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REVIEW ARTICLE

The Endocannabinoid System as Modulator of Exercise Benefits in Mental Health

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Abstract: According to the World Health Organization (WHO), 47 million people display mental health disorders Worldwide. In addition, epidemiological studies have shown that the extension of life expectancy and the increase in aged population will significantly impact the prevalence of several mental impairments. Although there are strategies for preventing and alleviating mental illnesses, such as pharmacological and psychological approaches, limited results have been observed. Thus, the search for new therapeutics for managing psychiatric disorders has explored multiple roads. In recent years, it has been demonstrated that physical activity and exercise promote health benefits. On the other hand, among the neurobiological systems that participate in the genesis and development of mental disruptions, the endocannabinoid system has been suggested as an active player. Supporting this hypothesis, data suggest that the elements comprising the endocannabinoid system, such as the CB_1/CB_2 cannabinoid receptors, endogenous ligands (*N*-arachidonoylethanolamine [anandamide, AEA] and 2-arachidonoylglycerol [2-AG]), transporters and the enzymes involved in the biosynthesis and degradation of the AEA and 2-AG, modulate mental diseases. In this review, we discuss that the endocannabinoid system might be considered as a modulator for the positive outcomes of exercise in the management of mental disorders. Clinically, this promising field might be exploited by targeting the elements of the endocannabinoid system aimed to increase the exercise benefits applied to patients with mental illnesses.

Keywords: Anandamide, endocannabinoids, physical activity, mental health, exercise, depression.

1. INTRODUCTION

The burden of mental disorders continues to grow up world-wide with significant impacts on multiple areas, including health. According to the literature, two key factors seem to participate in the increase of the prevalence of mental diseases: (*i*) The decline of mortality rates and, (*ii*) The expansion of life expectancy [1-4]. With the enhancement of aged population, an increase in the number of mental disorders, including depression, bipolar disorders, schizophrenia, and many others is expected in parallel [1, 5, 6].

Although a diversity of treatments aimed for managing mental diseases are currently used, such as pharmacological means and psychosocial support, limited results have been observed [7-10]. Additional efforts have been achieved by using non-pharmacological approaches for treating mental illnesses, including phototherapy, nutritional supplements, and physical exercise [11-14]. In this regard, multiple findings have demonstrated that physical activity and exercise promote health benefits in patients with psychiatric disorders

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[15-18]. Exercise influences multiple neurobiological networks, including the endocannabinoid system [19-22], therefore, it is likely that this endogenous signaling arrangement might influence the effectiveness of exercise as a treatment for managing mental disorders.

2. THE ENDOCANNABINOID SYSTEM

Cannabis sativa contains over 100 compounds called cannabinoids, among the most abundant are delta-9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD) [23-25]. Whereas Δ^9-THC binds to transmembranal receptors to induce multiple neurophysiological effects, the mechanism of action of CBD remains to be fully described [23, 26, 27]. With the characterization of the receptors that recognized Δ^9-THC, named CB_1 and CB_2 cannabinoid receptors, the search for their natural endogenous ligands was driven during the 1980s-1990s until the discovery of lipids that were produced by the mammalian body that naturally bind to the cannabinoid receptors. These endogenous compounds, anandamide (arachidonoylethanolamine [anandamide, AEA]) and 2-arachidonoylglycerol (2-AG) were eventually named endocannabinoids [28, 29]. Further elements were added to the endocannabinoid system family, including enzymes responsible for the synthesis and degradation of AEA and 2-AG, transporters, and additional endogenous ligands [30, 31].

At this date, the endocannabinoid system is a complex signaling network comprised of at least two G-protein coupled receptors, the CB_1 and CB_2 cannabinoid receptors, their endogenous ligands (AEA and 2-AG, as the most studied so far), and the enzymes involved in the synthesis and degradation of AEA and 2-AG, as well as a membrane transporter [28-31]. Although the description of the functioning of the endocannabinoid system is complex and goes beyond the scope of this review, briefly (Fig. **1**) AEA is generated from its membrane precursor, *N*-arachidonoyl phosphatidylethanolamine (NAPE), through cleavage by a phospholipase D (NAPE–PLD) whereas AEA´s degradation includes the engagement of ethanolamine and arachidonic acid *via* the activity of the fatty acid amide hydrolase (FAAH) enzyme. It has been suggested that once synthesized, AEA crosses the cellular membrane *via* the action of the anandamide membrane transporter (AMT).

On the other hand, 2-AG is formed by the activity of phospholipase C (PLC) and diacylglycerol lipase (DAGL), whereas its degradation is mediated by_monoacylglycerol lipase (MAGL) [32, 33]. Once synthetized, AEA and 2-AG bind to the cannabinoid receptors for triggering a diversity of intracellular responses, such as increasing Ca^{2+} influx and decreasing K^+ outflux, leading to a short- or long-term suppression of the release of neurotransmitters.

The distribution of the endocannabinoid system elements (*i.e*., the CB_1 and CB_2 cannabinoid receptors) in the whole body, including the central nervous system, has been a point of interest in the function of memory and learning, brain plasticity, neuronal development, modulation of stress and emotions, among many others [34-37] (Fig. **1**). The activation of the endocannabinoid system has been recently recognized as an important modulatory network for controlling the function of the brain by regulating the secretion of a diversity of neurochemicals.

3. A COMPREHENSIVE OVERVIEW OF MENTAL HEALTH DISORDERS

Mental disorders are a wide term considering health complex problems characterized by patterns of behaviors with dysfunctional processes of thoughts, emotions, or perceptions [38, 39]. In addition, the mental illnesses include specific symptoms and signs inducing distress or limiting personal functioning in multiple areas of life [40]. The compendium of mental disruptions comprises depression, anxiety disturbances, post-traumatic stress disorder (PTSD), and schizophrenia, among many others. The major categories of mental disturbances described in the latest edition of the Diagnostic and Statistical Manual of Mental Disorders Fifth Edition provide standardized diagnostic criteria are also present in the eleventh edition of the International Classification of Diseases [41, 42]. Further studies have revealed interesting interactions between mental health disorders and neurobiological signaling, including the endocannabinoid system [43-48].

4. THE MODULATORY ROLE OF THE ENDOCANNABINOID SYSTEM IN MENTAL DISORDERS

Basic and clinical studies have explored the causal relationship and likely involvement of the endocannabinoid system in the genesis and development of mental disturbances [49-54]. In the following sections, we provide a broad revision of the current knowledge in the field of neurobiological role of the CB_1/CB_2 cannabinoid receptors, AEA and 2-AG, and the enzymes NAPE, NAPE–PLD, FAAH, AMT, MGL in mental health issues. However, given the expansion of the knowledge in the area, it is indeed ambitious to describe all the experimental findings related to the modulatory properties of the endocannabinoid system on psychiatric disturbances. Thus, we highlight the current comprehension of the functional role of the endocannabinoid system in common mental health disorders, including depression, anxiety, PTSD, and schizophrenia [1, 55-57].

