



# An Update on Role of Aerobic Exercise and Endocannabinoids Over Stress Controlling Along with Brain Reward System: A Narrative Reviews

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## Abstract

Aerobic exercise is a broadly used methodology, apart from escalating fitness, decreasing risk of different diseases, it gets further used for mood enhancement, tackling depression and anxiety. Earlier we had detailed role of endocannabinoids (eCBs) in obesity initially when rimonabant, a cannabinoid-1 receptor (CB1R) antagonist was observed to be efficacious in obesity treatment although later discarded, due to endocannabinoids role in Raj yoga meditation by the liberation of anandamide. Here we have detailed crosstalk amongst aerobic exercises along with endurance running regarding management of stress as well as brain's reward system. Additionally, it delves into ECS along with its signalling modes, displays the aftermath of aerobic exercises on HPA axis regarding physiological controlling of stress, updating neural circuits underscoring reward in addition to mood enhancement in the form of results of aerobic exercises performance. The present insight over the manner aerobic exercise influences mental health as well as mood enhancement continues to be uncertain. Moderate along with high intensity aerobic exercise modulate stress via negative feedback which targets hypothalamic-pituitary-adrenal (HPA) axis along with sympathetic nervous system (SNS) therefore promoting stress controlling having a key part in eCBs generation with finally cessation in mediating negative feedback organization over plethora of HPA axis tiers correlated with its impact over cortical along with subcortical brain structures. The eCBs have been observed in controlling liberation of neurotransmitters, from variable neuronal populations, pointing to a ubiquitous mode which finetunes neuronal actions & sequentially modulate emotional & stress correlated reactions. Furthermore, eCBs, possess part in brain rewards working basically modulate by CB1R organized over variable cerebral centres. Noticeably these eCBs participate in natural rewards events, by modulating omit by after modulate the way exemplified by aerobic exercise in getting synergistic with dopaminergic brain's reward system. Generation of these reward can be traced back to ventral tegmental area (VTA) with dopamine neurons basically projecting to nucleus accumbens (NAc) therefore stimulating dopamine liberation in reaction to rewarding stimuli.

**Keywords:** Endocannabinoids; Acute Exercise; Aerobic Training; Mood; HPAaxis; Anandamide; 2AG

## Introduction

In plethora of decades studies have concentrated on evaluating the influence of exercise with regards to human cognition as well as health in addition to probing the modes behind the manner physical exercise impact the wellbeing [1,2]. In the simultaneous time, aerobic exercises are broadly accepted for escalating cognitive functions in addition to mood getting elevated. Whereas the physiological element of cardiorespiratory adaptation has been well corroborated, the modes behind the attenuation of depression, anxiety, mood escalation via physical exercise needs to be evaluated [3]. How resistance exercises aid in positive mood changes is being evaluated, with particular studies pointing that resistance exercises for instance - weight lifting, might

rival aerobic exercises in their effectiveness in mood escalation. Nevertheless, modes behind the mood getting elevated by aerobic exercises vs anaerobic exercises might vary [2,4,5]. Moreover, of the aerobic as well as anaerobic exercises mind-body works like yoga in addition to particular exercises believed to be specialized exercises for instance Raj yoga meditation rev by us whole-body vibrations have plausibility of escalating wellbeing [6-8].

Subsequent to their isolation in the 1990's endogenous cannabinoids (endocannabinoids) [eCBs] have attracted interest of investigators from the medicine arena, in particular regarding their plausible influence over human wellbeing along with health.

The landmark original experimental study was performed by Sparling et al. in 2003 which displayed the part of eCBs in mood enhancement, which generated relief of pain aid in cardiorespiratory as well as metabolic benefits correlated with physical exercise [9]. A close correlation is existent amongst stress along with eCBs, implicating the activation of the endocannabinoid system (ECS) in response to physiological along with stress factors [10].

Endocannabinoids, the lipid obtained signalling molecules generated in the neuronal membrane, are involved in the mood enhancement actions of acute aerobic exercises. eCBs crosstalk with the cannabinoid-receptors (CBRs) in variable brain areas, manipulating working where full insight is lacking. Variation of exercises result in liberation of N- arachidonoyl ethanolamine (AEA) alias anandamide, in addition to 2-arachidonoylglycerol (2-AG) [11]. Binding of these eCBs binding takes place to the CB1 receptor as well as CB2 receptor in the central (CNS) as well as peripheral nervous system (PNS). Such binding is implicated in controlling events for instance mood, food consumption along with immune reactions. In the form of retrograde eCBs aid in neurotransmitters liberation, contributing to adaptation of the nervous system to stress in addition to sustenance of homeostasis [12].

Escalation of circulating quantities of AEA at the time of robust acute exercises might be having a part in the prompt sensation of feeling of wellbeing, giving understanding to the generation of addiction to exercises on their repetitive performance [13].

As per the proposal of some researcher's mood enhancement stimulated in quantities might portray an evolutionary adaptation that is corroborated by the survival of the early humans at the time of environments which were substantially challenging. This was correlated with the pain-relieving characteristics of the eCBs liberated at the time of physical exercises that helped our predecessors to travel considerable space for fetching food [14]. In recent advances in rodent experimental evolution studies, it was posited that Brain rewards stimulated by eCBs in reaction to exercise might be an event of natural selection. This might illustrate the normal susceptibility for the recurrent use of exercise in the form of a habit seen in human, as well as over various mammalian species (spp) [15]. The escalated circulating quantities of AEA at the time of robust acute exercises might be probably aiding in part in prompt sensation of feeling of wellbeing, giving insight in the exercise addiction generation by performance of such actions [16].

