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Review Article

The Endocannabinoid System , Hemostasis and Mental Health Disorders-A Review

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Introduction

The term endocannabinoid comes from the word endogenous, which roughly means 'from in- side. 'The Endocannabinoid system which we will refer to, moving forward, as the ECS, is a neuromodulatory network that is responsible for homeostasis. It regulates learning, memory, cardiovascular activity, Gastrointestinal activity, sleep, temperature, pain, immune response, inflammation, appetite and is neuoprotective. Whenever we get ill, the ECS works to maintain the balance through their signaling system. Is there anything the ECS cannot do?

I will be reviewing the role of the ECS in mental health disorders and how it impacts this vulnerable patient population. Simply put, how does the ECS work? Should patients with mental health disorders even consider using cannabis and what is the evidence to support for or against its use?

The Endocannabinoid System

We know that the ECS is a neuromodulatory network that is responsible for homeostasis which basically means it helps to maintain the balance via a chemical messenger system between different body systems. It exerts its effects on the various systems mentioned earlier which help modulate, for example, sleep and pain. It comprises of endocannabinoids (eCB), proteins that help to transport and enzymes that breakdown the endocannabinoids. The receptor proteins are found in the central nervous system as well as in the peripheral nervous system. The CB1R (cannabinoid receptor) is present in the CNS and exerts effects also through various neurotransmitters such as serotonin, but there are more. These are off site target effects. Remember serotonin and how it regulates emotions? That's how antidepressants work by inhibiting reuptake of serotonin making more available or glutamate and memory? How about norepinephrine in fight or flight response? This is part of our sympathetic nervous system. All these neurotransmitter are regulated by the cannabinoid receptors. It regulates the activity by feedback.

The CB2R are present on immune cells which means its helps with inflammation. You can find them in the GI tract (hence why it may have a role in inflammatory bowel disease), Spleen etc whereas CB1R in addition to the brain are also found in the heart, GI tract, skeletal muscles liver to name a few.

Now that we know what makes the ECS, we need to understand how it works.

How many of you know that we have our own naturally occurring endocannabinoids? They are derived from arachidonic acid. The two most well known and naturally occurring are 2 AG and anandamide. The former was discovered by Mechoulam in 1995. Fun Fact the word ananda comes from Sanskrit which means 'bliss'. So how does the ECS work? We have pre synaptic and post synaptic neuron with a space in between. The presynaptic neuron releases the neuro- transmitter and it is received by the post synaptic neuron causing the cell to make the endo- cannabinoid. Think of the endocannabinoids as a key. Our naturally occurring endocannabinoids synthesized in the post synaptic cell then go in a retrograde fashion across the synapse to stimulate the CB receptors by inserting itself as a key which in turn regulates firing from the neuron and causes neurotransmitter release to correct the signal in order to maintain balance or homeostasis. The endocannabinoids are then broken down by enzymes. So this is our own endogenous cannabinoid.

So now that we have discussed our internal cannabinoid system, how does the external system work?

This is where exogenous cannabinoids comes into play. It comes from outside our body. If we take THC or CBD,

how does it exert its effects? If we take THC, (tetrahydrocannabinol) it acts on the CB1 receptor in the brain and causes changes in mood, perception , sensation ,and influences how we perceive pain. It does this by disturbing GABA and dopamine release. Think of screen time and dopamine release .It also disturbs the balance resulting in its psychoactive effects. Too much THC can cause difficulty with recall, feeling "high" and cognitive dysfunction. This is dissimilar to Cannabidiol (CBD). There is no "high" with CBD. CBD is unique in that it also binds to serotonin ,mu and kappa receptors in addition to the low affinity for CB1 and CB2 receptors by which exerts therapeutic effects in anxiety and pain. To further this, the modulation of serotonin (5-HT) and noradrenaline (NA) in the hippocampus by CBD is thought to exerts its antidepressant effects We won't go into the signaling pathway as it is beyond the scope of this review.[1]

We can now discuss the ECS in mental health disorders.

The ECS is important in mental health disorders particularly Schizophrenia and Bipolar disor der. We know that the term schizophrenia was initially came to fruition in 1911 and represents about 1% of the worlds' population. As you may be already aware, the common age of onset is typically between the early 20's to mid 20's. They may present with auditory hallucinations, social dysfunction, paranoia and delusions.[2]

So now let's dive into the various studies that discuss cannabis in mental health.

Based on Speilman et al we know that cannabis use is considered to be a risk factor for schizo- phrenia. This does not mean that it leads to Schizophrenia. These individuals may have a family history of schizophrenia. Given the age of onset is 20-25, if cannabis is used in this population, they may be at risk for or developing mental health disorder.[3]

Another study reviewed 45,000 Swedish military personnel who used marijuana at least once, were followed for 15 years. They concluded that this group had 2 times increased risk of developing schizophrenia than those who did not use marijuana.[3]

Moore et al 2007 showed that the risk of psychotic disorders and schizophrenia in people who used marijuana was higher. This was especially the case with frequent users.[3]

What about in bipolar disorder? There is conflicting data. It is thought that THC is a mood stabi- lizer when experiencing a manic episode. Chronic use of chemotype[1] where THC>CBD, in- creases the manic symptom burden in this patient populations.[2]

Large et al noted the onset of psychosis in patients who use cannabis occurred at an earlier age than those who did not. This many occur given brain development during adolescence which has an impact. It can also lower their chance at academic success.

What about the use of cannabis in other disorders? Presently, there are no randomized controlled trials for use of cannabis in anxiety. In fact, its shows it exerts more harm. Cannabis use in depression has led to increased risk of suicide as per the American Psychiatry Association.[4]

How many of you have heard of Cannabis use and addiction?

Cannabis use disorder (CUD) refers to ongoing use of cannabis/ marijuana despite impairment to the body resulting in cravings, withdrawal and interference with personal relationships and social life. These individuals continue to take it despite physical harm. The DSM 5 now recognizes CUD.

To conclude, like everything else in research, especially with cannabis, we need more studies. Till then we can follow the standard practice in management of these mental disorders.

So let's go over and revise some key points.

Key Points

Let's review the key points:

- ECS is a neuromodulatory network that is responsible for homeostasis which basically means it helps to maintain the balance between different body systems
- The ECS system is a complex system that is composed of endocannabinoids, receptors and proteins
- THC acts on the CB1 receptor in the brain and causes changes in mood, perception, sensation and influences how we perceive pain.
- There is evidence that cannabis is a risk factor for developing schizophrenia

Check for Understanding

Let's see what you understood from the review today.

Question 1:

Which one of the following is True?

(a) The ECS is a complex system of endocannabinoids, receptors and proteins

(b) THC can be safely used in schizophrenia

(c) There are no naturally occurring endocannabinoids in the body

(d) Family history of psychotic disorders is not important when considering cannabis use.

Answer A: The ECS is a complex system of endocannabinoids , receptors and proteins

Question 2:

Which of the one is False?

(a) Chronic use of THC does not increase manic episodes

(b) Anandamide is a naturally occurring endocannabinoid.

(c) THC is psychoactive

(d) The ECS helps to regulate messages between cells to maintain balance/homeostasis.

Answer A. There is an association between chronic THC use and manic episodes

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