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A short communication: Cannabidiols role and function in anti-aging and longevity.

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Abstract

Ageing is associated with a decline of performance in terms of both body and mind. As with all age-related health issues, there is a wide spectrum of potential outcomes. Thus, a better understanding of the molecular and cellular processes that contribute to, or protect against aging, may offer novel routes for therapy and prevention. The endocannabinoid system is a promising target in the treatment of age-related disease, given the diverse physiological processes it regulates. As societal opinions of aging as a disease and cannabinoids as medicine shift, further inquiry of cannabidiol application and its effects on genetic epigenetic metabolic markers and signalling pathways during aging process may prove greatly beneficial to human health. CBD seem to attenuate age-related declines, extend lifespan and drastically improve activity levels.

Keywords: Cannabidiol (CBD), Anti-aging, Longevity, Genes, Endocannabinoid system.

Ageing is a complex of changes in an organism that progressively and deleteriously leads to a general decline of its biological functions, rendering it more prone to illness and, ultimately, to death. Although it is very difficult to unravel the complexity of this process, that includes genetic and environmental causes, growing evidence points to a pivotal role of the immune system. With the passing of time, our immune system goes towards a slow and inexorable functional decline, generally coupled to a low-grade inflammatory state and, in some pathologies, to an excessive inflammatory condition. This state of local or generalized chronic inflammation (which is accompanied by typical cellular ageing phenomena such as telomeric loss, oxidative stress, DNA defects) damages all the organs, leading in the course of time to the development of age-related diseases, such as osteoporosis, osteoarthritis, atherosclerosis, neurodegenerative disorders and cancer. Here are some aspects given how to revert and modify the aging process *via* Cannabidiol (CBD) in order to access a possibility for longevity.

Homeostasis, any self-regulating process by which biological systems tend to maintain stability while adjusting to conditions those are optimal for survival. If homeostasis is successful, life continues; if unsuccessful, disaster or death ensues. With all the complex cell signals, genetic mutations, and outside influences, how do we manage to stay at homeostasis? The answer is the endocannabinoid system. It is present nearly everywhere in the human body and functions by maintaining the homeostasis of the human body. For example, a fracture in the toe would result in cell death. The resulting lymphatic response would increase blood flow and the migration of white blood cells to the surrounding areas. The Endocannabinoid System (ECS) would then recognize the excess lymphatic signals, and after deciding that there is no longer a need for the increase of inflammation, the cannabidiol receptors in the surrounding immune cells and tissues will begin to bind with cannabinoids and start to slowly reduce these inflammatory responses [1].

The ECS is one of the, if not the most, important systems in our body. Its role in the homeostatic function of our body is undeniable, and its sphere of influence is incredible. Additionally, it also plays a major role in apoptotic diseases, mitochondrial function, and brain function. Its contribution is more than maintaining homeostasis; it also has a profound ability in regulation. The ECS may not only provide answers for diseases with no known cures, but it could change the way we approach medicine. This system would allow us to change our focus from invasive pharmacological interventions (i.e. SSRIs for depression, benzodiazepines for anxiety, and chemotherapies for cancer) to uncovering the mystery of why the body is failing to maintain homeostasis. In the past few years the pharmacological research focused on the development of synthetic compounds that, by modulating the Endocannabinoid System (ES), could become potential drugs. In particular through its well-documented immunomodulatory activity, and together with its neuroprotective and antioxidative effects, drugs that are able to modulate the endocannabinoid binding (eCB) metabolism might be also effective anti-ageing therapeutics. In the context of complex regulative

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mechanisms, eCBs may play an important role by virtue of their well-known neuro- and immuno-modulatory effects, inside and outside the central nervous system [2]. The easiest option to do this is application of CBD.