A rapidly flourishing corroboration recently reinforces implications of ECS in controlling of central stress reactions. Nevertheless, the exact part of eCBs signalling amongst phases of the hypothalamic-pituitary-adrenal (HPA) axis controlling in addition to particular neural loci inclusive of amygdala, hypothalamus, are believed to be taking part in eCBs modulated stress manipulation via the HPA axis [17].

Earlier we had detailed the role of the endocannabinoids in obesity initially when rimonabant, a cannabinoid-1 receptor antag-

onist was observed to be efficacious in the treatment of obesity, although later discarded due to suicidal tendencies as well as endocannabinoid's role in Raj yoga Meditation by the liberation of anandamide [7,18,19]. Here we have detailed crosstalk amongst aerobic exercises along with endurance running regarding management of stress as well as brain's reward system. Additionally, it delves into ECS along with its signalling modes, displays the aftermath of aerobic exercises on HPA axis regarding physiological controlling of stress, updating neural circuits underscoring reward in addition to mood enhancement in the form of results of aerobic exercises performance.

## Methods

Here we conducted a narrative review utilizing search engine PubMed, google scholar ;web of science ;Embase; Cochrane review library utilizing the MeSH terms like aerobic exercises; endocannabinoid system; N- arachidonoyl ethanolamine (AEA) alias anandamide; arachidonoyl glycerol (2-AG); Cannabinoid-1 Receptor; exercise addiction; Endocannabinoid metabolism; N-acyl phosphatidylethanolamine - phospholipase D (NAPE-PLD); Fatty acid amide hydrolase (FAAH) ;monoacylglycerol lipase (MAGL); Acute Aerobic Exercises; mood getting elevated; chronic Exercises; stress relief; anxiety ;depression; limbic structures from 1985 till 2024 till date in April.

## Results

We found a total of 300 articles out of which we selected 97 articles for this review. No meta-analysis was done.

## Endocannabinoids along with Endocannabinoid Like Substances

The eCBs portray the lipid obtained substances dependent on arachidonic acid, generated in the neuronal membrane [20]. Arachidonic acid, mirrors the maximum active  $\omega$  polyunsaturated chain fatty acids (PUFA's). 2 kinds of eCBs recognition has been done in the form of neurotransmitters: AEA as well as 2-AG. AEA is a family member of N-acyl ethanolamine (NAE), while 2-AG class is monoacylglycerol [21]. NAE family further incorporates N-oleoyl ethanolamine (OEA), an appetite repressing substance along with palmitoyl ethanolamine (PEA), having anti-inflammatory as well as antiproliferative characteristics [22]. Both classification of OEA and PEA is done in the form of endocannabinoid like substances instead of true eCBs in view of basically their binding does not take place to the CBRs, however illustrate cannabimimetic actions via the activation of alternate molecular targets [22].

Endocannabinoids storage does not take place amongst vesicles, their generation occurs rapidly in reaction upon an influx of  $Ca^{2+}$ -ions subsequent to the neuronal depolarization. The quantities of 2-AG in the brain are about 200fold greater in contrast to AEA quantities [23]. Endocannabinoids working is in the form of retrograde neurotransmitter synaptic messengers which traverse a synapse subsequent to liberation along with binding to the presynaptic CBRs resulting in hampering of the further liberation of neurotransmitters. Various posits have pointed to reason out the manner by which AEA transportation take place over the plasma membranes (PM). These are inclusive of passive dif-

fusion, a particular carrier aiding in bidirectional transport referred to as endocannabinoid transporter (eCBT) in addition to the caveolae correlated endocytosis [24].

## Cannabinoid Receptors

The primary cannabinoid receptors CB1 as well as CB2 have been invented. The localization these receptors is mainly on the presynaptic nerve terminals. Expression of CB1-receptor (CB1R) is considerable over different brain areas illustrating maximum enrichment of the G- protein coupled receptors (GPCRs) amongst brain areas [25,26]. Conversely, CB2-receptor (CB2R) are predominantly existent in the immune tissue and inflammatory tissue, illustrating minimal concentrations in the brain [26]. Cloning of the CB1 as well as CB2R has been attained which cements their part in the form of primary targets for the ECBs [26,27].

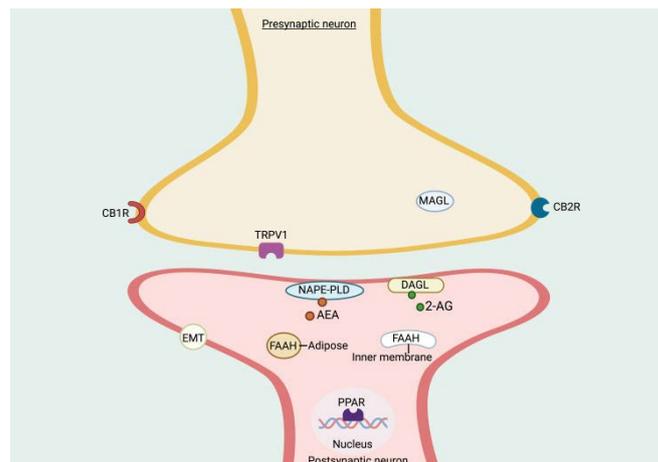
Despite, lesser affinity of 2-AG for CB1R in contrast to AEA, it possesses the capacity of activating CB2R apart from CB1R. Although, 2-AG has lesser affinity for CB1R, noticeably it works in the form of a full agonist compared to AEA, that works as a partial agonist [28]. Noticeably, whereas sustenance of conformation once activated in case of CB2R, CB1R goes through substantially greater conformational alterations in reaction to agonists. This escalated flexibility on CB1R at the time of modulation escalates its capability of reacting to different ligands in contrast to CB2R [29].

