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Neuro-Gastro-Cannabinology: A Novel Paradigm for Regulating Mood and Digestive Health

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Abstract
The maintenance of homeostasis in the gastrointestinal (GI) tract is ensured by the presence of the endocannabinoid system (ECS), which regulates important physiological activities, such as motility, permeability, fluid secretion, immunity, and visceral pain sensation. Beside its direct effects on the GI system, the ECS in the central nervous system indirectly regulates GI functions, such as food intake and energy balance. Mounting evidence suggests that the ECS may play an important role in modulating central neurotransmission which affects GI functioning. It has also been found that the interaction between the ECS and microbiota affects brain and gut activity in a bidirectional manner, and a number of studies demonstrate that there is a strong relationship between GI dysfunctions and mood disorders. Thus, microbiota can regulate the tone of the ECS. Conversely, changes in intestinal ECS tone may influence microbiota composition. In this mini-review, we propose the concept of neuro-gastro-cannabinology as a novel and alternative paradigm for studying and treating GI disorders that affect mood, as well as mood disorders that imbalance GI physiology. This concept suggests the use of prebiotics or probiotics for improving the tone of the ECS, as well as the use of phytocannabinoids or endocannabinoid-like molecules, such as palmitoylethanolamide, to restore the normal intestinal microbiota. This approach may be effective in ameliorating the negative effects of GI dysfunctions on mood and/or the effects of mood disorders on digestive health.

Introduction

Homeostasis is derived from the ancient Greek words ὅμοιος and στάσις, meaning "staying the same". As a biological concept, it refers to the attitude of living organisms toward maintaining a steady balance when their conditions are optimal [1]. This can be regarded as a natural adaptive process of preservation of nearly constant conditions in the internal environment. As with other areas of the human body, the maintenance of intestinal homeostasis is fundamentally relevant to health. It is

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crucial that the digestive and defensive functions of the gut are integrated and balanced to protect the body against insults caused, i.e., by indigestion, pathogens, and toxins. Intestinal equilibrium is maintained by a variety of pathways and cells, including immune, epithelial, neuronal, glial, and endocrine cells [2]. Microbiota-gut-brain interactions also play an important role in this process [3]. It is in this context that the endocannabinoid system (ECS) emerges as a key modulator of intestinal homeostasis. Several intestinal physiological processes are regulated by the ECS, a network of lipid mediators that have been found ubiquitously throughout the entire gastrointestinal (GI) system. The presence of the ECS in the GI tract has been extensively described elsewhere [4, 5]. Briefly, the gut is home to both cannabinoid (CB) receptors, CB1 and CB2, their endogenous ligands, termed endocannabinoids, such as anandamide and 2-arachidonoylglicerol (2-AG), and the enzymes responsible for their biosynthesis and degradation. Several non-typical cannabinoid members are also expressed, including the transient receptor potential (TRP) channels, such as TRPV1 and TRPM8, proliferator-activated receptors (PPARs), G protein-coupled receptors (GPRs), and endocannabinoid-like molecules, including palmitoylethanolamide (PEA) and oleoylethanolamide (OEA) [4, 5]. In the human body, the endocannabinoid signaling pathways are involved in regulating a variety of biological and cognitive processes (such as appetite, pain sensation, and mood) and in mediating the pharmacological effects of cannabis [6–12]. The ECS in the GI tract regulates important physiological activities, such as intestinal motility, permeability, fluid secretion, immunity, and visceral pain sensation [12, 13]. Apart from the direct effects on the GI system, the ECS in the central nervous system (CNS) indirectly controls intestinal functions, such as food intake and energy balance [10, 14, 15]. It is now well established that the brain and gut communicate bidirectionally to control a variety of physiological processes, through the gut-brain axis. Evidence suggests that the ECS may play an important role in modulating central neurotransmission which affects GI functioning [3, 16–19]. It has also been found that the interaction between the ECS and microbiome affects brain and gut activity in a bidirectional manner [20–22]. The ECS plays a role in modulating both emotional and non-emotional behavior [23–26]. Signals originating from the ECS are known to influence the hypothalamic-pituitary-adrenocortical (HPA) axis, which is the mammals' primary stress response system [27–29]. It has been demonstrated that dysbiosis and/or altered endocannabinoid tone contribute to mood changes and that mood disorders affect gut physiology [30–32]. Moreover, growing evidence suggests a role of the ECS in regulating the circadian sleep-wake cycle, and dysregulation of this circuit can lead to both mood and GI disorders [33–35]. The ECS is also involved, at least in part, in the induction of placebo effects, especially in placebo analgesia [36]. Bringing all this evidence together, we propose the concept of neuro-gastro-cannabinology as a novel and alternative paradigm for studying and treating GI disorders that affect mood, as well as mood disorders that imbalance GI physiology.