Antioxidants prevent free radical reactions by inhibiting the formation of these radicals, scavenging them, or by promoting their decomposition and then reducing tissue damages. Unlike other cannabinoids, CBD contains two phenolic groups. It has antioxidant activity by a mechanism including inhibition of oxidative stress and CBD [3] also prevents the generation of reactive oxygen species factors ROS leading to an unhealthy aging [4]. Oxidative stress, resulting from an overproduction of ROS, is related to numerous negative effects and can lead to the development or exacerbation of different pathological states. It has been seen that the EC can modulate oxidative stress. In this sense, CBD shows promising pharmacotherapeutic properties [5]. CBD seems to be preferred over other compounds belonging to the group of phytocannabinoids, thanks to the lack of psychotropic effects and a better safety profile.

Peroxisome proliferator-activated receptors (PPARs) are a family of nuclear receptors acting as transcription factors to regulate the expression of a plethora of target genes involved in metabolism, immune reaction, cell differentiation, and a variety of other cellular changes and adaptive responses. PPARs are activated by a large number of both endogenous and exogenous lipid molecules, including phyto- and endo-cannabinoids, as well as endocannabinoid-like compounds [6]. It has been demonstrated that CBD attenuate neuroinflammation and neurodegeneration through activation of cannabinoid receptors and PPAR pathway and CBD acts as an agonist on PPAR [7]. PPAR-γ agonists directly activate genes of the glucose-sensing apparatus in liver and pancreatic β-cells. CBD might serve as the basis for design of new insulin resistance and anti-obesity drug also by protecting the liver and pancreas [8] and using PPARγ agonists like CBD promotes healthy aging and extends lifespan [9]. CBD is able to reduce oxidative stress, inflammation, cell death, and vascular hyperpermeability associated with diabetes and it is clear that oxidative stress and inflammation play critical roles in the development of diabetes and its complications [10]. In fact endocannabinoids and CB (1) receptors in this context are to enhance energy storage into the adipose tissue and reduce energy expenditure by influencing both lipid and glucose metabolism. Although normally well controlled by hormones and neuropeptides, both central and peripheral aspects of endocannabinoid regulation of energy balance can become dysregulated and contribute to obesity, dyslipidemia, and type 2 diabetes, thus raising the possibility that CB(1) antagonists might be used for the treatment of these metabolic disorders. On the other hand, evidence is emerging that some nonpsychotropic plant cannabinoids, such as cannabidiol, can be employed to retard β-cell damage in type 1 diabetes [11]. More than a third of prescription drugs, including those for diabetes, are made to bind to GPCRs and they come along with their adverse effects; but CBD targets G-protein coupled receptors (GPCRs) directly and affect insulin resistance in an entirely positive manner and for example many endothelial diseases could be halted.

Stress causes aging. CBD is reported to have anti-depressive actions, the basis for which is not established although activation of 5-HT1A receptors may be involved at least at higher concentrations. Growing evidence in recent years has implicated pro-inflammatory cytokines, free radical species, and oxidants in the aetiology of depression. One explanation is that the resultant oxidative stress adversely affects glial cell function and leads to neuron damage in the brain and CBD counteracts these negativities[12] also by modulating the unwanted serum cortisol levels fluctuations and by doing so also hindering the insulin resistance.

CBD may offer therapeutic benefits for a large variety of disorders. The effects of CBD confirmed in clinical studies to date suggest that this compound might become a candidate pharmacological adjunct to any disorder presenting with high levels of inflammation [13]. In most cases, studies show an action profile with fewer side effects than the pharmacological therapy currently used to treat the disorders investigated. Even in high doses, CBD is well tolerated with acceptable adverse event profiles when administered short term and has confirmed antioxidant and immunomodulatory properties.