Apart from CB1R as well as CB2R, eCBs crosstalk with receptors in addition to ion channels, inclusive of a minimum of 3 orphan GPCRs for instance GPR55, GPR18, GPR19 along with Peroxisome Proliferator Activated Receptor (PPARs), transient receptor potential (TRP) channels for instance transient receptor potential vanilloid 1 (TRPV1) cation channel, GABA channel, calcium, sodium, potassium channels [30]. CB1 as well as CB2R are associated with Gi/o proteins, therefore hampering adenylyl cyclase along with leading to activation of variety members of the mitogen activated protein kinase (MAPK) family [31]. In case of humans 2 varieties of CB2R have been isolated. One of the variants has been observed in testis, with a lesser degree in brain rewards regions, whereas one is found in spleen along with decreased quantities of brain [32].

Binding of AEA, however not 2-AG, noticeably takes place to the TRPV1 or (Ca<sup>2+</sup>) channels. The PPARs are comprised of a family of nuclear receptors which incorporates PPAR $\alpha$ , PPAR $\gamma$ , PPAR $\beta/\delta$  working in the form of transcription factors which control the expression of a plethora of target genes implicated in metabolism, immune reactions, cell differentiation as well as different cellular reactions along with adaptive reactions.

## Endocannabinoid System Along with Expansion of Endocannabinoid System/ Endocannabinoidome

The ECS gets constituted by eCBs CBRs, in addition to enzymes implicated in generation along with breakdown of the eCBs substances (see Figure 1) [rev in ref no 33].



### Legend for Figure 1

Courtesy ref no-33-Illustration Depicting the Components of the Endocannabinoid System

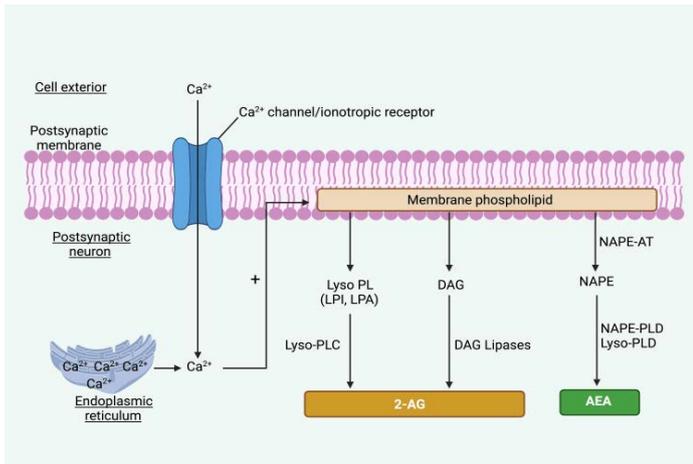
Notes: AEA: N-arachidonoyl-ethanolamine; 2-AG: 2-arachidonoylglycerol (2-AG); CB1R: cannabinoid receptor type 1; CB2R: cannabinoid receptor type 2; DAGL: diacylglycerol lipase; EMT: endocannabinoid membrane transporter; FAAH: fatty acid amide hydrolase; MAGL: monoacylglycerol lipase; NAPE-PLD: N-acyl phosphatidylethanolamine-phospholipase D; PPAR: nuclear peroxisome proliferator-activated receptor; TRPV1: transient receptor potential vanilloid type 1.

The ECS which got completely illustrated in 1990 incorporates 2 ligands AEA as well as 2-AG, 2 CBRs- CB1R as well as CB2R in addition to 5 enzymes responsible for the generation along with breakdown of the ECB ligands. The primary enzymes implicated in bio generation of these ligands inclusive of N-acyl phosphatidylethanolamine - phospholipase D (NAPE-PLD) for the AEA bio generation, for 2-AG bio generation diacylglycerol lipase-alpha as well as acylglycerol lipase beta (DAGL's) for the 2-AG bio generation in addition to Fatty acid amide hydrolase (FAAH) for the AEA breakdown monoacylglycerol lipase (MAGL) for the breakdown of 2-AG [34]. These days endocannabinoidome /expanded ECS incorporates 23 constituents in addition to 3 transporters (FAAH being correlated with endoplasmic reticulum (ER)) along with nuclear transcription factor as well as PPAR which persistently crosstalk with ECBs [35]. Although the introduction of this exhaustive concept, clinicians continue to be reluctant in using this terminology of endocannabinoidome, it is usually referred to as expanded ECS.

## Generation along with Breakdown of the ECBs

### A. Generation

Endocannabinoid precursors lying amongst the lipid membranes go through enzymatic conversion for the formation of ECBs. AEA as well as 2-AG are generated in the form of a reaction to neuronal depolarization along with or/ influx of Ca<sup>2+</sup>, attained by the cleavage of membrane phospholipids. Generation of ECBs take place by the postsynaptic neurons as per 'requirement of its use' (see Figure 2).



