The Endocannabinoid System: Treatment Implications in ASD

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Overview

- Cannabidiol (CBD) – What is CBD?
- Endocannabinoid System (ECS) – What is ECS?
- How does the ECS work?
- How is the ECS related to ASD?
- How can CBD be used to treat ASD?
- How to use CBD for patients?
What is CBD?

- Cannabidiol (CBD) is a phytocannabinoid
- Derived from Agricultural Hemp (Cannabis Sativa L.)
- Hemp is refined into products such as hemp seed foods, hemp oil, wax, resin, rope, cloth, pulp, paper, and fuel.
- Hemp is nutrient rich, ecofriendly, sustainable
What is CBD?
What is CBD?

- Hemp is not Marijuana
  - Marijuana is also a Cannabis plant
  - Marijuana contains tetrahydrocannabinol (THC)
  - THC causes psychotropic effects
- Hemp does not contain THC
- Hemp is not psychoactive
- Hemp products, including CBD, have an excellent safety record
- CBD is a nutritional supplement available in all 50 states

Global Hemp, 2015, Hemp Since the Beginning of Time
J. Hicks, 2015, The Medicinal Power of Cannabis
What is CBD?

Figure 1: The structure of THC

Figure 2: The structure of CBD
What is the ECS?

- Central regulatory system designed to maintain and restore Homeostasis
  - Homeostasis: The tendency of an organism or a cell to regulate its internal conditions, usually by a system of feedback controls, so as to stabilize health and functioning regardless of the outside changing conditions
  - ECS regulates homeostasis through a wide variety of mechanisms, including facilitation of intercellular communication between different cell types

D. Sulak, et al, Introduction to the Endocannabinoid System
G. T. Griffing, et al, Endocannabinoids Overview
What is the ECS?

The ECS is comprised of:

- Cannabinoid receptors
- Endogenous ligands (binding molecules) for those receptors referred to as Endocannabinoids
- Enzymes that synthesize and degrade the endocannabinoids

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What is the ECS?

- Cannabinoid receptors
  - The most well known cannabinoid receptors are CB1 and CB2
  - Both types of cannabinoid receptors are found throughout the entire body, but are distributed differently
  - CB1 receptors are concentrated primarily in the CNS, also in peripheral tissues
  - CB2 receptors are mainly found in the peripheral tissues, notably the immune system, also in the CNS

I. Svizenska, P. Dubovy, A. Sulcova, Pharm Biochem and Behavior. 2008; 90:501-11
What is the ECS?
What is the ECS?

- Endocannabinoids for CB receptors
  - Anandamide
    - Discovered in 1992
    - Endogenous ligand for the CB1 receptor
    - Chemical structure is very similar to tetrahydrocannabinol
  - 2-Arachidonoyl Glycerol (2-AG)
    - Discovered in 1995
    - High affinity for activating both CB1 and CB2 receptors
- Additional Endocannabinoids
  - Palmitoylethanolamide (PEA), Dososatetraenylethanolamide (DEA), homo-gamma-linoenlethanolamide (HEA), virodhamine, noland ether, oleamide, oleoylethanolamine (OEA)

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What is the ECS?

- Enzymes that synthesize and degrade the ligands
  - Synthesis
    - Synthesized from Arachidonic Acid
    - Unsaturated fatty acid ethanolamides
    - Anandamide: NAPE-PLD (N-acylphosphatydlethanolamine-specific phospholipase)
    - 2-AG: DAGL (D Phospholipase C compound – sn-1-diacylglycerol lipase)
  - Degradation
    - Anandamide: FAAH (Fatty acid amide hydrolase)
    - 2-AG: MAGL (Monoacylglycerol)

What is the ECS?
How does the ECS work?

- The ECS affects all systems, organs and tissues to promote homeostasis
- When cells communicate, neurotransmitters normally flow from presynaptic neurons to postsynaptic neurons
- Based upon the interaction between the transmitter and receptor, neurotransmitters may trigger a variety of effects in the post-synaptic cell, such as excitation, inhibition, or the initiation of second messenger cascades
- Endocannabinoids are unique, being able to travel in the opposite direction and deliver feedback to the presynaptic cell
- This process is a fundamental mechanism by which endocannabinoids maintain homeostasis

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How does the ECS work?