4.1. Cannabinoid Receptors and Depression, Anxiety, PTSD, and Schizophrenia

4.1.1. Cannabinoid Receptors and Depression

Several studies suggest the putative role of the cannabinoid receptors in the modulation of mental health disorders such as depression (Table **1**). For instance, administrations of the inverse agonist CB_1 cannabinoid receptor, rimonabant, induces symptoms of anxiety and depression and even suicidal ideation [58-60]. Conversely, antidepressive effects have been found by using CB_1 cannabinoid receptor antagonists [61-63]. In line with the current pharmacological findings, mice lacking the CB_1 cannabinoid receptor display abnormal patterns at different behavioral paradigms associated with mood disorders. These alterations include a wider spectrum of neurobiological variables, from disturbed molecular functions to dysregulation of neurotransmitter systems related to depression [64-66].

In conclusion, the current evidence supports the hypothesis that the CB_1 cannabinoid receptor plays an important role in depression and suggests that modulation of the activity of this receptor might be a pharmacological target for novel

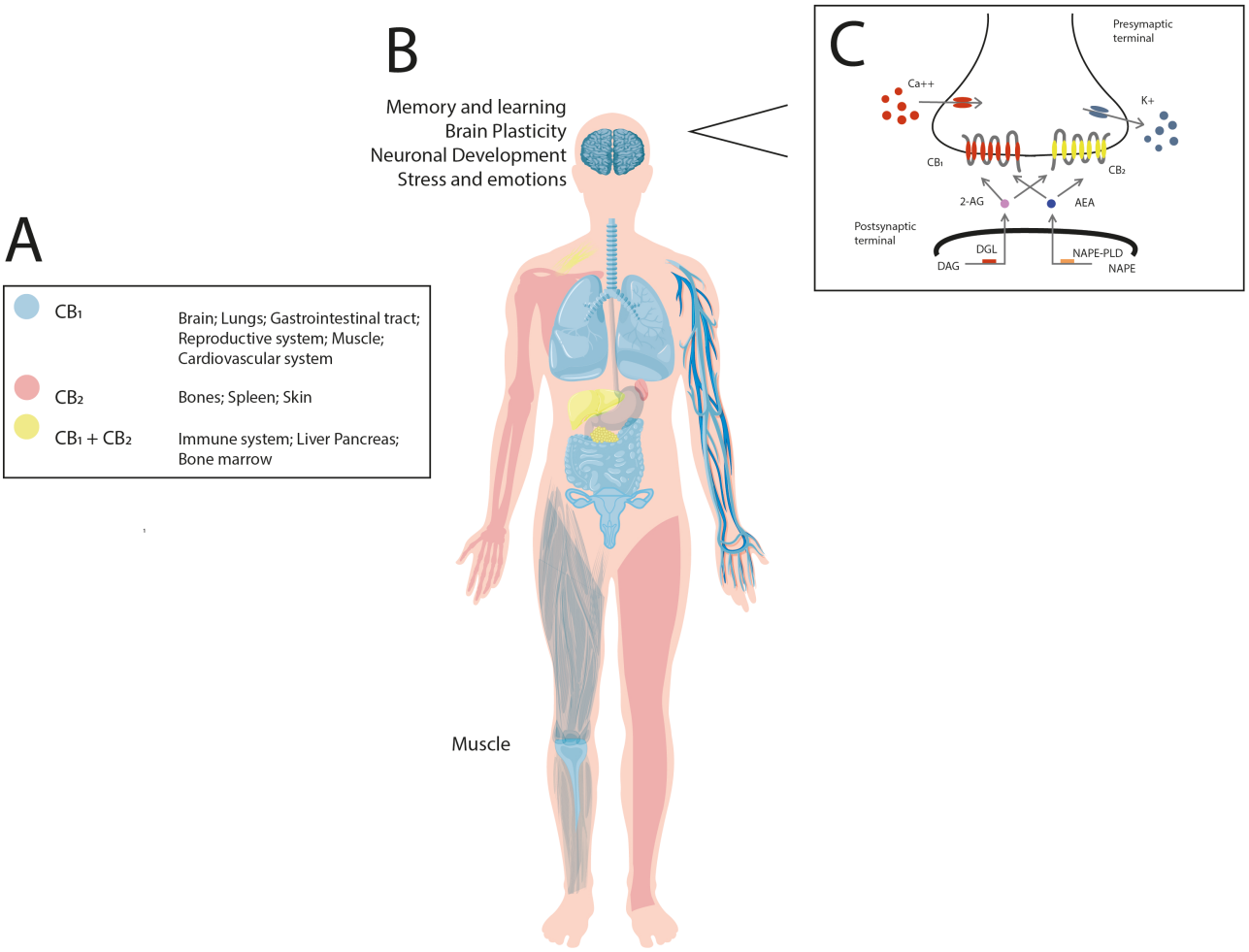

Fig. (1). The endocannabinoid system. The drawing represents the distribution in human body of the endocannabinoid components, including the CB_1 and CB_2 cannabinoid receptors, as well as the biosynthesis and degradation enzymatic routes for arachidonoylethanolamine (anandamide, AEA) or 2-arachidonoylglycerol (2-AG) governed by the fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively. Once synthetized, AEA and 2-AG bind to the cannabinoid receptors via the involvement of membrane transporter (for AEA, anandamide membrane transporter [AMT]). As shown, the presence of the cannabinoid receptors in multiple physiological systems such as brain, lung, gastrointestinal tract, *etc*. (**Panel A**) suggest the modulatory role of both receptors in the control of a diversity of complex functions, including memory and learning, brain plasticity, neuronal development, stress and emotions, among many others (**Panel B**). In addition, the image illustrates that arachidonic acid-containing diacylglycerol (DAG), diacylglycerol lipase (DAGL) synthesizes 2-AG whereas NAPE (*N*-arachidonoyl phosphatidylethanolamine) and *N*-acyl phosphatidylethanolamine phospholipase D (NAPE-PLD) participates in the formation of AEA. Once released, both lipids (2-AG and AEA) bind and activate the cannabinoid receptors, which in turn, promotes calcium (Ca^{2+}) influx and potassium (K^{+}) efflux for modulating neurotransmission (**Panel C**). (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

antidepressant therapeutical approaches for treating mood disorders. Moreover, the comprehension of the mechanism of action of the CB_1 cannabinoid receptors on depression has fostered the development of synthetic compounds that regulate the function of these receptors; howbeit, targeting the CB_1 cannabinoid receptors only in those target brain areas where there is a presumably perturbed mood-related function will be the new challenge in future studies [67, 68]. While a possible therapeutic use of the CB_1 cannabinoid receptor in depression has been discussed in this review, the findings in regards the engagement of the CB_2 cannabinoid receptor in mood disturbances should be determined.

