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Discovery of the Endocannabinoid System: A Breakthrough in Neuroscience

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Context: Involvement of the endocannabinoid system (eCBs) in a wide variety of physiological and pathological processes has attracted a growing interest. In fact, identification of this ubiquitous signaling system has provided new insights into the underlying pathophysiologic mechanisms of various diseases which may lead to development of novel therapeutic strategies.

Evidence Acquisitions: The limited efficacy of current pharmacological treatments for neurological disorders has led to considerable research interests in new drug development. Based on the modulatory effects of the eCBs on neuroinflammatory and neurodegenerative processes, pharmacological manipulation of the eCBs may prove beneficial in neurological problems.

Results: The eCBs is involved in the survival signaling pathways, neural plasticity, and neuroprotection. Furthermore, the eCBs has proved therapeutic effects against the neurological diseases such as multiple sclerosis, epilepsy, mood and movement disorders, spinal cord injury, stroke, and Alzheimer's disease.

Conclusions: In the present manuscript, an overview on the regulatory role of the eCBs in neurological disorders underscores the importance of systematic analysis of the efficacy and mechanisms of action of cannabinoid-based drugs. Based on the anti-neuroinflammatory and anti-neurodegenerative effects of cannabinoids, the development of drugs without psychoactive effects would be a promising therapeutic alternative for neurological diseases.

Keywords: Endocannabinoids; Nervous System Diseases; Nerve Degeneration

1. Context

Over the last few decades, the endocannabonid system (eCBs) has emerged as a topic of great interest in pharmacology. The eCBs refers to a group of neuromodulatory lipids and their receptors which are implicated in a wide variety of physiological and pathological processes (1). Cannabinoids (the active components of cannabis or marijuana), plant-derived phytocannabinoids, and synthetic cannabinoids have shown a variety of peripheral and central effects. Endocannabinoids, anandamide and 2-arachidonoylglycerol (2-AG), are produced on-demand from the membrane lipid precursors. These compounds are ligands for two types of G protein-coupled receptors, cannabinoid CB_1 and CB_2, which are predominantly located in the central nervous system (CNS) and immune cells, respectively (2). Cannabinoid receptors regulate the activation of adenylyl cyclase isozymes, protein kinase A, phosphatidylinositol 3-kinase (PI 3-K), mitogen-activated protein kinase (MAPK), and nitric oxide (NO). They may also be coupled to the ion channels via the Golf protein leading to the inhibition of Ca2+ influx through L, N, and P/Q type calcium channels and activation of inwardly rectifying potassium conductance (1). In the mammalian brain, CB_1 receptors are highly expressed in the areas that control cognitive, emotional, sensory and motor functions. Endocannabinoids are released from the postsynaptic neurons and act on the presynaptic CB_1 receptors (retrograde signaling) and suppress the release of the inhibitory and excitatory neurotransmitters via their inhibitory effect on calcium channels (3). The modulatory action of the eCBs on neuronal differentiation and survival as well as synaptic remodeling indicates the critical role of this signaling system in the development of brain circuits and information processing (2). The eCBs exert their regulatory role on the motivated behaviours and emotional responses by affecting the peripheral sensory system and reward circuits (1). Meanwhile, the comprehensive analysis of the eCBs functions is beyond the scope of this manuscript.

Following the different types of diseases, the activity of the eCBs is enhanced leading to different therapeutic effects (1). In this respect, development of cannabinoid receptor agonists, selective inhibitors of endocannabi-

Implication for health policy/practice/research/medical education:
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noid degradation, and anandamide uptake blockers, has triggered an exponential growth of studies (4, 5). Based on the protective effects of the eCBs against the neuronal insult and excitotoxic damage (6), this ubiquitous signaling system may be an emerging target for therapeutic interventions in neurological disorders including movement disorders, multiple sclerosis, spinal cord injury, epilepsy, ischemic stroke, Alzheimer's disease, amyotrophic lateral sclerosis, pain, and insomnia.

2. Evidence Acquisitions

2.1. Implication of the Endocannabinoids in the Neural Plasticity and Neuroprotection

The eCBs is involved in the regulation of neuronal proliferation, specification and maturation (2). In the embryonic and adult brain, CB_1 receptors are involved in the regulation of neuritogenesis and synaptogenesis (7). As aforementioned, endocannabinoids travel backward across the synapse and activate presynaptic CB_1 receptors to modulate presynaptic functions (3). In this context, retrograde endocannabinoid signaling plays a pivotal role in short- and long-term synaptic plasticity, indicating the contribution of the eCBs to the different brain functions. Furthermore, endocannabinoids control the excitability of neocortical GABAergic interneurons and exert neuroprotective effects in acute neuronal injuries and chronic neurodegenerative diseases. Endocannabinoids also prevent microglia-mediated neurotoxicity and protect neurons against the cytotoxic effects of excitatory amino acids (8). The neuroprotective effects of endocannabinoids are mediated through a variety of mechanisms. These ubiquitous lipid mediators exhibit antioxidative properties (9), inhibit the release of glutamate and NO (10), prevent calcium influx (11), and elevate the production of brain-derived neurotrophic factor (BDNF) (12). Moreover, activation of the CB_1 receptors results in the stimulation of PI 3-K/AKT signaling pathway and cell survival promotion (7).