**Legend for Figure 2**

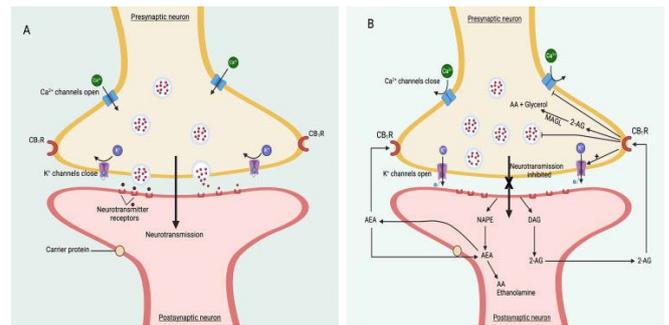
Courtesy ref no-33-Diagrammatic Depiction Elucidating the Biosynthesis of Endocannabinoids

Notes: 2-AG: 2-Arachidonoylglycerol, AEA: Arachidonoyl ethanolamine, DAG: Diacylglycerol, LPA: Lysophosphatidic acid, LPI: Lysophosphatidylinositol, NAPE: N-Acyl phosphatidylethanolamine, NAPE-PLD: NAcylphosphatidylethanolamine-specific phospholipase D, NAPE-AT: N-acylphosphatidylethanolamineacyltransferase, Lyso-PLC: Lys phospholipase C, Lyso PL: Lys phospholipid, Lyso-PLD: Lys phospholipase D, LPI: lysophosphatidylinositol.

The metabolic pathways of AEA as well as 2-AG are elementally unique. The generation of 2-AG is well displayed, while the modes behind AEA generation understanding have not been properly acquired. 2-AG generation goes via 3 basic routes from the membrane phospholipids possessing arachidonic acid i) via diacylglycerol(DAG) lipase ii) from the acyl lysophosphatidic acid(LPA) through 2 LPA phosphatase iii) origin from the lyso phosphatidyl inositol( LPI) through lysophosphatidic lipase C[36]. AEA gets generated from arachidonic acid via 1 2 step event promoted by NAPE particular PLD(NAPE -PLD). 3 unique as well as independent modes have been isolated in the form of aiding in the AEA formation[36]; Nevertheless, the primary pathway implicated for the neuronal AEA formation continue to be not unraveled.

### B. Breakdown

The working time period of eCBs in the synaptic space is dependent on the processing through the enzymatic pathways. A key catabolic actor regarding AEA is FAAH that enzymatically leads to cleavage of AEA into ethanolamine as well as arachidonic acid[37,38]. The breakdown of 2-AG at the primary level takes place through MAGL, resulting in generation of glycerol as well as arachidonic acid in the form of byproducts [38,39]. Furthermore, the arachidonoyl constituent of 2-AG might be oxygenated through cyclooxygenase(Cox) along with 5' lipooxygenase(LOX)[40] (see Figure3).



**Legend for Figure 3**

Courtesy ref no-33-Diagrammatic Depiction of the ECBs Signalling System.

Notes: In conditions devoid of exercise or stress, the uninterrupted flow of synaptic transmission persists, primarily attributed to the paucity or nearly negligible presence of endocannabinoids (ECBs) (A). However, a substantial surge in ECB secretion emanates from the post-synaptic membrane upon engaging in aerobic exercise of requisite intensity. These ECBs undergo retrograde diffusion, subsequently binding to CB1Rs situated upon the presynaptic membrane. This interaction culminates in the suppression or blockade of synaptic transmission (B). AEA: Anandamide, 2-AG: 2-Arachidonoylglycerol, CB1Rs: Cannabinoid Receptor Type 1, FAAH: Fatty Acid Amide Hydrolase, MAGL: Monoacylglycerol Lipase, COX-2: Cyclooxygenase-2, NAPE: N-acyl phosphatidylethanolamine phospholipase, DAG: Diacylglycerol, AA: Arachidonic acid; MAGL: Monoacylglycerol Lipase.

### C. Signaling of the Endocannabinoid System

The mechanism by which ECBs crosstalk with their receptors(see Figure3) unravels a dynamic event; ECBs generated amongst post synaptic neurons have retrograde effects presynaptic ally at CB1R's[41]. Corroboration indicates ECBs possess the capacity of occupying localized CB1R's post synaptically [42,43]. Actually, activation of CB1R's by ECBs reduces the chances of neurotransmitter liberation via a multiple crosstalk incorporating the hampering of influx of Ca<sup>2+</sup>, in addition to activation of K<sup>+</sup> channels[41-44]. The cessation of ECBs actions goes through reuptake with the subsequent breakdown of ECBs; 2-AG by MAGL, along with AEA by post synaptic FAAH, the manner detailed previously. Moreover, a noticeable percentage (45-8%) synapses of over variety of brain areas stick to the tripartite architecture, implicating a presynaptic neuron, a post synaptic neuron, in addition to usually an- astrocytes-a glia which bears CB1R expression[42].

It has been posited that clearing of ECBs takes place from the synaptic area through an uptake mode with the following enzymatic hydrolysis[24], similar to the event found with other neurotransmitters/neuromodulators for instance dopamine transporter(DAT). Although, the ECBs transporters have not been completely figured out till now, their display is going on the manner illustrated by studies [45].