4.1.2. Cannabinoid Receptors and Anxiety

Since the CB_1 cannabinoid receptor has been localized in several brain areas, including the amygdala, the activation of this receptor has been related to a modulatory function of aversive memories [69-71]. For example, the CB_1 cannabinoid receptor knockout mice show an increase in anxiety-like behavior [72]. In addition, pharmacological experiments have demonstrated that the activation of the CB_1 cannabinoid receptor precipitates the episodes of anxiety, whereas its blockade exerts anxiety-related behaviors [73-75] (Table **1**).

Table 1. Effects of the elements of the endocannabinoid system on the modulation on depression, anxiety, post-traumatic stress disorder (PTSD), and schizophrenia. Further studies have described the physiological role of the cannabinoid receptors, AEA, 2-AG, the enzymes engaged in the biosynthesis and degradation of the endocannabinoids (NAPE, NAPE-PLD, FAAH, AMT, DAGL, and MAGL) on control depression, anxiety, PTSD, and schizophrenia.

-	Depression	Anxiety	PTSD	Schizophrenia
Cannabinoid receptors	The activation of the CB_1 cannabinoid receptor induces depression-like behavior The role of the CB_2 cannabinoid receptor in depression is unknown	The absence of the CB_1 cannabinoid receptor increases depression-like behavior The role of the CB_2 cannabinoid receptor in anxiety is unknown	Th activation of the CB_1 cannabinoid receptor reduces PTSD symptoms The engagement of the CB_2 cannabinoid receptor role in PTSD is unknown	The levels of the CB_1 cannabinoid receptor mRNA in schizophrenia is decreased The role of the CB_2 cannabinoid receptor role in schizophrenia is unknown
AEA and 2-AG	The levels of the endocannabinoids in depression are decreased	Stress reduces levels of the endocannabinoids	The contents of the endocannabinoids in PTSD are decreased	The levels of the endocannabinoids in schizophrenia are increased
NAPE, NAPE-PLD, FAAH, AMT, DAGL, and MAGL	The NAPE-PLD contents are decreased in depression The FAAH gene has been related to depression The FAAH levels are enhanced in depression The DAGL contents are decreased in depression The MAGL levels are increased in depression The AMT activity in depression is unknown	The blockade of FAAH and MAGL activity decreases anxiety-like behavior The role of NAPE, NAPE-PLD, AMT, DAGL, and MAGL in depression is unknown	Inconclusive results of role of FAAH in PTSD The role of NAPE, NAPE-PLD, AMT, DAGL, and MAGL in PTSD is unknown	The FAAH and MAGL levels are enhanced in schizophrenia The NAPE and DAGL contents are decreased in schizophrenia The NAPE-PLD and AMT levels in schizophrenia are unknown

Thus, since the CB_1 cannabinoid receptor is widely localized in the central nervous system, then it displays a complex signaling network that responds to different modes of synaptic neurotransmission modulation. For instance, the high levels of the CB_1 cannabinoid receptors on inhibitory (GABAergic interneurons) and at a lesser extent on excitatory (glutamatergic) terminals [76], as well as on dopamine D1-expressing neurons, play a modulatory role on different emotional behaviors such as social and cognitive activity, which are affected in mental health illness [77-79]. This is why such psychiatry disorders are modulated by this complex circuitry expressed at some synapses in all brain regions related to the processes of stress. Finally, and because the localization of the CB_2 cannabinoid receptor has been widely described outside of the central nervous system [37], no current data in regards to the role of this receptor in anxiety is available.

4.1.3. Cannabinoid Receptors and PTSD

The management of PTSD includes pharmacological intervention by using diverse compounds, such as antidepressive drugs [80]. However, in recent years, it has been studied the likely neurobiological role of the CB_1 cannabinoid receptors as a therapeutic element for the management of PTSD (Table **1**). In this regard, the very first evidence showing the specific involvement of the CB_1 cannabinoid receptors in neurons expressed dopamine D1 receptors in extinction of aversive memories was reported from Carsten T. Wotjak´s laboratory [79, 81]. The same group reported for the first time that the enhancement in contents of AEA controlled acute fear relief, while the increase in 2-AG levels promoted the expression of conditioned fear primarily *via* the involvement of the CB_1 cannabinoid receptor on GABAergic neurons [82]. Further advances have been achieved in the field. For example, the administration of nabilone, a synthetic CB_1 cannabinoid receptor agonist, induces positive outcomes for the treatment of PTSD since 72% of participants reported total cessations of severity of the symptoms of this disease [83]. Complementary studies have demonstrated that using *in vivo* imaging studies in subjects with PTSD, there was an increase in the CB_1 cannabinoid receptor availability [84]. Despite the psychiatric side effects of the administrations of rimonabant such as anxiety, depression and suicidal tendencies, there is still interest in the development of CB_1 cannabinoid receptor antagonists, including TM38837, as a pharmacological approach for the management of fear. In this regard, Micale and coworkers (2019) reported that TM38837, given either *per os* (100mg/Kg) or icv (10 or 30μg), increased fear response in mice subjected to tone fear conditioning paradigm. Importantly, authors reported that pharmacological effects induced by TM38837 were only at a dose 10 times higher than rimonabant [85]. Due to the distribution of the CB_1 cannabinoid receptors in the central nervous system, it became a target over the CB_2 cannabinoid receptors, which have been mapped at peripheral sites [34-37]; however, their localization may not imply direct neural connections between the external tissues - indeed several body regions might not directly innervate to the brain centers involved in fear control. Instead, these conditions might be proposed as hypothesis-generating, addressing future likely functional connectivity studies.

Finally, PTSD is a complex clinical outcome of experiencing a severe emotional trauma, and importantly, not all

subjects exposed to the same traumatic experience develop PTSD; the existence of individual susceptibility conditions has been suggested [86, 87]. Thus, the research of individual susceptibility on animal models that mimic the symptoms of PTSD has a limited coherent framework. Indeed, more studies are needed to explore the functional role of the CB_1 or CB_2 cannabinoid receptors on PTSD, considering the individual susceptibility and resilience factors.

