

The Endocannabinoid System as it Relates to Autism

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The importance of the discovery and continued elucidation of the crucial role that the endocannabinoid system (ECS) plays in human health and disease cannot be understated. Cannabinoid receptors are the most highly expressed of any GPCR. They're the only ones to play a direct role in virtually every aspect of the human body (CNS and immune systems, throughout the periphery, presynaptic, and postsynaptic). (Alger 2013)

The growing body of data in regards to this aspect of physiology continues to lead to the further elucidation of the physiological basis in a growing number of diseases (including psychiatric) (Pacher 2006). One reason that this is important is because one such pathogenesis is for that of autism (ASD). There are a number of direct correlations between ASD and the ECS. Some will be outlined in this paper.

NL3 Mutations Inhibit Tonic Endocannabinoid Secretions

“Rare mutations in neuroligins and nerexins predispose to autism” (Földy 2013). Neuroligin-3 is the only known protein required for tonic secretion of endocannabinoids that include AEA and 2-AG (Földy 2013). Neuroligin-3 mutations have been shown to inhibit tonic endocannabinoid secretion (Földy 2013). These alterations in endocannabinoid signaling may contribute to autism pathophysiology (Földy 2013, Krueger 2013, Onaivi 2011, Siniscalco 2013). These findings have in part prompted researchers to apply to conduct research with nonhuman primates in order to further elucidate this link (Malcher-Lopes 2013).

Endocannabinoid system deficiencies are suggested to be involved in the pathophysiology of a growing number of diseases (Marco 2012, Russo 2003). Pacher and Pertwee both cover the endocannabinoid system in detail (Pacher 2006, Pertwee 2010). The number of functions that endocannabinoid signaling regulate in the human body is extensive and beyond the scope of this paper (Pertwee 2010). For sake of brevity only a few potentially relevant aspects will be listed:

- “Endocannabinoids are key modulators of synaptic function” (Castillo 2012).
- Tonic secretions of endocannabinoids regulate GI functions (including metabolism) (Di Marzo 2011, Li 2011).
- Endocannabinoids (and exogenous cannabinoids) suppress proliferation and cytokine release (Cencioni 2010).
- Endocannabinoids regulate stress responses, in part via the modulation of the 5-HT system (Haj-Dahmane 2011).

- CB2 is expressed in Purkinje cells (Gong 2006). “In the cerebellar cortex, CB1Rs regulate several forms of synaptic plasticity at synapses onto Purkinje cells, including presynaptically expressed short-term plasticity and, somewhat paradoxically, a postsynaptic form of long-term depression (LTD) (Carey 2011).”
- “CB1 variations modulate the striatal function that underlies the perception of signals of social reward, such as happy faces. This suggests that CB1 is a key element in the molecular architecture of perception of certain basic emotions. This may have implications for understanding neurodevelopmental conditions marked by atypical eye contact and facial emotion processing, such as ASC” (Chakrabarti 2011).
- Additional targets of endocannabinoids (and exogenous cannabinoids), PPAR α , PPAR γ , and GPR55 expression levels have shown reductions in a valproic acid model of autism in rats (Kerr 2013).
- Endocannabinoids and CB1 agonists increase cerebrocortical blood flow (Iring 2013).
- “The expression patterns in malformations of cortical development highlight the role of cannabinoid receptors as mediators of the endocannabinoid signaling and as potential pharmacological targets to modulate neuronal and glial cell function in epileptogenic developmental pathologies” (Zurolo 2010).
- The endocannabinoid signalosome is “a molecular substrate for fragile X syndrome, which might be targeted for therapy” (Jung 2012).

Exogenous cannabinoids from cannabis display similar pharmacological characteristics to that of endogenous cannabinoids (Pertwee 2010). The potential therapeutic value of systemic administration of phytocannabinoids has been suggested in the treatment of a number of diseases with suspected underlying endocannabinoid deficiencies (Russo 2003). Documentation of their safety and clinical efficacy in a variety of treatments continues to grow (Hazekamp 2013). Some similar characteristics include:

- Neurogenesis (Galve-Roperh 2007, Jiang 2005, Avraham 2014, Campos 2013)
- Neuroprotection (Hampson 2003, Lara-Celador 2013, Sanchez 2012)
- Antioxidants (Borges 2013, Pertwee 2010, Hampson 1998, Hampson 2003)
- Neuromodulation (Davis 2007, Lara-Celador 2013, Pertwee 2010, Youssef 2012)
- Anti-inflammatory (Pertwee 2010, Izzo 2009, Nagarkatti 2009, Klein 2005)

Based on their relative safety, the similar pharmacological characteristics to endocannabinoids that are inhibited in ASD, and the significant role those endogenous cannabinoids play in human health, it’s possible that cannabinoids from cannabis could prove therapeutic value in treatments.