## Acute Aerobic Exercises along with Endocannabinoid System Breakdown

Aerobic exercises envisage noticeable positive psychological alterations inclusive of mood enhancement, decreased stress, as well as antidepressant along with anxiolytic actions. Usually, one aerobic exercise session has always illustrated correlation with diminished anxiety state as well as physiological arousal persisting for 2-4 hrs [50]. Sparling et al. [9], initially conducted the experiment which displayed the impact of physical activity on ECBS in case of humans [9]. Their evaluation displayed escalated quantities of AEA subsequent to 45' of moderate intensity exercise over a treadmill or cycle ergometer. Following human studies have validated escalated quantities of AEA, although interestingly not of 2- AG subsequent to aerobic exercise of 30-45' time period in addition to even up till 5hrs [15,46,47].

Such mood modification actions of the endurance exercises have been posited in aiding in survival benefits in case of humans in an environment not conducive as well as at the time of persistent foraging actions, without breaking down in reaction to fatigue [13]. The euphoria which results is usually referred to as a 'runner's high' that explains human along with other animals' proneness inherently towards voluntary exercise. Noticeably, exercise stimulated ECBS actions in humans is apparently dependent on modulation by the intensity of exercise in agreement with the insight regarding neurobiological implications of exercise are closely associated with its intensity [15,46].

The ideal intensity of aerobic exercise which evokes the maximum ECBS reactions persistently is a debatable topic. Brelenthin et al [48]. reported maximum enhancement of AEA, as well as 2- AG quantities amongst a cohort going through high intensity exercise [48]. On the other hand, Sparling et al. found enhanced AEA, quantities omit been at the time of moderate intensity exercise which was equivalent 70-80% of the maximum Heart rate (HRmax) [9]. Richian et al [15]. illustrated in case of humans along with dogs, AEA, quantities illustrated enhanced AEA quantities at the time of moderate intensity exercise (70% of the maximum Heart rate in humans) instead of at lesser intensities (45% of HRmax). Changes in ECBS in addition to their analogues were found to ECBS which possessed a positive association with the intensity of the exercise (estimated in the form of percentage of VO<sub>2</sub>peak) as well as adiposity of the person [47].

Despite, the close association amongst intensity of aerobic exercise as well as quantities of ECBS is not completely clarified, understanding can be obtained from a study performed by Richian et al [49]. They showed post exercise increases in AEA quantities subsequent to slow jogging in addition to moderate intensity exercise in subjects who by themselves reported to be fit in healthy women as well as men compared to pre exercise quantities [49]. Thus aerobic exercise evokes activation of ECS amongst particular variety of exercise intensities.

This work underpins the intensity of exercise while evaluating neurobiological actions of ECBS signaling, acknowledged that substantially greater or substantially lesser intensities might not evoke ECBS actions [47,49].

## Aerobic Training along with Reactions of Endocannabinoid System

There is considerable equivocal existence amongst the influence of aerobic exercise over mood enhancement regarding conclusions made. Escalating thought process revolves around gathering understanding over the implications of the aerobic exercise over a person's psychological status, in specifically regarding mood, anxiety as well as depression, at the time of rest as well as subsequent to sub maximum or maximum exercise performance. However, regarding current thought process, psychological switch stimulated by chronic exercise are of lesser degree in contrast to that of acute exercise [3,50]. In case if psychological status changes are missing as well as transitory escalation of psychological status might take place from acute exercise.

The work underpins the importance that subjects feeling moderate depression might find significant abrogation subsequent to persistence of exercise at regular intervals. On the other hand, switch in case of standard subjects possess a tendency to be of lesser degree or might not present at all [51]. Thereby exercise possesses a tendency of not being considerably efficacious in escalating well-being of the subjects who to start with have the canonical spectrum of anxiety and depression.

In case of humans persistent finding illustrate that acute aerobic exercise result in a surge of AEA quantities [46]. Noticeably, Gasperi et al [52]. unraveled accelerated upregulation in addition to actions of FAAH, an enzyme key in controlling AEA breakdown amongst lymphocytes in physically active in young in contrast to their sedentary opponents. This suggests an escalated AEA peripheral metabolism, simultaneously with escalated exercise quantities. An interesting fact is the influence of AEA over mitochondrial working in addition to oxidative metabolism pathways [53]. This understanding makes one to posit regarding the plausible association amongst changes of AEA quantities as well as alterations in cardiorespiratory fitness. Nevertheless, studies evaluating the precise correlation amongst exercise training, cardiorespiratory fitness along with AEA continue to be restricted. Moreover, a study assessing male runner's illustrating symptoms of exercise addiction revealed lesser plasma AEA quantities, at rest in addition to post-acute exercise on superimposing with their non addicted counterparts [54]. Akin to that Jurado Fasoli et al. illustrated that performing moderate to vigorous aerobic in addition to resistance exercise for 24 wks. resulted in diminished blood ECBS quantities amongst young adults earlier living a sedentary life [47].

## Stress controlling via Exercise – Modulated Endocannabinoid Manipulation

Stress possesses the properties of being a condition in which the balance of homeostasis gets hampered by external or internal stimuli that are plausibly inimical [53]. In case of no stress sustenance of normal AEA quantities takes place, causing stabilization of the glutamate activity over basolateral amygdala (BLA) neurons without influencing hypothalamic-pituitary-adrenal (HPA) axis [17].