Role of the ECS in Mediating Gut and Brain Interactions

In both the peripheral nervous system and the CNS, the ECS plays a critical role in modulating and fine-tuning synaptic transmission. CB1 and, to a lesser extent, CB2 are located in nerve fibers throughout the gut, but their concentration is highest in the myenteric and submucosal plexi [37]. Importantly, CB receptors are believed to be localized only to excitatory nerves in the gut [38]. The endocannabinoids function as retrograde neurotransmitters since they are synthetized in the postsynaptic cell, then cross the synapse and activate CB receptors presynaptically [39]. Conversely, CB2 and, to a lesser extent, CB1 are mainly expressed in intestinal immune cells, where they are involved in modulating intestinal inflammation as well as abnormal motility, visceral sensitivity, and pain [40]. ECS activation induces an overall inhibitory effect on gut cells' functions, particularly on cholinergic neurons. This inhibitory physiological mechanism may be exploited in pathological conditions, by enhancing or decreasing the ECS tone; indeed, the ECS affects motility, pain, secretion, and inflammation; moreover, the brain and the GI system are intimately connected. Accumulating evidence is suggestive of the ECS linking gut microbiota to CNS pathophysiology (shown in Fig. 1) [20, 41]. Besides helping to digest nutrients and protect against pathogenic bacteria, the gut microbiota has a significant impact on the activities of the CNS, particularly mood. There is a strong relationship between GI dysfunctions and mood disorders [42]; both functional and chronic inflammatory GI disorders, such as irritable bowel syndrome (IBS) and inflammatory bowel disease (IBD), are often associated with affective ailments, such as depression, anxiety, panic, and post-traumatic stress disorder (PTSD) [43]. Conversely, mood disorders can lead to the development of GI diseases, such as functional dyspepsia and gastric ulcer [44, 45]. A possible link between gut and brain disorders may be represented by the crosstalk between the gut microbiota

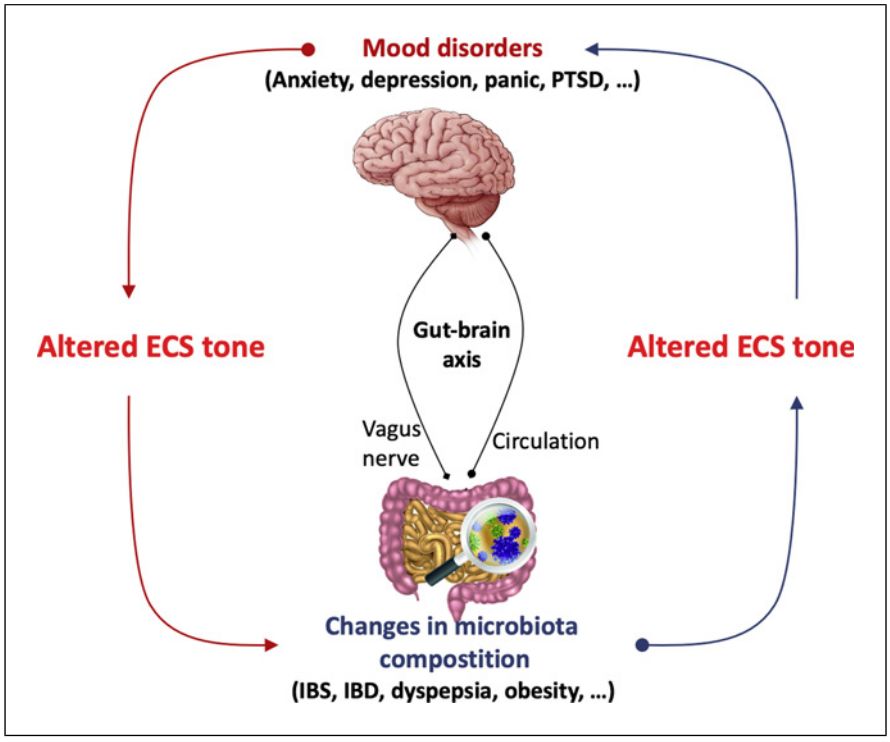

Fig. 1. Alteration of the endocannabinoid system (ECS) in mood and gastrointestinal (GI) disorders. The interaction between the gut and the brain can be mediated either by the vagus nerve or by circulating metabolites. Alterations in the composition of the microbiota can modulate the tone of the ECS, leading to central modifications that influence mood. Conversely, mood disorders can modify the tone of the ECS, which in turn can alter the composition of the microbiota, potentially resulting in the development of GI disorders. IBS, irritable bowel syndrome; IBD, inflammatory bowel disease; PTSD, post-traumatic stress disorder.