4.1.4. Cannabinoid Receptors and Schizophrenia

Since the wider distribution of the CB_1 cannabinoid receptors is present in the central nervous system [36, 38], then it has been suggested to display critical functional properties in the regulation of mental disorders, including schizophrenia. From imaging studies to pharmacological experiments and genetic analyses, the current data suggest that the CB_1 cannabinoid receptor is engaged in the genesis, development, and control of schizophrenia [88-92] (Table **1**). A closer look at the studies shows a significant decrease in the CB_1 cannabinoid receptor mRNA levels in postmortem brain of subjects that displayed schizophrenia [93], whereas autoradiographic studies of the same receptor have shown higher binding in the prefrontal cortex in schizophrenic subjects [94, 95]. In addition, recent pieces of evidence have demonstrated that there was an epigenetic alteration of the CB_1 cannabinoid receptors in the peripheral blood mononuclear cells collected from schizophrenic patients. Moreover, data suggested that due to the transcriptional regulation of the CB_1 cannabinoid receptor found in schizophrenic subjects through the DNA methylation might be considered as a biomarker for the disease [96]. Similar findings were reported by Stark, *et al.* (2019) using an animal model of schizophrenia, induced by prenatal methylazoxymethanol acetate (MAM) exposure. According to the report, animals under the MAM experimental condition showed a reduction in DNA methylation at the *CNR1* promoter, which was associated with an enhancement in the CB_1 cannabinoid receptor gene and protein expression. Moreover, the changes observed in the CB_1 cannabinoid receptor matched with the negative symptoms displayed by the MAM rats [97].

Lastly, in a review, Kucerova *et al.* (2014) discussed the preclinical and clinical findings linked to the dysfunction of the CB_1 cannabinoid receptors in schizophrenia. In addition, the authors summarized the promising therapeutic approaches for treating schizophrenia by using CB_1 cannabinoid receptor antagonists/inverse agonists, such as AVE1625, which seems to ameliorate the positive-like symptoms in psychotomimetic-induced hyperactivity and latent inhibition deficit models. Notwithstanding, it is recognized that the involvement of the CB_2 cannabinoid receptors in schizophrenia still lacks sufficient experimental evidence [92].

4.2. Endocannabinoid Levels and Depression, Anxiety, PTSD, and Schizophrenia

4.2.1. Endocannabinoid Levels and Depression

Experimental and clinical studies aimed to characterize the levels AEA and 2-AG in depression have found lower profiles of these lipids in such mental conditions [98-102] (Table **1**). These associative data have been consistent with pharmacological studies, which have demonstrated that targeting the endocannabinoid endogenous tone by enhancers or inhibitors of AEA or 2-AG seem to exert positive therapeutic outcomes for mental disorders [103, 104]. Given the recent discovery of new lipids with cannabimimetic properties, such as *N*-arachidonoyl dopamine (NADA) and virodhamine [105], then, limited current data are available in regards to their involvement in depression.

4.2.2. Endocannabinoid Levels and Anxiety

The endocannabinoids exert effects on emotional functions since their contents have been described in recent years [106-110]. For instance, exposition to stressful conditions causes anxiety-like behavior and reduces AEA brain contents by enhancing the activity of the FAAH in the amygdala [106]. Although the knowledge about new elements belonging to the endocannabinoid system has brought advanced insights, including the characterization of NADA and virodhamine [105], no evidence is available regarding their neurobiological role on the modulation of anxiety (Table **1**).

4.2.3. Endocannabinoid Levels and PTSD

Fascinating data have been reported in PTSD since the levels of the endocannabinoids are decreased if the traumatic experience occurred during childhood. Further complexity to the phenomena is added due to other variables, such as the age of the subject, which play a critical contribution in the likely role of the endocannabinoids and PTSD [110, 111]. Recent discoveries have reported the likely link among the contents of endocannabinoids and the severity of PTSD [111-113]. However, further studies are needed for describing the mechanism of action of AEA or 2-AG into the regulation of PTSD (Table **1**).

4.2.4. Endocannabinoid Levels and Schizophrenia

Most of the findings point out that there is an increase in the levels of endocannabinoids in schizophrenic patients (Table **1**). Data from several biological samples have reached out similar conclusions [113-116]. Due to that the descriptive studies do not allow to discriminate whether the disrupted levels of the endocannabinoids are cause or consequence of schizophrenia; further studies still are needed to describe the mechanism of action of AEA and 2-AG in the establishment of schizophrenia. Moreover, the participation of additional components of the endocannabinoid signaling, including NADA and virodhamine, in schizophrenia, remains to be addressed as well.

4.3. The Engagement of NAPE, NAPE-PLD, FAAH, AMT, MGL, and DAGL in Depression, Anxiety, PTSD, and Schizophrenia

4.3.1. Enzymes Involved in the Functioning of the Endocannabinoid System Participating in Depression

As described previously, the route for AEA synthesis engages the activity of NAPE-PLD, whereas 2-AG is synthesized from membrane phospholipids *via* sequential activation of the PLC as well as DAGL. Following their release, AEA and 2-AG´s neurochemical functions are terminated through

their subsequent hydrolysis by the activity of either the FAAH or MAGL, respectively [116-118]. In recent years, data suggest that the enzymatic activity of FAAH, DAGL, or MAGL is associated with mental alterations [119-121] (Table 1). For example, a polymorphism of the *FAAH* gene has been associated with depression [122]. In line with this finding, Vinod *et al.*, (2012) reported that Wistar Kyoto rat strain, a genetic model of depression, displayed higher levels of FAAH in frontal cortex and hippocampus [123]. Similar results were published by Smaga *et al.*, (2017) since the authors found that using an experimental model of depression, the removal of olfactory bulb, caused a decrease in the levels of NAPE-PLD, MAGL whereas contents of FAAH and DAGL were enhanced [124]. Although some achievements have been made in the field of the engagement of the enzymes involved in the functioning of the endocannabinoid system in depression, it remains to be described whether the pharmacological manipulation of the activity of NAPE, NAPE–PLD, FAAH, AMT, MGL, and DAGL might cause positive effects for managing depression.

4.3.2. Enzymes Involved in the Functioning of the Endocannabinoid System Participating in Anxiety

Anxiety is also a mental disorder that has been associated with the dysregulation of the endocannabinoid system (Table **1**). For example, the knockout mice lacking DAGL show significant behavioral alterations such as reduction in the exploration of the open field as well as anxiety-related behaviors [125]. Similar findings have been reported when FAAH or MAGL activity is blocked by pharmacological means. In this regard, the inhibition of the enzymatic activity of either FAAH or MAGL has been associated with reducing anxiety-like behaviors [126, 127]. Despite these interesting results, it is worthy to mention that the blockade of FAAH or MAGL promotes an endogenous increase of AEA and 2-AG, respectively. Thus, the link among the functioning of these enzymes and anxiety modulation might be an indirect effect since it is likely that outcomes might be the result of the influence of the enhanced levels of AEA and 2-AG. Whereas whether NAPE, NAPE–PLD, and AMT participate in anxiety, remains to be studied.