2.2. The Endocannabinoid System as a Target for the Treatment of Neurological Disorders

2.2.1. Mood Disorders

These chronic and debilitating medical conditions are highly prevalent worldwide, however, the currently available drugs have limited efficacy. According to a previous report, compounds that affect the function of the eCBs, usually regulate the monoamine-mediated neurotransmission and activity of hypothalamic-pituitary-adrenal (HPA) axis (13). In a previous study by the same author, it has been shown that the eCBs is implicated in doxepin-induced suppression of HPA axis activity (14). In fact, the regulatory role of endocannabinoid enhancers (e.g. the fatty acid amide hydrolase [FAAH] inhibitors) on mood (15), has opened a new line of research in antidepressant drug discovery. Endocannabinoids may be found at moderate to high levels in limbic brain regions where the neuronal activity is altered in depression (16). In addition, deficiencies in the endocannabinoid signaling are associated with a behavioural phenotype similar to the symptom profile of severe depression. Therefore, development of novel antidepressants which enhance the endocannabinoid neurotransmission may be a promising therapeutic strategy. Cannabinoids may also be beneficial in the treatment of anxiety-related disorders; as CB_1 receptor antagonist, SR141716A, has been shown to induce anxiety-like responses (17). Regarding the mechanism (s) linking the eCBs with antidepressant activity, it seems that activation of the eCBs, results in the enhancement of serotonergic and noradrenergic transmission and cellular plasticity (18). We have recently shown that chronic exposure to a wide range of psychotropic medications leads to a significant elevation of endocannabinoid contents in the brain regions which are implicated in the regulation of emotional behaviour and synaptic plasticity (19-22). Additionally an interaction was found between the CB_1 receptors and neurotensin neurotransmission (23, 24). Altogether, the brain regional distribution of endocannabinoids following psychotropic treatment suggests that the eCBs plays an important role in the developing effective coping strategies to the emotional responses.

2.2.2. Movement Disorders

Endocannabinoids as well as their synthesizing and degrading enzymes are found abundantly in the basal ganglia (25). Furthermore, the high expression of CB_1 receptors on the terminals of striatal projection neurons (26), indicates the implication of the eCBs in the central regulation of voluntary movements. In Parkinson's disease (PD) which is the most prevalent neurodegenerative disorder affecting the basal ganglia, dopamine depletion results in a cascade of neurochemical events within the basal ganglia. In an experimental model of PD, the striatal eCBs has been shown to undergo a profound neurophysiological alteration in order to restore the homeostasis within the basal ganglia (27). According to a previous report, WIN55212-2, a cannabinoid receptors agonist, exerts therapeutic potential against the nigrostriatal cell loss (28). The eCBs is also involved in the pathogenesis and/or progression of Huntington's disease (HD). The reduced expression of CB_1 receptors in the basal ganglia is one of the earliest changes in HD (29). In a rat model of HD, the levels of endocannabinoids were decreased in the striatum (30), indicating the low function rate of the eCBs in HD. Furthermore, CB_1 agonists and the inhibitors of endocannabinoid transport are able to attenuate the hyperkinesia associated with the disease (31). Altogether, the hypokinetic profile of cannabinoids as well as their neuroprotective effects, designate them as the alternative therapeutic agents in HD.

2.2.3. Multiple Sclerosis

In recent years, a growing interest has been attracted towards the therapeutic potential of endocannabinoids in multiple sclerosis (MS). According to the historical records from China and India, the preparations of Cannabis indica were commonly prescribed to ameliorate MS-like symptoms such as tremor and muscle pain (32). In an experimental model of MS, the stimulation of CB_1 or CB_2 receptors resulted in the anti-inflammatory effects that may involve the modulation of cytokine and chemokine production, adenosine signaling, and apoptosis of the inflammatory cells (33). Moreover, CB_1 agonists promote mRNA expression in myelin protein and oligodendrocyte survival (34), indicating that cannabinoids not only attenuate the symptoms of MS, but also improve the function of oligodendrocytes. Cannabinoids also induce symptomatic relief in patients with MS (35) that may be due to their neuroprotective and anti-inflammatory effects.

2.2.4. Spinal Cord Injury

Stretch of the spine or contusive/compressive injuries due to the fractured or dislocated spinal column may result in spinal cord injury (SCI) in which the neuropathic pain and spasticity are the most common symptoms. A cascade of molecular and cellular events that occur after the initial damage, may be considered as a main target for the therapeutic interventions. Unfortunately, because of the limited efficacy of currently available drugs, symptomatic treatment remains the cornerstone of the medical management of SCI (36). After the acuteSCI, a remarkable elevation of the endocannabinoid contents has been observed in the spinal cord of rat (37), suggesting that activation of the eCBs is a part of the neuroprotective response triggered following SCI. In this respect, the blockade of CB_1 or CB_2 receptors has been shown to result in the impairment of spontaneous locomotor activity, re-expansion of oedema, and increased microgliosis (38).