and the ECS. A study in 2007 reported that the commensal bacterium *Lactobacillus acidophilus* increased intestinal epithelial CB2 expression when administered orally to mice and rats [46]. Changes in gut microbiota also affect the levels of fatty acid amide hydrolase (FAAH), monoacylglycerol lipase (MAGL), and CB1 mRNA [47, 48]. By treating mice with the commensal bacterium *Akkermansia muciniphila*, levels of endocannabinoids in the gut are increased, and the metabolic dysregulation caused by a high-fat diet can be reversed [49]. Also, in obese mice, CB1 antagonist SR141716A increases *Akkermansia muciniphila* levels and decreases Lachnospiraceae and Erysipelotrichaceae levels, which are implicated in gaining weight and induction of metabolic syndrome [50]. A common feature of GI diseases, such as IBS, IBD, and functional dyspepsia, is dysbiosis, a disturbance in gut microbial composition and function caused by both environmental and internal factors. Dysbiosis has been repeatedly associated with chronic GI disorders and metabolic disorders, such as IBD, obesity, diabetes mellitus, cancer, and cardiovascular diseases [51–53]. Furthermore, dysbiosis, as well as intestinal inflammation and loss of gut integrity, is also linked to mood disorders, such as anxiety and depression, as well as more severe psychiatric and neurologic conditions, such as schizophrenia, autism, or neurodegenerative diseases [54, 55]. Changes in microbiota composition induced by dysbiosis are correlated with hippocampal and gut alterations in some members of the ECS [48]. Interestingly, probiotic supplementation reduced gut inflammation and decreased depression-like behavior by normalizing gut microbiota and reversing biochemical and functional changes in the hippocampus [48]. Dysbiosis-induced changes in the ECS tone can also induce pain, which can be reverted with PEA supplements that restore the microbiota and endocannabinoid tone to normal [55]. Intriguingly, a significant increase in *Akkermansia muciniphila*, *Eubacterium*, and Enterobacteriaceae is observed following PEA administration, suggesting that PEA has anti-inflammatory properties as well as the ability to regulate gut dysbiosis [56]. Fecal microbiota transplantation from mildly stressed mice, a mouse model of depression, caused depression-like behavior in recipient mice [57]. There were significant molecular and behavioral alterations in the recipient mice associated with reduced serum lipid precursors for the production of ECS ligands, as well as a decrease in brain endocannabinoids levels, supporting the hypothesis that stress causes a lower endocannabinoid tone, where gut microbial composition imbalance might be a factor. Other studies have shown dramatic changes in the intestinal ECS in germ-free mice, including reduced gene expression of CB1, GPR55, and PPARα in the gut, and fecal transplants

partially reversed these changes, suggesting that microbiota composition profoundly affects the intestinal endocannabinoid tone [58]. Human studies have shown that dysbiosis triggers gut-microbial alterations that contribute to anhedonia and amotivation via the ECS, especially through changes in PEA serum levels [59]. Taken these data together, it seems that the ECS is implied in the CNS consequences of gut dysbiosis. One explanation may be that commensal microorganisms affect ECS signaling by directly producing endocannabinoid-like molecules able to bind the receptors of the ECS [52]. Furthermore, as CB1 is expressed in vagal afferents that innervate various regions of the GI tract, the ECS may also modulate vagus nerve transmission, which is crucial for controlling food intake, hedonic feeding, visceral pain, aversion, and emotions by modulating the microbiota-gut-brain axis [47]. Studies using germ-free mice further confirm the relationship between the microbiota, ECS, and brain. As reported in a 2017 paper, the alterations in gut microbiota composition affect both brain and gut levels of endocannabinoids [60]. This study suggests that the endocannabinoid-like compound OEA, through its binding to GRP111 receptors, influences the secretion of the satiating hormone GLP-1, thus improving cognitive functions in patients with mood disorders [60]; therefore, microbiota have the potential to regulate the tone of the ECS. On the other hand, alterations in the intestinal ECS tone could also have an impact on the composition of the microbiota. An altered intestinal ECS modifies microbiota composition and may contribute to chronic abdominal pain, a common symptom of anxiety and depression, as well as GI disorders [56]. Intestinal permeability and metabolic endotoxemia are reduced by a CB1 antagonist, which also induces an imbalance in gut microbiota composition and a decrease in inflammation and macrophage levels in the adipose tissue of diet-induced obese mice. Conversely, a probiotic strain of *Escherichia coli* engineered to produce endocannabinoids can reduce adiposity in mice on a high-fat diet by suppressing food intake, improving insulin sensitivity, and reducing liver fibrosis [61]. Thus, by using engineered bacteria, it may be possible to manipulate gut ECS signaling to provide therapeutic benefits. Numerous studies have demonstrated the interaction between the gut microbiota and the HPA axis, indicating that stress-induced activation of this neuroendocrine system may be affected by the composition of the gut microbiota [62, 63]. There is also evidence suggesting that stress reduces the levels of endocannabinoids, especially 2-AG, which may lead to GI issues [64]. It is unclear whether stress-induced microbiota modification affects the ECS tone or if the effect of stress on the ECS changes microbiota composition. However, restoring normal microbiota or improving the ECS tone may be effective in counteracting the negative effects of stress on mood or digestive health.