4.3.3. Enzymes Involved in the Functioning of the Endocannabinoid System Participating in PTSD

Few findings are available in regards to the role of NAPE, NAPE–PLD, FAAH, AMT, MAGL, and DAGL on PTSD [128]. Among the current data, Vimalanathan *et al.*, (2020) used an experimental model or PTSD finding that the blockade FAAH activity by URB597 did not reduce the anxiety-like behavior in experimental models [129]. However, this result is not in concordance to previous reports since other groups have shown that chronic administrations of URB597 (0.2, 0.3, 0.4 mg/kg, i.p.) controlled PTSD symptoms [130]. The differences in results among comparative studies, including experimental design, dosage, animal strain, limit to drawing solid conclusions in regards to the role of the enzymes engaged in the biosynthesis and degradation of the endocannabinoids in the modulation of PTSD. As one can assume, future studies are requested to address the functional role of NAPE, NAPE–PLD, FAAH, AMT, MAGL, or DAGL in PTSD (Table **1**).

4.3.4. Enzymes Involved in the Functioning of the Endocannabinoid System Participating in Schizophrenia

From imaging studies to pharmacological experimental reports, current findings suggest that the enzymes involved in the synthesis and degradation of endocannabinoids play a modulatory role in schizophrenia [131, 132]. For example, patients with the first episode of psychosis showed an increase in the expression of FAAH and MAGL, whereas a decrease in the levels of NAPE and DAGL was found as compared to healthy controls [133]. Due to the relative recent focus of studying the importance of the function of NAPE, NAPE-PLD, FAAH, AMT, MAGL or DAGL on schizophrenia, limited data are available. We hope that in the future, data from basic and clinical trials describing the importance of NAPE, NAPE–PLD, FAAH, AMT, MAGL or DAGL on schizophrenia might consider these enzymes as biological markers to allow earlier diagnosis and treatments of patients with schizophrenia (Table **1**).

5. BENEFITS OF PHYSICAL EXERCISE IN MENTAL DISORDERS

Mental disorders represent a significant economic cost for society and health care system [134]. Globally, an estimated 264 million people suffer from depression, 284 million subjects complain about anxiety disorders, whereas 20 million patients present schizophrenia [1]. Remarkably, the burden of mental disorders continues to grow causing serious impacts on additional areas such as social relationships and economics around the world [135]. Further complexity in mental disorders includes the impact of comorbidity of suffering from various diseases simultaneously [136]. In addition, mental disabilities are commonly linked to non-communicable chronic illnesses, such as cardiovascular diseases, type 2 diabetes, cancer, and chronic respiratory, among many other health issues [137]. The causes of mental disruptions comprise genetic and external influences [138-144], where the lifestyle seems to impact the onset and development of psychiatric disturbances. For example, low rates of exercising along with higher rates of smoking induce mental disorders [145, 146]. Thus, as we can assume, external factors also exert an influence on the genesis and development of mental diseases.

Mental disorders have been tackled using several treatments, such as cognitive behavior therapy and pharmacological interventions [147-149]. Interestingly, physical activity and exercise have shown to produce benefits in the prevention and the delaying of the onset of several psychiatric disorders [150]. For the purpose of the current review, we would like to provide the following definitions of physical activity and exercise. While physical activity is defined as any bodily movement produced by the contraction of skeletal muscles, being an umbrella term that includes subcategories like sports, leisure activities, dance, exercise is understood as every planned, structured, repetitive, and purposeful intervention [151, 152]. It is worthy to mention that exercise is always physical activity, but physical activity is not necessarily an exercise [152, 153].

There are data supporting that insufficient physical activity is one of the leading risk factors for death worldwide [154]. Between 60 to 85% of people in the world show sedentary lifestyles leading to health complications. In this era of exponential growth of sedentarism, the implementation of lifestyle modifications might be a cost-effective way to improve the health status of the population. Moreover, the benefits of regular physical activity or exercise on mental disorders have been previously demonstrated [1]. Since exercise has been linked to neuronal processes such as neurogenesis and synaptogenesis, then the positive effects of exercise have been associated with such neurobiological phenomena leading to promote additional outcomes in cognitive, emotional, and behavioral measurements [155]. For example, exercise interventions seem to facilitate certain brain areas functioning, inducing well-being and controlling mental disorders such as depression and anxiety [156]. The positive impact of exercise on mental health has been recently suggested as a therapeutic mean for the management of mental impairments during pandemic periods [157, 158]. In sum, the available literature suggests that exercise produces benefits in health and these strategies might be considered as therapeutic elements for managing mental disorders.

5.1. Exercise and Depression

The association between exercise and depression has been addressed since the early 1900s. Several studies addressing depression and exercise include case studies, cross-sectional designs, meta-analyses, and systematic reviews of meta-analyses, among many other approaches. Currently, the consensus accepts the positive outcomes of the treatment of depressive symptoms with exercise interventions [159, 160]. However, some findings support that subjects suffering from depression tend to be less physically active than healthy peers [161, 162]. This phenomenological issue might limit the exerting positive effects of exercise in patients with depression. In line with this perspective, Rethorst *et al.*, (2009) reported that participants displaying depression showed significantly lower depression-related scores than the control group after acute exercise [163]. Similarly, significant benefits in the relief from depressive disorders were found after chronic exercise interventions in children, adolescent and adult subjects [164-166]. Moreover, there is cross-sectional data of the inverse association among physical inactivity and mental health. The Aerobics Center Longitudinal Study (ACLS) [167] evaluated the associations between physical activity and mental health, in which a lower depressive symptomatology and greater emotional well-being was found in physically active subjects. It is worthy to mention that the type and mode of exercise interventions varies between studies, leading to suggest that the impact of exercise might depend on the kind and method of exercise applied. However, aerobic exercise has been the most widely implemented intervention in depression [164-168]. Nevertheless, the efficacy of other types of exercise such as resistance/strength has been demonstrated as well [169]. In this regard, endurance and resistance exercise interventions displayed equally effective outcomes in the amelioration of depressive symptoms [163-170] and the combination of both types of exercise in the same intervention resulted in larger effects than practicing endurance exercise or resistance exercise separately [163].