The stress reaction gets constituted of the 2 parts i) liberation of noradrenaline as well as adrenaline from the sympathetic nervous system(SNS) along with ii) liberation of circulating cortisol via HPA axis . Whereas CB1R signaling has been accepted regarding, its capability of hampering noradrenaline liberation, a greater degree of insight is accessible regarding its controlling of the HPA axis. SNS along with HPA axis work concurrently escalating the adaptive reactions to instant stressors in addition to ameliorating further ones[54-57]. If rectification of the homeostasis is hampered, culmination of the stressors or continued disturbance takes place, such reactions for instance escalated cortisol quantities or continued sympathetic activation might become pathogenic or take the form of disease generation. Clinically, assessment of stress reactions might be performed by evaluation of one or both its constituents. In reaction to stress the HPA axis gets activated for ensuring the survival of the organism [17].

Cortisol quantities are canonically evaluated for assessing the actions of HPA axis, with acute stress associating with escalated cortisol quantities . At the time of stress degradation of FAAH takes place in all the brain areas. Concurrently, 2-AG quantities in the amygdala as well as hypothalamus continue to be unaltered or decline. This leads to aberrations of AEA/ CB1R signaling resulting in escalated glutamate input on the BLA neurons[17].The eCBs signaling system is key modulator of the stress reaction, similar to its part in aerobic exercise. It is key for reverting to non-stressed status. The ECS controls the degree stress stimulated reaction correlated with exercise contributing in normalization of the HPA axis towards baseline levels, thus aiding in getting used to exercise stimulated reaction via aerobic training [58].

Furthermore, it directly counters the stress correlated events incorporating fear, anxiety, depressive predisposition, inflammation escalated sensitivity to pain. Concurrently, the ECS facilitates behaviors hampered by stress reaction for instance feeding in addition to sleep patterns. During chronic stress the insufficient escalation of 2-AG / CB1R signaling secondary to variable stressful conditions result in downregulation of CB1R signaling in the medial prefrontal cortex(PFC) along with hypothalamus, initiating a state referred to ‘‘hypo cannabinoid state ‘’[59].

### A. Endocannabinoids in Modulation of Sympathetic Nervous System Stimulation

Observational corroboration regarding for the eCBs guided amongst presynaptic hampering SNS is noticeably restricted[60]. Nevertheless, occasional studies have pointed regarding activation of peripheral presynaptic CB1R results in hampering of noradrenaline liberation from sympathetic nerve ends [61].

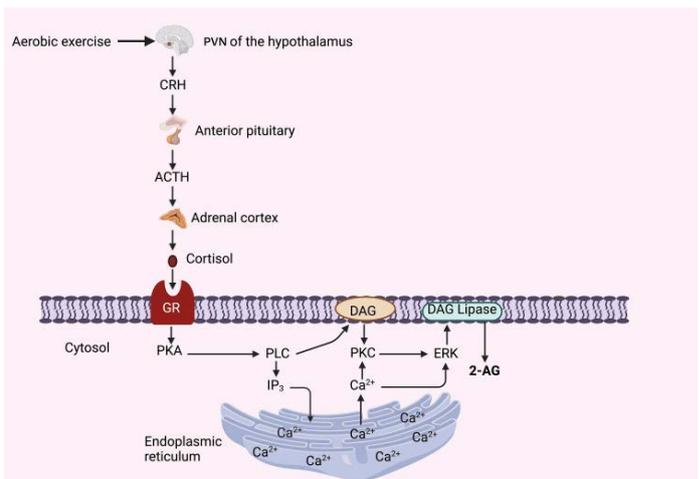
### B. Endocannabinoids-Modulated controlling of Hypothalamic-Pituitary-Adrenal Axis

The HPA axis comprises the main circuit reacting to stress as well as other stress stimulating conditions[60,62]. Subsequent to aerobic exercises, neurons amongst the hypothalamic para-

ventricular nucleus(PVN) liberate considerable levels of corticotropin releasing hormone(CRH) into the portal vessels of the median eminence. amongst the pituitary gland, CRH stimulates adrenocorticotropin releasing hormone(ACTH) liberation, thus stimulating the liberation of glucocorticoids, mainly cortisol from the inner adrenal cortex into the blood stream.

On liberation cortisol initiates the pacey mobilization of the energy reserves stores mediating a measure for countering the stresses stimulated by exercise. Noticeably, cortisol induces rapid formation of eCBs amongst the neuroendocrine cells through activation of CB1R .This pacey eCBs formation gets invoked transiently by potent postsynaptic depolarization in addition to influx of Ca<sup>2+</sup> ions through voltage gated - Ca<sup>2+</sup> channels[63], stimulated by synaptic activity[64] as well as stimulation of GP-CR correlated with phospholipase C(PLC) sig [63,65].

It has further been displayed that for eCBs formation it is essential that protein kinases participate. particularly cAMP based protein kinase A(PKA) in addition to protein kinase (PKC) have both been found to aid in eCBs liberation[66]. Nevertheless, the exact part of kinase actions in eCBs liberation is still going through evaluation. An exhaustive model is described in Figure 4



**Legend for Figure 4:** Illustration of the signalling cascade governing cortisol induced Endocannabinoid (2-AG) synthesis

Notes: This intricate process can transpire during various stress-inducing scenarios, including aerobic exercise. However, the knowledge concerning the membrane-associated glucocorticoid receptor (GR) remains rather enigmatic. This entity could manifest as either the nuclear glucocorticoid receptor at the membrane's interface Oran undiscovered G protein-coupled receptor.