Potential Interventions Targeting the ECS in GI and Mood-Related Disorders

A number of studies have described the use of prebiotics, probiotics, or both in treating anxiety and depression both in animal and human studies [47, 65–70]. Notably, in vagotomized mice, probiotic-related effects on neurochemical changes as well as on behavior were abolished, again suggesting a role of the vagus nerve in these beneficial reactions [65]. In light of these findings, our review suggests the modulation of the microbiota composition as a first-line treatment or an adjuvant to psychiatric intervention for anxiety and depression, using prebiotics or probiotics (shown in Fig. 2). Such treatments may be especially beneficial to patients who suffer from GI co-morbidities, such as IBS or dyspepsia [71]. Additionally, phytocannabinoids can also be used to improve the composition of the microbiota. The chronic treatment of obese rodents with tetrahydrocannabinol (THC) caused an altered microbiota with a higher *Firmicutes:Bacteroidetes* ratio, an increase in *Akkermansia muciniphila* abundance, and reduced obesity concurrently [72]. Capsaicin, a TRPV1 agonist, increased butyrate-producing Ruminococcaceae and Lachnospiraceae in obese rodents while decreasing LPS production [73]. Fecal microbiota transplant into germ-free mice revealed that capsaicin-induced obesity resistance was transferrable, demonstrating the importance of the microbiota [73]. Researchers examined the gut microbiome of mice treated with cannabidiol (CBD)-enriched cannabis extracts as well as the associated histomorphological and molecular changes in their gut mucosa [73]. There was a significant increase in *Akkermansia muciniphila* relative abundance; nevertheless, the colon tissue had increased levels of pro-inflammatory cytokines and chemokines, and gut integrity was decreased. As a result, questions have been raised about the potential long-term effects on the microbiome of therapeutic CBD application in humans. Interestingly, the mice used in this study were not pathological, so the situation may have differed if an induced pathological state, such as obesity or gut inflammation, had been present [74]. In addition to phytocannabinoids, endocannabinoid-like molecules, such as PEA and OEA, by restoring microbiota normal composition and counteracting central and peripheral neuroinflammatory responses, may be beneficial in improving both brain and gut health simultaneously (shown in Fig. 2) [56, 60, 75]. Furthermore, because mood disorders, such as