On the other hand, the length of the interventions in exercise is a variable that plays a critical role as part of the therapeutic effects of exercise in depression. For example, acute bouts of exercise as well as chronic exercise interventions have showed positive outcomes in the remission of depressive symptoms and mood related disorders. In line with this observation, Bartholomew *et al.*, (2005), focusing on patients with major depressive disorder, demonstrated that a single bout of moderate-intensity aerobic exercise (30 min of moderate-intensity treadmill training) exerted greater effects on depression than a 30 min period of quiet rest [171]. Furthermore, single studies with chronic exercise interventions also demonstrated validity to ameliorate depressive symptoms. The SMILE study [172] describes a randomized controlled trial that included 202 adults with major depressive disorder and randomized them to one of four conditions during 16 weeks: Condition 1= Supervised exercise in a group setting (45 min sessions, 3 times per week including 10 min of warm-up, 30 min of walking or jogging on a treadmill at an intensity range between 70-88% of their maximum heart rate [HRmax], and 5 min of cool-down); Condition 2= Home-based exercise (with participants receiving the same exercise prescription but exercised at home on their own with minimal contact from the study staff); Condition 3= Antidepressant medication and Condition 4= Placebo pill. The remission rates of depressive symptoms were found as follows: Condition 1: Supervised exercise group= 45%; Condition 2: Home-based exercise group= 40%; Condition 3: Medication group= 47%; Condition 4: Placebo pill group= 31%. Similar findings have been reported in the Depressed Adolescents Treated with Exercise (DATE) study [173] since vigorous exercise intervention (>12 Kcal/kg/week [KKW]) or a control stretching group (< 4 KKW) for 12 weeks showed a decrease in depressive symptoms. In addition, Brand *et al.*, (2018) studied 129 inpatients from a psychiatric hospital suffering different mental disorders and showed that a single session at a moderate intensity of Nordic walking, workout/gymnastics or ball sports produced benefits on mood [174].

Despite the promising findings of exercise in depression, further complexity has been added to the interventions since additional variables play an active role in the modulation of depression. For example, the age of the subjects as well as the intensity of the exercise exert influence in the remission of depression [175]. In this regard, there is still no agreement on the precise exercise intensity to achieve the best dose-response, with intensities ranging from high to moderate or from moderate to mild for endurance exercise interventions [176, 177]. Besides, limited evidence is available regarding the influence that exercise intensity exerts on depressed mood [178]. Although most of the literature reports the positive effects on the mental health of moderate intensity in the exercise interventions, there is a need for developing research defining the dose-response relationship and prescription of exercise for the improvement in depression [179]. Taking together, we conclude that results have demonstrated the efficacy of exercise interventions in patients with major depressive disorders and outcomes from these non-invasive treatments seem to be comparable to the use of antidepressant medications.

5.2. Exercise and Anxiety

Anxiety disorders have been considered the most frequent mental disorders (14.0%) in European countries across all age groups [180], as well as the most common mental disorder in the USA, affecting more than 25 million subjects [181]. Anxiety is managed by using psychological programs as well as pharmacological treatments, including the prescription of antidepressant [182-184]. However, these therapeutic approaches show limited results. The search for novel medical options for managing anxiety has focused on exercise. In this regard, a reduction of anxiety symptoms when comparing exercise programs with no-treatment has been demonstrated [184-189]. However, contradictory data have been published since non-significant benefits of exercise on anxiety symptoms have been observed as well. For example, a bout of 15 min running at a moderate intensity (65-75% of their HRmax) did not produce significant improvements in anxiety symptoms as well as in cortisol levels [165]. Thus, the research of the influence of exercise on anxiety disorders remains to be explored in detail.

5.3. Exercise and PTSD

Only a few randomized controlled trials have been reported studying the impact of exercise programs on PTSD. Despite the limitation of available data in this field, the results are encouraging. For example, a 12-week exercise program showed positive outcomes in adults suffering with PTSD [190, 191]. The exercise intervention group displayed a reduction of PTSD and depressive symptoms as well as an improved sleep quality in comparison with the control group only receiving the usual PTSD care. Complementary studies using endurance exercise interventions showed positive outcomes on PTSD symptoms [192].

As mentioned previously, the lack of data regarding the influence that chronic exercise interventions have on PTSD, as well as on the response of biochemical markers, including cortisol, highlights the need to explore the involvement of physical activity and exercise on the modulation of PTSD *via* the engagement of biochemical markers. Researchers suggest that after 8-week exercise, intervention promoted changes in the cortisol and endocannabinoid contents in juvenile subjects [193]. Whether the physical activity or exercise interventions might exert log-term effects on the symptoms in PTSD remains to be elucidated.

5.4. Exercise and Schizophrenia

The benefits that different exercise interventions induce on patients with schizophrenia have been reported [184]. For instance, Oertel-Knöchel *et al.*, (2014) showed that a combination of 30 min of cognitive training followed by 45 min of endurance exercise that included 10 min warm-up, 25 min of circuit training at an intensity of 60-70% of their HRmax, and 10 min of cool-down, performed 3 times per week for 4 weeks, induced a positive effect on cognitive performance and individual psychopathology on both, depressive and schizophrenic patients [194]. Additional data have shown that 12 weeks of endurance training (cycling) decreased the severity of schizophrenia symptoms in comparison with the control group that played table football. The exercise group attended 30 min sessions, 3 times per week at an intensity corresponding to a blood lactate concentration of about 1-5 to 2mmol/L [195]. Similar results were found by Wang *et al.* (2018) on the symptomatology of adult schizophrenic patients receiving antipsychotic treatment. The participants were randomly assigned to a high-intensity endurance intervention (exercise training that included 40 min sessions with 5 min of warm-up (walking), 30 min of exercise, and 5 min of cool-down) or a control group attending a low-intensity stretching program that included, among others, flexibility and balance exercises. The authors found that severities of schizophrenic symptoms were diminished in patients that attended the endurance exercise intervention [196]. Regarding the exercise intensity in both groups, the authors stated that the intensity of the endurance intervention was based on each individual´s age adjusted HRmax. However, the exact intensity was not specified for any of the two groups. Moreover, Gorczynski and Faulkner (2010) examined the health benefits of exercise in schizophrenic patients and found that in spite of the small number and size of the randomized controlled trials and the implementation of various measures of physical and mental health, regular exercise programs shows beneficial effects on schizophrenia [197]. However, it remains to tackle some limitations of considering exercise as part of medical programs for managing schizophrenia since patients suffering from this mental disease tend to have less-active lifestyles compared to healthy controls [198].

Finally, Duraiswamy *et al.*, (2007) compared the effects of a 4-month exercise or yoga intervention in schizophrenic patients. The exercise intervention included brisk walking, jogging and several exercises in standing posture [199]. The yoga group performed an integrated yoga treatment. Both interventions included 15 days of directed training (60 min sessions, 5 days per week for 3 weeks) and 3 months of auto-training following the same sequence. Results showed a reduction in the symptoms of schizophrenia in both groups after the intervention.