**PVN:** Paraventricular Nucleus, **CRH:** Corticotropin-Releasing Hormone; **ACTH:** Adrenocorticotropin Hormone, **DAG:** Diacylglycerol; **2-AG:** 2-Acylglycerol, **PKA:** Protein Kinase A, **PLC:** Phospholipase C; **IP3:** Inositol Triphosphate, **PKC:** Protein Kinase C, **ERK:** Extracellular Signal-Regulated kinase.

### C. Threshold for Intensity of Exercise is must for Cortisol Liberation

Cortisol liberation to take place from the adrenal cortex apparently is dependent on crossing a threshold regarding exercise intensity. A plethora of studies have corroborated regarding minimum exercise intensity required for cortisol reaction is approximately 60% of VO<sub>2</sub> max or involves performance of moderate activity at the time of sub maximum exercise [67,68]. On crossing this threshold, a direct in addition to positive linear association comes out amongst cortisol quantities liberated as well as exercise intensity, with a noticeable along with significantly increased cortisol liberation found at greater sub maximum work rates[67,68].

### D. Endocannabinoids-Modulated Negative Feedback on the HPA axis

Escalated cortisol liberation stimulates the rapid feedback modes over the HPA axis. This initiates the eCBs bio generation activating CB1R in the glutamate terminals. Sequentially, this diminishes or represses glutamate liberation in addition to hampers further retrograde generation of CRH. Furthermore, negative fast feedback in the amygdala is promoted via eCBs signaling in the BLA- GABAergic outflow [69]. Cortisol liberation works via direct along with indirect pathways. The direct feedback works at the level of hypothalamus along with pituitary[70]. Indirect hampering by cortisol amongst the HPA axis gets regulation by upstream limbic structures for instance - hippocampus, paraventricular thalamus, PFC, amygdala, prefrontal cortex (PFC), bed nucleus of stria terminalis(BNST), with all projections to the paraventricular nucleus(PVN)[62,71]. PFC in addition to hippocampus/subiculum outputs incorporate excitatory projections which travel to the PVN through main neurons, whereas their trajectory gets reverted via hampering relays having placement amongst BNST in addition to periPVN hypothalamic areas [62,71].

In inimical feedback modulation of the HPA axis, aerobic exercise(along with physiological stressors basically influence the fast direct pathways. As compared to psychological stress basically leverages the axis via the slower, upstream limbic structures. The organization of CB1R is specifically greater in limbic structures in addition to subcortical areas inclusive of BNST as well as PVN. Moreover, CB1Rs have placement amongst these structures at the presynaptic region of GABAergic along with the glutamatergic synapses resulting in activation of hampering actions on the neurotransmitter liberation [72]. Despite, expression of CB1Rs is to a lesser degree in the glutamatergic neurons in contrast to GABAergic neurons, the diminished glutamate liberation from the glutamatergic synapses in view of activation of CB1Rs possesses a key part in the glucocorticoids modulated feedback controlling of the HPA axis[73].

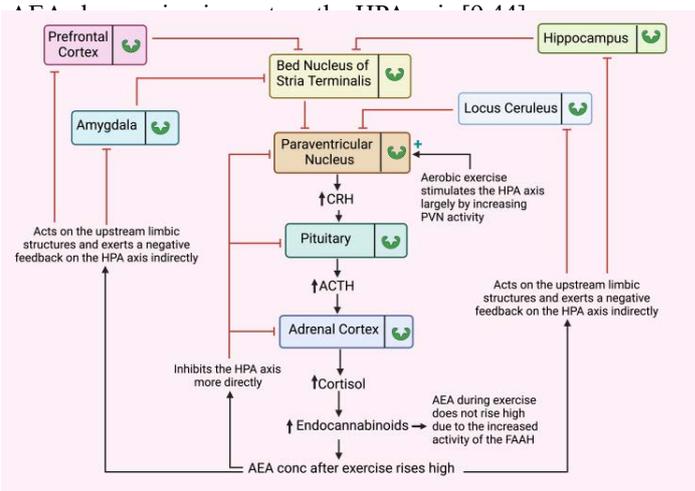
Noticeably, CB1Rs are further, observed in the intermediate along with anterior lobe of the pituitary gland in addition to the outer area of the median eminence[74,75]. Furthermore, eCBs, 2-AG as well as AEA have been isolated amongst the pituitary

gland [75].

Acknowledged that CB1R are further existent in adrenal gland[77], accumulated corroboration underpins the key part of CB1Rs in contrast to CB2Rs in controlling the HPA axis.

### E. Tonic Hampering of the HPA axis Stress Reactions through CB1R Signaling

The existence of a stressor associates with continued repression of AEA quantities. This takes place in view of pacey surge of the CRH signaling in the limbic structures subsequent to exposure to acute stressor, that accelerates the enzymatic actions of FAAH(see Figure5). Sequentially, a rapid amelioration of the



**Legend for Figure 5:** Schematic depiction of aerobic exercise's impact on the hypothalamus-pituitary-adrenal (HPA) axis.