Increased Expression of CB2 Receptors Associated with ASD

The second direct link, of possibly equal or greater relevance for treatment, is the upregulation of CB2 receptors in the brains of those with ASD (Siniscalco 2013). This is believed to be part of an endogenous neuroprotective role of the endocannabinoid system:

- “CB2 receptors have been identified in the healthy brain, mainly in glial elements and, to a lesser extent, in certain subpopulations of neurons, and that they are dramatically up-regulated in response to damaging stimuli, which supports the idea that the cannabinoid system behaves as an endogenous neuroprotective system. This CB₂ receptor up-regulation has been found in many neurodegenerative disorders including HD and PD, which supports the beneficial effects found for CB₂ receptor agonists in both disorders. In conclusion, the evidence reported so far supports that those cannabinoids having antioxidant properties and/or capability to activate CB₂ receptors may represent promising therapeutic agents” (Fernández 2011).
- CB2 “expression is increased by inflammatory stimuli suggests that they may be involved in the pathogenesis and/or in the endogenous response to injury... receptors may be part of the general neuroprotective action of the ECS by decreasing glial reactivity. Neuropathological findings in human brains suggest that the upregulation of CB₂ receptors is a common pattern of response against different types of chronic injury of the human CNS. In addition, their selective presence in microglial cells is highly suggestive of an important role in disease-associated neuroinflammatory processes. The anti-inflammatory effects triggered by the activation of the CB₂ receptor make it an attractive target for the development of novel anti-inflammatory therapies” (Benito 2008).

Given that CB2 is upregulated, and that it's believed to play a neuroprotective role in the human brain, CB2 activation is believed to be a potential target for treatment of ASD (Siniscalco 2013). Endocannabinoids (AEA, 2-AG) and the most prominent cannabinoids in cannabis (including THC) are CB2 agonists (Izzo 2009).

Elevated Cytokine Levels Associated with ASD

Elevated cytokine levels are associated with ASD (Napolioni 2013). Whether this is a direct result of inhibited tonic secretion of endocannabinoids remains uncertain. However, endocannabinoids (AEA, 2-AG) have been shown to play key roles inhibiting cytokines via CB2 activation (Cencioni 2010, Panikashvili 2006). “Both THC and CBD have been shown to decrease cytokine production” via CB1/CB2 dependent and independent mechanisms (Juknat 2012, Kozela 2010). The majority of cannabinoids are PPAR gamma agonists (Izzo 2009), which have been shown to inhibit cytokine production (Jiang 1998).

Clinically Diagnosing ASD

A team of researchers recently discovered and patented a process that claims that it's possible to clinically diagnose ASD, and susceptibility to it, via observation of the degree of modulation that acetaminophen has on endocannabinoid levels (Schultz 2012).

Botanical Extracts > Dronabinol

Of equal relevance to this issue is the substantial data, including clinical studies, suggesting that the combined administration of CBD along with THC (and possibly other cannabinoids/terpenes present in cannabis) exhibit additive and synergistic effects resulting in greater clinical efficacies when compared to either cannabinoid alone (McPartland 2001, Izzo 2009, Russo 2011). The second most prominent cannabinoid in cannabis is CBD (Gertch 2010). CBD has been shown to inhibit intoxication, sedation, and tachycardia associated with THC (Russo 2006). It's been shown to increase the clinical efficacy of THC, while adding therapeutic value in its own right (Russo 2006).