Additional research is needed to elaborate a comprehensive hallmark of the positive therapeutic effects of exercise on schizophrenia. Moreover, the integration of current knowledge of the diversity of methodological approaches, including sample sizes, proper control groups, evaluation tools, physical exercise and training variables such as type, mode, volume, frequency, and different approaches prescribing physical interventions regarding dose-response relationship is demanded [179, 200].

6. MODULATION OF THE ENDOCANNABINOID SYSTEM AS MEDIATOR FOR ENHANCING THE BENEFITS OF EXERCISE ON MENTAL HEALTH

Although the exercise modulates mental disturbances, the neurobiological mechanism involved in this phenomenon remains to be described in detail [201]. Multiple explanations have been offered for the understanding of the positive effects of exercise by modulating brain systems and in turn, promoting mental health [202]. Amongst the neurobiological networks that respond to exercise, the endocannabinoid system is included [203]. Remarkably, the research on the field has situated the endocannabinoid system as one of the possible moderators through which exercise may cause benefits

on mental disturbances [19, 20, 204]. Following this idea, current findings have demonstrated an increase in the levels of the endocannabinoids after acute sessions of exercise. Elevated AEA contents were found in runners and cyclists but not in sedentary controls after 1 hour of moderate intensity exercise (70-80% of their HRmax), whereas 2-AG displayed no significant changes [204]. Similar results were reported by posterior studies where the levels of AEA were increased after 30 min of treadmill running (70-80% of their HRmax) in a posterior study [205]. Another study showed that AEA levels also increased in a group of cyclists during intense exercise (60min at 55% of their maximal power output [Wmax] followed by 30 min at 75% of their Wmax) and in the 15 min of recovery, whereas 2-AG concentrations remained stable [206]. However, the exercise-induced psychological modifications modulated, among others, by endocannabinoid signaling changes might be dependent on the intensity of the intervention [207]. In this regard, high-intensity running for 30 min promoted a significant increase in exercise-induced contents of AEA, while low-intensity walking for 30 min caused no significant variations of AEA levels [205]. Furthermore, the contents of the endocannabinoids were described after four different treadmill running intensities (walk= <50%, light jog= 70%, moderate-intensity run= 80%, and high-intensity run= 90% of the HRmax) in a posterior study [207]. The results showed that the two exercise interventions with a moderate intensity (70-80% of the HRmax) promoted variations in the levels of AEA. In a similar line, a sample of female subjects suffering from depression that exercised in separate sessions for 20 min on a cycle ergometer at both moderate-intensity or preferred-intensity, only found an enhancement in the AEA levels after the moderate-intensity session [21]. The intensity was established to be a "13" in the rating of perceived exertion (RPE), according to Borg *et al.* (1998) rating scale from 6 to 20 for the moderate-intensity session. It is worthy to mention that intensity was freely manipulated by the participants in the preferred-intensity session [208]. The reported heart rates of both groups (M = 126.7; SD = 20.8 for the moderate-intensity and M = 131.1; SD = 28.7 for the preferred-intensity group) as well as the RPE (M = 13.1; SD = 0.18 for the moderate-intensity and M = 12.7; SD = 1.9 for the preferred-intensity group) did not show significant differences between groups. According to the authors, the intrasubject variability in the way participants exercised during the preferred-intensity session (both lower or harder intensity compared to the compulsory moderate intensity) might hide the potential effect of exercise if the intensity is a necessary threshold to elicit exercise-induced changes in endocannabinoids [21]. Comparable studies have shown significant increases in circulating endocannabinoids (AEA and 2-AG) in healthy adults subjected to low, moderate or high levels of moderate to vigorous physical activity [MVPA] per week after their participation in prescribed or preferred exercise [201]. The prescribed exercise included a 60 min session with 10-min warm-up at 40-60 % of their estimated maximal oxygen consumption [VO2max], 45 min at 70-75% of their VO2max, and 5 min of cool down, in the preferred exercise session, participants self-selected the intensity and the length of the session. Overall, participants performed significantly more work (% VO2max × duration in minutes) in the prescribed versus the preferred condition. It should be noted that increases in AEA were larger in the prescribed condition in comparison with the preferred one, but both activated the endocannabinoid system. However, there were non-significant differences in the endocannabinoid's concentration between samples with varying physical activity levels.

As reviewed, exercise influences several neurobiological elements, including the endocannabinoid system, suggesting a putative modulatory role of the endocannabinoid system on the effectiveness of physical activity and exercise as treatments for managing mental disorders [19-22]. Despite the

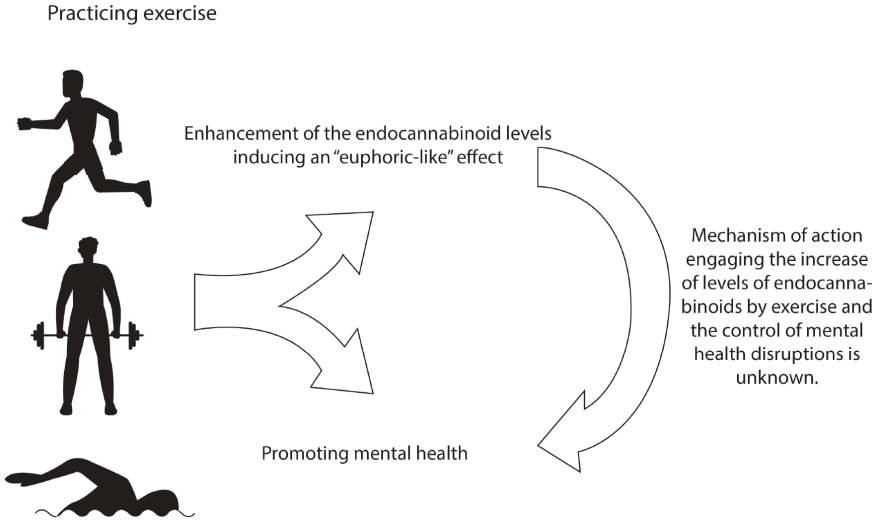

Fig. (2). The benefits of physical exercise benefits in endocannabinoid system and mental health. The positive effects of physical exercise on boosting the endocannabinoid system activity for modulating the mental health functioning. Current evidence has shown that exercise increases the activity of the endocannabinoids by presumably inducing an "euphoric-like" effect. In addition, practicing exercise controls mental health symptomatology. However, further studies are needed to describe the mechanism of action that engages the increase in the contents of the endocannabinoids and the control of mental health disruptions. (*A higher resolution/colour version of this figure is available in the electronic copy of the article*).

