AR, *et al* (1995). Identification of an endogenous 2-monoglyceride present in canine gut that binds to cannabinoid receptors. Biochem Pharmacol. **50**(1): 83–90.
17 Mechoulam R (2004). The Cannabinoid System in Neuroprotection. Lecture, Third National Clinical Conference on Cannabis Therapies. Charlottesville, VA. May 20–22.
18 Molloy CA, Morrow AL, Meinzen-Derr J, Schleifer K, Dienger K, Manning-Courtney P, Altaye M, Wills-Karp M (2006). Elevated cytokine levels in children with autism spectrum disorder. J Neuroimmunology. **172**(1–2): 198–205.
19 Pertwee RG (2001). Cannabinoids and the gastroentestinal tract. Gut **48**(6): 859–867.
20 Richardson JD, Aanonsen L, Hargreaves KM (1997). SR 141716A, a cannabinoid receptor antagonist, produces hyperalgesia in untreated mice. Eur J Pharmacol. **319**(2–3): R3–4.
21 Richardson JD, Kilo S, Hargreaves KM (1998). Cannabinoids reduce hyper-algesia & inflammation via interaction with peripheral CB1 receptors. Pain. **75**(1): 111–119.
22 Robinson SA, Loiacono RE, Christopoulos A, Sexton PM, Malone DT (2010). The effect of social isolation of rat brain expression of genes associated with endocannabinoid signaling. Brain Research. **1343**: 153–167.
23 Russo EB (2004). Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? Neuro Endocrinol Lett. **25**(1–2): 31–9. Review.
24 Russo EB (2008). Clinical endocannabinoid deficiency (CECD): can this concept explain therapeutic benefits of cannabis in migraine, fibromyalgia, irritable bowel syndrome and other treatment-resistant conditions? Neuroendocrinology Letters. **29**(2): 192–200.
25 Schneider M, Koch M (2005). Deficient Social and Play Behavior in Juvenile and Adult Rats after Neonatal Cortical Lesion. J Autism and Developmental Disorders. **30**(5): 944–957.
26 Siniscalco D, Sapone A, Giordano C, Cirillo A, de Novellis V, de Magistris L, Rossi F, Fasano A, Maione S, Antonucci N (2012). The expression of caspases is enhanced in peripheral blood mononuclear cells of autism spectrum disorder patients. J of Autism & Developmental Disorders. **42**(7): 1403–1410.
27 Siniscalco D, Sapone A, Giordano C, Cirillo A, de Magistris L, Rossi F, Fasano A, Bradstreet JJ, Maione S, Antonucci N (2013). Cannabinoid Receptor Type 2, but not Type 1, is up-regulated in peripheral blood mononuclear cells in children affected by autistic disorders. J Autism Dev Discord. **43**(11): 2686–2695.
28 Volfe Z, Dvilansky A, Nathan I (1985). Cannabinoids block release of seratonin from platelets induced by plasma from migraine patients. Int J Clin Pharmacol. Res **5**(4): 243–246.