- “CBD is demonstrated to antagonize some undesirable effects of THC including intoxication, sedation and tachycardia, while contributing analgesic, anti-emetic, and anti-carcinogenic properties in its own right. In modern clinical trials, this has permitted the administration of higher doses of THC, providing evidence for clinical efficacy and safety for cannabis based extracts in treatment of spasticity, central pain and lower urinary tract symptoms in multiple sclerosis, as well as sleep disturbances, peripheral neuropathic pain, brachial plexus avulsion symptoms, rheumatoid arthritis and intractable cancer pain. Prospects for future application of whole cannabis extracts in neuroprotection, drug dependency, and neoplastic disorders are further examined. The hypothesis that the combination of THC and CBD increases clinical efficacy while reducing adverse events is supported” (Russo 2006).
- “Several studies suggest that CBD is non-toxic in non-transformed cells and does not induce changes on food intake, does not induce catalepsy, does not affect physiological parameters (heart rate, blood pressure and body temperature), does not affect gastrointestinal transit and does not alter psychomotor or psychological functions. Also, chronic use and high doses up to 1,500 mg/day of CBD are reportedly well tolerated in humans” (Machado 2011).

An argument could be made that botanical extracts with CBD present offer safer options for patients, with greater clinical efficacy, when compared to THC (Dronabinol) alone (Russo 2006). CBD offers more than simply increasing the safety and efficacy of THC (Izzo 2009).

- “CBD has been shown to have an inhibitory effect on the inactivation of endocannabinoids (i.e. inhibition of FAAH enzyme), thereby enhancing the action

of these endogenous molecules on cannabinoid receptors, which is also noted in certain pathological conditions. CBD acts not only through the endocannabinoid system, but also causes direct or indirect activation of metabotropic receptors for serotonin or adenosine, and can target nuclear receptors of the PPAR family and also ion channels” (Campos 2012).

Here are some of the demonstrated pharmacological characteristics of CBD that may be relevant:

- CB1/CB2 agonist blocker (can inhibit overstimulation of CB1 by THC)
- FAAH inhibition increases endocannabinoid levels (including AEA, 2-AG)
- AEA reuptake inhibitor
- 5-HT1a agonist
- Suppressor of tryptophan degradation
- PPAR alpha and gamma agonist
- Positive allosteric modulator at glycine receptors
- TRPV1 and TRPV2 agonist
- Adenosine uptake competitive inhibitor
- Antagonist at abnormal-CBD receptor
- Regulator of intracellular Ca²⁺
- T-type Ca²⁺ channel inhibitor (Izzo 2009)

If we accept that tonic secretions of AEA and 2-AG are inhibited via NL3 mutations in ASD (both of which being CB1 and CB2 agonists), then it might be possible to suppose the potential benefits of low doses of THC in treatments as well. This seems especially true when the striking pharmacological similarities between THC and AEA are reviewed (Pertwee 2010). The majority of the research conducted thus far with ASD and cannabinoids has been with THC alone. Dronobinal has indicated potential in a single adolescent case study of autism (Kurz 2010). This might suggest that THC along with CBD might offer increased clinical efficacy (Russo 2006).

Treating Symptoms Associated with ASD

A considerably greater body of data can be gathered in regards to aspects of the involvement (and targeting for treatment) of the endocannabinoid system in a number of the symptoms, and diseases, associated with ASD (in comparison to the pathophysiology of ASD itself):

- G.I. Disorders (Camilleri 2013, Di Sabatino 2011, Wright 2008,)
- Repetitive Behaviors (Casarotto 2010, Deiana 2012, Gomes 2011, Kinsey 2011)
- Seizures (Jones 2012, Porter 2013, van Rijn 2011)
- Sleep Dysfunction (Murillo-Rodriguez 2011, Ware 2010)
- Self Injurious Behavior and Tantrums (Müller-Vahl 2004, Onaivi 2011, Passie 2012)
- Tuberous Sclerosis (Krueger 2013, Shu, Hai-Feng 2013, Zurolo 2010)

- Cerebral Ischemia (Schmidt 2012, Choi 2013, Murikinati 2010, Garcia-Bonilla 2014)
- Depression/Anxiety (Hill 2009, Almeida 2013, Campos 2013, Schier 2012)
- Cachexia (Engeli 2012, Gamage 2012, Marco 2012)

Conclusion

Given the known role of the endocannabinoid system in ASD it seems entirely possible, if not likely, that cannabinoid rich botanical extracts from cannabis can be utilized as useful agents targeting the pathophysiology of ASD, as well as the many debilitating symptoms and conditions associated with it. We believe that families and physicians should have the legal right to explore these options on an individual basis without fear of prosecution.

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