- In the central nervous system, CB1 receptors influence neuronal excitability, reducing the incoming synaptic input.
- This mechanism, known as presynaptic inhibition, occurs when a postsynaptic neuron releases endocannabinoids in retrograde transmission, which then bind to cannabinoid receptors on the presynaptic terminal.
- CB1 receptors then reduce the amount of neurotransmitter released, so that subsequent excitation in the presynaptic neuron results in diminished effects on the postsynaptic neuron.

How does the ECS work?
How does the ECS work?

- Neuronal excitation example
  - Neuron is firing messages too quickly
  - Endocannabinoids (usually 2-AG) instruct it to slow down by traveling upstream and activating presynaptic CB1 receptors to decrease firing

- Tissue Injury example
  - Endocannabinoids
    - Decrease the release of activators and sensitizers from the injured tissue
    - Stabilize nerve cells to prevent excessive firing
    - Stabilize immune cells to prevent release of pro-inflammatory substances
  - Three different mechanisms of action on three different cell types for a single purpose to minimize the pain and damage caused by the injury to promote healing and homeostasis

How is the ECS related to ASD?

- **Mouse Models of ASD and ECS**
  - NL3 Mutations Inhibit Tonic EC Secretions
    - NL3 is required for tonic secretion of ECs
    - NL3 mutations inhibit tonic EC secretion which may contribute to pathophysiology in ASD
  - Fragile X
    - The ECS is implicated in FXS behavioral, synaptic and molecular manifestations
    - CB1 and CB2 are pharmacological targets to reduce cognitive deficits and anxiety
  - CB2 Upregulated in ASD
    - CB2 is believed to be neuroprotective in presence of inflammatory stimuli
    - CB2 as potential target for treatment in ASD

How can CBD be used to treat ASD?

- Loss of tonic secretions of EC lead to imbalance in the ECS resulting in a loss of homeostasis in multiple organ systems
  - CNS dysfunction
  - GI dysfunction
  - Immune dysregulation
  - Endocrine dysfunction
- Restoring balance of the ECS can provide relief of symptoms
  - Exogenous EC can be supplemented in the form of CBD

How can CBD be used to treat ASD?
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- CBD supporting normal ECS function
  - Provide relief of symptoms
  - Promote neurogenesis
  - Provide neuroprotection
  - Provide potent antioxidant effect
  - Support neuromodulation
  - Provide anti-inflammatory effect

How can CBD be used to treat ASD?

- CBD supporting normal ECS function can provide relief of symptoms
  - CNS Symptoms
    - Repetitive behaviors/stereotypies
    - Appetite disturbances (hyperphagia, anorexia, nausea, ematophobia)
    - Mood disturbances (Anxiety, depression, OCD, aggression, rage)
    - Seizure
    - Self injurious behavior (SIB)
    - Sleep dysfunction
  - GI Symptoms
  - Immune Symptoms
  - Endocrine Symptoms

How to use CBD for patients?
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CBD Oil Forms
- Oil in liquid form administered in sprays or squirts
- Oil in paste form administered in rice grain size doses
- Oil in capsule form
- Essential Oil form administered in drops, diluted in water

CBD Oil Dosing
- Start low and increase dose slowly, monitoring for clinical effect
- Typical regimen: 3 mg at bedtime, increase by 3 mg weekly to goal dose of 12 to 24 mg
- Doses can range from 2 mg to 200 mg
- More is not necessarily better
How to use CBD for patients?

- Clinical Cases
  - 9 yo girl with ASD and PANS bedtime phobia and anxiety
  - 6 yo boy with ASD and PANS nausea and ematophobia
  - 18 yo girl with ASD anxiety and insomnia
Contact Information

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The Medicinal Power of Cannabis
by John Hicks, MD