Evidence is mounting that CBD impacts all these different pathways and molecules for anti-aging healthy aging and longevity. Preclinical models have provided a great insight into the aging process with consistent data considering the role of the GH/IGF-1/insulin system in the modulation of lifespan. While it is well known that enhanced insulin sensitivity and low insulin levels are associated with an improved survival, there are several evidences showing that attenuation of the GH/IGF-1 axis may have beneficial effects in extending lifespan in humans. CBD appears to modulate a cellular membrane channel called TRPV1, which, in turn, plays a role in cancer cell growth through IGF-1. A growing list of evidence suggests that mTOR signaling influences longevity and aging. Inhibition of the mTOR complex 1 (mTORC1) increases lifespan in all model organisms studied. CBD has been observed to slow mTOR signaling. CBD has been shown to suppress the activity of genes involved in some cancers by activating AMPK similar to autophagy to protect cells from mitochondrial dysfunction. Telomeres are nucleoprotein structures that define the ends of linear chromosomes. Telomere dynamics have been found to be better predictors of survival and mortality than chronological age. Telomeres, the caps that protect the end of linear chromosomes, are known to shorten with age, inducing cell senescence and aging. Telomere elongation is one of the hallmarks of the reprogramming process. SIRT1 is necessary for Proficient Telomere Elongation and Genomic Stability [14]. SIRT1 protein, a member of Silent Information Regulator 2 (Sir2) protein family, has gained considerable attention as epigenetic regulators for a great area in the human physiology. Changes in sirtuin expression are critical in several diseases, including metabolic syndrome, cardiovascular diseases, cancer and neurodegeneration. Enhancing the expression of SIRT1 points the importance of epigenetics in several age-related diseases to provide a healthy aging by developing novel therapies, which can prevent or damp the progression of some diseases.

SIRT1 regulates many endocrine functions, protects organism from oxidative stress-related cellular events, promotes DNA stability, and decreases various age-related disorders, such as neurodegenerative disease, metabolic abnormalities, and cancer [15]. Cannabidiol protects cells from mitochondrial dysfunction by upregulating SIRT1 to Inhibits NF-κB and NOTCH Pathways and increases the expression of SIRT1 one of the most studied signal pathway involved in longevity. These are clinically proven main pathways in charge of longevity [16].

During the past few years, awareness of the cannabinoid system in the pathophysiology of liver disease has gained momentum. Both CB1 and CB2 receptors have been shown to be upregulated in the early stages of liver injury. There has been growing evidence in recent years to suggest that endocannabinoids may regulate the pathophysiology of liver diseases, including both acute forms of hepatic injury, liver fibrosis and cirrhosis. CBD also reduces alcohol-related steatosis and fibrosis in the liver by reducing lipid accumulation, stimulating autophagy, modulating inflammation, reducing oxidative stress, and by inducing death of activated hepatic stellate cells. In fact "*Caenorhabditis elegans*" is often used in preclinical lifelong toxicity studies, due to an estimated 60-80% of their genes having a human orthodox, and their short lifespan of ~2-3 weeks. Whole-life exposure of *C. elegans* to 10-100 μM CBD revealed a maximum life extension of 18% observed at 40 μM CBD. In addition, motility analysis of the same groups revealed an increase in late-stage life activity by up to 206% compared to controls with a lack of long-term toxicity at physiologically relevant concentrations [17,18].

Conclusion

The fact that both CB1 and CB2 receptors have been found on immune cells suggests that cannabinoids play an important role in the regulation of the immune system. Recent studies demonstrated that administration of THC into mice triggered marked apoptosis in T cells and dendritic cells, resulting in immunosuppression. In addition, several studies showed that cannabinoids downregulate cytokine and chemokine production and, in some models, upregulate T-regulatory cells (Tregs) as a mechanism to suppress inflammatory responses. The endocannabinoid system is also involved in immunoregulation. For example, administration of endocannabinoids or use of inhibitors of enzymes that break down the endocannabinoids, led to immunosuppression and recovery from immune-mediated injury to organs such as the liver. Manipulation of endocannabinoids and/or use of exogenous cannabinoids in vivo can constitute a potent treatment modality against inflammatory disorders. CBD has been found to affect gene expression and inflammation and is under investigation for several potential therapeutic applications against cancer various inflammatory diseases, anti-aging and longevity.

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