lack of a mechanism of action that might provide further comprehension of the process in which the endocannabinoid system moderates the positive effects of exercise in depression, anxiety, PTSD and schizophrenia, it has been suggested that one critical element engaged in this putative mechanism might involve a euphoric-like feeling (Fig. **2**). This assumption is based on previous reports that suggest that a euphoric feeling is present in subjects after exercise, leading to the release of several neurochemicals, including the endocannabinoids [19-22, 208, 209]. Thus, the data suggest that physical activity and exercise could increase the levels of the endocannabinoids, which in turn might produce changes in mood [21, 210-212]. Whether the increase in AEA and 2-AG or the involvement of the enzymes that modulates the functioning of the endocannabinoid system may underlie the rewarding and pleasurable effects of exercise promoting the positive outcomes described in mental health issues, it is a gray area that remains to be studied as a potential mechanism of action. Moreover, future studies should consider the patience's preference to a specific exercise routine that influences the endocannabinoid system.

CONCLUSION

The demographic projections suggest a growth in longevity worldwide in the next years [1-4]. The increase in the number of aged populations will be also associated with the coexistence of medical conditions, including mental health disorders [1, 5, 6]. Despite the further advances for managing mental disturbances, such as the pharmacological means, limited results have been observed, leading to the search for novelty approaches. In this regard, promising strategies include the endocannabinoid system as an effective tool for the enhancement of the positive effects of exercise in the treatment of mental issues [19-22]. In this review, we summarize results collected in studies aimed at evaluating the role of the endocannabinoid system as a modulator for the positive outcomes of exercise in the control of mental disorders, including depression, anxiety, PTSD, and schizophrenia.

The endocannabinoid system comprises a multiple biological elements such as the CB_1/CB_2 cannabinoid receptors, endogenous ligands -AEA and 2-AG-, AMT and enzymes involved in the biosynthesis and degradation of the AEA and 2-AG, including NAPE, NAPE–PLD, FAAH, DAGL, and MAGL [28-33]. Because the distribution of the endocannabinoid system components has been mapped in multiple organs, including the central nervous system, it has been suggested that this signaling system might be engaged by controlling several complex phenomena such as pain perception, emotion modulation and, mental health disparities [34-37]. Through the selective pharmacological or genetic manipulations of the CB_1 cannabinoid receptors [1, 55-68], AEA, 2-AG [98-106, 110-116], enzymes related to the functioning of the endocannabinoid signaling sch as FAAH, DAGL, and MGL [119-133], their relationship with a wider variety of mental disfunctions has been demonstrated [1, 55-68]. However, the role of the CB_2 cannabinoid receptors, NAPE, NAPE–PLD, FAAH, AMT, MGL, and DAGL on depression, anxiety, PTSD, schizophrenia is not fully known. Perhaps due to the limited distribution of the CB_2 cannabinoid receptors, expression in brain areas implicated in the development of psychiatric disorders or the recent discovery of the enzymes linked to the endocannabinoids biosynthesis and degradation, scarce evidence is available in regards the relationship of these endocannabinoid system components in mental disturbances. Indeed, future experiments should be aimed at unlocking the putative role of the CB_2 cannabinoid receptors, NAPE, NAPE–PLD, FAAH, AMT, MGL, and DAGL on depression, anxiety, PTSD, schizophrenia and describe the mechanisms by which elements might exert their modulatory properties in psychiatric disorders.

While the work outlined above does clearly delineate the relevance of the endocannabinoid system on mental health issues, additional elements may be related to the control of psychiatric disturbances. Such variable, exercise, seems to exert positive effects on the management of mental illnesses [159, 160]. For example, it has been reported that different exercise interventions modulate depressive symptoms [161-179]. In addition, clinical evidence has demonstrated that practicing exercise induces positive results for the management of anxiety, [161-189], PTSD [190-192], and schizophrenia [194-199].

It has been proposed that exercise modulates mental health issues by controlling multiple neurobiological networks [201, 202]. Remarkably, the endocannabinoid system is also related to exercise outcomes [203]. In this regard, several studies have shown that exercise enhances the endogenous tone of the endocannabinoids, including practicing high intensity running for 30 min [19, 20, 204-212].

Due to the relationship between endocannabinoid signaling and exercise, it is crucial to clearly distinguish the possible result of modulation of the positive effects of exercise in mental illness by the engagement of the endocannabinoid system. Given the functional link between the elements that comprise the endocannabinoid network and exercise, it bears speculation that these two variables work in concert to control psychiatric disturbances. However, the set of data certainly suggest that the endocannabinoid signaling modulates exercise outcomes. Thus, it remains to be determined how the functioning of the endocannabinoid system regulates the positive effects derived from exercise in the control of psychiatric disturbances.

Indeed, there are gray areas that require further attention to explore the likely enhancement of the endocannabinoid tone for increasing the exercise benefits for managing depression, anxiety, PTSD, and schizophrenia. In addition, the implications of variables such as exercise intensity, volume, type and mode of exercise, or length of the intervention, or type of exercise, require further attention in regards to the dose-response relationship and the likely impact on the endocannabinoid system functioning in mental health treatment. Especially, a standardization of the exercise intensities [152, 213] might facilitate the accurate assessment of the real benefits that training at different intensities might have in the treatment of specific disorders as well as for the change of the endocannabinoids concentration. Given that the endocannabinoid system shows deteriorating profile in mental disorders, thus, creative strategies targeting the enhancement of this neurobiological signaling network, beyond the pharmacological perspectives, will be needed in the future.

FUTURE PERSPECTIVES

An outbreak caused by a novel coronavirus (SARS-CoV-2, previously known as 2019-nCoV), the coronavirus disease 2019 (COVID-19), which was originated in the Chinese city of Wuhan, has rapidly spread around the world causing severe acute respiratory syndrome [214, 215]. COVID-19 symptoms include cough, fatigue, fever, and gastrointestinal infection. Importantly, elderly subjects are susceptible to infection and prone to critical outcomes [216-219]. Recent articles suggest that COVID-19 could be associated with psychiatric disturbances [158, 159, 220-224]. For instance, current data have shown that patients that suffered and recovered from COVID-19 displayed significant rates of anxiety, depression, and PTSD [225-227]. We believe that the present review would provide further stimulation for assessing novel therapeutic means such as the manipulation of the endocannabinoid system to enhance the benefits of physical exercise in mental disorders, highlighting the recovered subjects from COVID-19 who could likely develop psychiatric diseases.

CONSENT FOR PUBLICATION

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CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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