2.2.5. Epilepsy

The imbalance between the excitatory and inhibitory neural circuits usually results in the excitotoxicity and neuronal death. In addition, excitotoxicity contributes to the progression of degenerative CNS disorders including various forms of epilepsy (39). According to the modulatory effects of the eCBs on the inhibitory and excitatory transmissions as well as the elevation of endocannabinoid contents in epilepsy (40), the eCBs may be a promising target for antiepileptic therapies. In the electroshock seizure model, intraperitoneal injection of CB_1 receptor agonist, WIN55,212-2, has shown anticonvulsant effect (41). Furthermore, in kainic acid-induced seizures associated with hyperexcitability and excitotoxic cell death in the hippocampal circuits (42), activation of CB_1 receptors has been shown to attenuate the excitotoxicity (43).

2.2.6. Ischemic Stroke

Ischemic stroke is one of the leading causes of disability and death affecting up to 0.2% of people in developed countries annually (44). Recombinant tissue plasminogen activator (r-tPA) is the only medication for the improvement of functional outcome in patients, however, it should be administered within a short period after the onset of symptoms. The non-psychoactive component of cannabis, cannabidiol, has been shown to inhibit the voltage-sensitive Ca^{2+} channels, leading to the reduction of excitotoxicity. Interestingly, even six hours after the cerebral ischemia, administration of cannabidiol resulted in the neuroprotective effects (45). Moreover, cannabidiol preserved the regional cerebral blood flow, reduced the number of glial fibrillary acidic protein (GFAP)-positive cells, and improved the motor coordination three days after the cerebral ischemia (46), indicating its long-lasting preventive effects on the post-ischemic cerebrovascular events. The cerebroprotective effects of another cannabinoid, dexanabinol, has been shown in an experimental model of focal cerebral ischemia (47).

2.2.7. Alzheimer's Disease

Alzheimer's disease (AD) is one of the most common types of dementia associated with neurodegeneration. Neuroinflammation in brain is the cardinal feature of AD resulting in the cognitive decline (48). Based on the neuroprotective and anti-neuroinflammatory effects of cannabinoids (6, 8, 37, 38, 45, 47), their therapeutic potential in AD has been the focus of many researches. Cannabinoids have shown neuroprotective properties in AD through the prevention of microglia-mediated neurotoxicity (49). Furthermore, cannabinoids by the activation of MAPK pathway and inhibition of NO release (via the inhibition of inducible NO synthase expression) exert protective effects against β-amyloid-induced neurotoxicity (50).

2.2.8. Amyotrophic Lateral Sclerosis

This debilitating neurodegenerative disorder which is characterized by the degeneration of motor neurons, usually results in death. Unfortunately, drugs currently in use do not prevent the disease progression. The eCBs has shown neuroprotective and anti-inflammatory effects in amyotrophic lateral sclerosis (ALS) through the preservation of glutamate homeostasis and prevention of excitotoxic damage (6, 43). In addition, activation of CB_1 receptors results in the enhancement of BDNF production and activation of phosphatidylinositol 3-kinase/Akt pathway that may result in neuroprotective effects (12, 51). CB_2 receptors have been identified in neural stem cells where they modulate the proliferation of precursor cells and neurogenesis (7). Moreover, activation of CB_2 receptors has been shown to reduce microglial activation and the release of proinflammatory cytokines (10). This, provides an additional evidence for the protective effects of the eCBs in ALS.

2.2.9. Pain

Identification of the endocannabinoid binding sites in substantia gelatinosa has opened new insights into the nociception. In both acute and chronic pain, anandamide and WIN 55,212-2 have shown antinociceptive effects (52). Furthermore, following the co-administration of cannabinoids with non-steroid anti-inflammatory drugs, a synergistic effect has been found. According to a previous report, the eCBs regulates the antinociceptive activity of indomethacin (53). The interaction between the eCBs and opioid signalling is also well-established. It seems that the eCBs induces analgesia through the stimulation of spinal dynorphin release (54).

2.2.10. Insomnia

Some chronic diseases particularly those associated with depression or pain may result in insomnia which is one of the most common types of sleep disorders. Patients who receive the cannabinoid-based medications for the symptomatic treatment of cancer, chronic pain, or MS usually exhibit improved sleep quality. It has also been demonstrated that anandamide induces slow-wave and rapid eye movement sleep through the activation of CB_1 receptors (55). Furthermore, anandamide elevates the extracellular levels of adenosine which is a sleep-inducing substance (56). Therefore, pharmacological manipulation of the eCBs may be a promising therapeutic strategy in insomnia.

3. Results

Identification of the biological functions of the eCBs has led to a better understanding of the pathological processes that occur in the CNS. Moreover, the compounds which modulate the activity of the eCBs, have been proved to be beneficial in fields of many disorders which the currently available drugs have shown limited in efficacy.

4. Conclusions

The eCBs as the modulator of neuroinflammatory and neurodegenerative processes, may be a promising target for the pharmacotherapy of chronic CNS diseases. In this respect, development of the cannabinoid-based medicines which are devoid of psychoactive side effects would be an emerging therapeutic strategy for the treatment of neurological diseases.

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