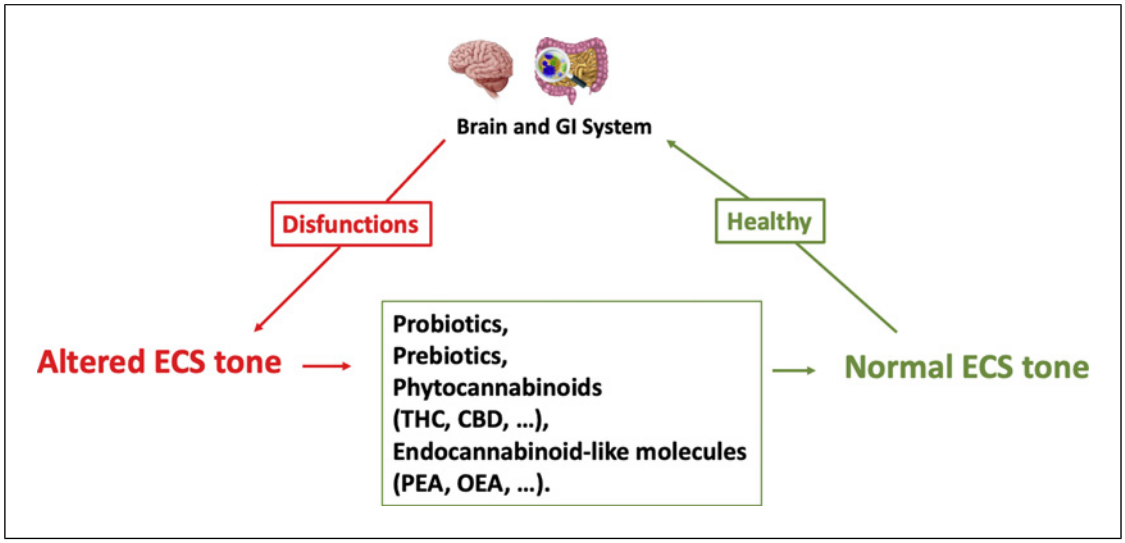

Fig. 2. Restoring normal brain and gastrointestinal (GI) functions by improving the endocannabinoid system (ECS) tone. Mood and GI disorders can alter the tone of the ECS. A normal ECS tone can be restored by using prebiotics, probiotics, phytocanbinoids such as tetrahydrocannabinol (THC) and cannabidiol (CBD), endocannabinoid-like molecules such as palmitoylethanolamide (PEA) and oleoylethanolamide (OEA), or compounds that modify the levels of endocannabinoids which, in turn, promote GI health and brain function.

depression, are preceded by patterns of poor appetite and skipping meals, improving the ECS tone (with prebiotics, probiotics, phytocannabinoids, endocannabinoids, endocannabinoids-like molecules, and compounds that modify the levels of endocannabinoids) may have a beneficial effect as it positively affects food intake and eating habits [15, 76, 77]. Mood and digestive disorders may be related to altered circadian rhythms, which can be disrupted by stress [33, 34]. Microbiota composition and abundance also follow circadian rhythms [35]; when stress-related alterations of the circadian rhythm occur because of the effects of the ECS on the sleep-wake cycle, restoring the microbiota's normal composition and enanchiong the endocannabinoid tone with phytocannabinoids or compounds that enhance endocannabinoids activity may provide benefits (shown in Fig. 2).

Conclusion

ECS signaling and gut microbiota have reciprocal interactions, which, in turn, influence the organism response via the gut-brain axis and may contribute to the protection from stress-related diseases and mood alterations, as well as from GI disorders. This is consistent with the fact that the ECS facilitates the homeostatic state of the organism and responds both to internal and external challenges [78]. Several mechanisms may be involved here, including intestinal barrier regulation, immune modulation, enteroendocrine system influence, mediators from the microbiome entering the body, and modulation of the vagus nerve. Therefore, approaches that promote the growth of "beneficial" bacteria could be favorable in conferring resilience against mood disorders. There were, however, differences between strains of probiotic, the dose, and the duration of treatment in the analyzed studies, and further research studies are needed to determine the optimal treatment regime. Nonetheless, this review claims for a consideration of administration of prebiotics and probiotics for the treatment of patients with mood disorders, such as anxiety, depression, and cognitive impairment, particularly those that are able to modulate the ECS in a beneficial manner. In addition to prebiotics and probiotics, endocannabinoid-like compounds, such as PEA and OEA, or compounds that increase the levels of endocannabinoids (i.e., through metabolic enzyme inhibitors), may be considered for patients with mood and GI disorders, and because of their ability to modulate neuroinflammation as well as microbiota composition, they may also be useful supplements that support both gut and brain health at the same time [56, 60, 71, 75]. In particular, the use of cannabis-derived compounds that decrease the impact of stress, regulate circadian rhythm, and improve mood may represent a winning strategy in case of functional GI

diseases. Co-morbidities between mood and GI health might benefit from treatments with prebiotics or probiotics and/or with compounds that modify the ECS tone to a more substantial degree. Overall, neuro-gastro-cannabinology represents a new clinical and research paradigm that focuses on the complex interactions between the CNS, the gut, and the ECS and investigates novel treatments for GI and mood disorders.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

F.T.: conceptualization (equal), methodology (lead), writing – original draft (lead), and writing – review and editing (equal). V.B.: conceptualization (equal), methodology (supporting), writing – original draft (supporting), and writing – review and editing (equal). R.A.: methodology (supporting), writing – original draft (supporting), and writing – review and editing (equal).

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