Notes: Aerobic exercise triggers HPA axis stimulation, primarily emanating from the hypothalamic paraventricular nucleus (PVN), culminating in the heightened secretion of cortisol and endocannabinoids. During the recovery phase, a notable elevation in endocannabinoid levels, particularly anandamide (AEA), engenders an indirect suppression of the HPA axis through the engagement of upstream limbic structures. Furthermore, endocannabinoids execute a more direct inhibitory influence on the HPA axis by acting upon the hypothalamus, pituitary, and adrenal cortex. While engaged in exercise, the elevation of AEA levels is hampered by the catabolic role of fatty acid amide hydrolase (FAAH) on AEA. Notably, all the limbic and sub-limbic structures illustrated in this diagram house Cannabinoid Receptor Type 1 (CB1R), denoted by underscoring their integral involvement in this intricate cascade. CRH: corticotropin-releasing hormone, ACTH: adrenocorticotrophic hormone. physical exercise stimulates cortisol surge, that the production of 2-AG in the hypothalamus along with other stress correlated brain areas. In turn, this stimulates negative feedback hampering of the HPA axis, therefore promoting the culmination of the of stress reaction [9].

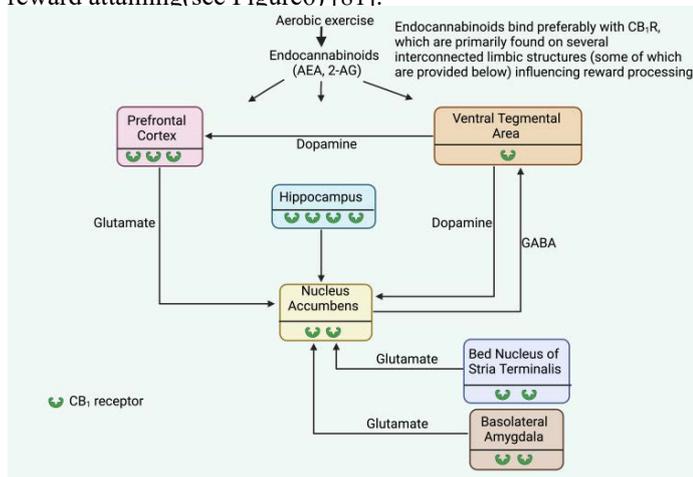
Aerobic training or sustenance of exercise evokes a propagative surge in 2-AG quantities amongst the forebrain stress centers. This escalated 2-AG quantities get followed by amplification

of CB1R signaling with the cessation in HPA axis getting habituated reactions[9]. This increased 2-AG generation might be accounted by the downregulation of the expression of MAGL.

### Plausible Brain Reward Circuit Correlated with Aerobic Exercise

The ECS possesses a significant part in the signaling of the reward processes. This is basically implicated to existence of CB1R in brain areas involved in reward events in addition to change in brain quantities of AEA along with 2-AG activation of activation of reward modes [77]. Endocannabinoids directly crosstalk with the reward system, imparting addictive characteristics to them. The underscoring actions of eCBs arise from their capacity of escalating dopamine quantities via CB1R based modes amongst ventral tegmental area (VTA) [78].

The ECS modulated reward processing basically works via a network of the structures that are intercommunicating, incorporating nucleus accumbens (NAc alias ventral striatum), VTA, PFC, amygdala, in addition to BNST. Other dopamine's well illustrated part, reward processing is considerably impacted by other systems for instance cholinergic, opioid peptide, GABAergic as well as glutamatergic systems. The existence of CB1R is observed in all of intercommunicated structures involved in reward processing [42,72,79], having ubiquitous modulatory actions on excitatory in addition hampering signaling therefore shaping dynamics of reward processing [77,80]. Specifically noticeable is the ECS's considerable implication in refinement of the actions of the VTA- NAc dopamine projections, therefore impacting go near along with preventive behaviors controlling reward attaining (see Figure 6) [81].



**Legend for Figure 6:** Potential reward pathways in the brain  
 Notes: The presence of CB1R, denoted by, is evident across diverse limbic regions, as elucidated in this presentation. The quantity serves the degree of CB1R abundance – a single denotes an exceedingly limited concentration, whereas a cluster of four signifies a markedly elevated concentration [105].

PFC: Prefrontal cortex, VTA: Ventral Tegmentum; HIPP: Hippocampus, NAc: Nucleus Accumbens; BNST: Bed Nucleus of Stria Terminalis, BLA: Basolateral Amygdala, GABA: Gamma-aminobutyric acid

The mesocorticolimbic dopamine pathways starting from the midbrain VTA, possess a key part in modulating reward reactions. Specifically, the VTA's dopamine projections to the NAc basically aid in positive strengthening leading to reward attaining. Aerobic exercise in addition to other natural rewards (for instance-food, sex, substance used for abuse) evoke an escalated NAc dopamine quantities which aid in our feelings of the reward as well as its strengthening [82]. VTA dopamine neurons further provide supply for extra limbic system constituents incorporating amygdala, hippocampus, orbito frontal cortex (OFC) along with particular PFC areas. These close circuits implicate excitatory (basically glutamatergic) as well as hampering (basically GABAergic) projections [83]. glutamatergic GABAergic.

Dopaminergic neurons illustrate 2 unique mechanisms of actions: tonic in addition to phasic firing [84]. Tonic actions involves pacemaker-like spontaneous single spikes, whereas phasic actions possess the characteristics of fast fleeting dopamine quantities surges leading to greater frequency bursts [84]. Phasic dopamine neuron action is imperative for the generation of continued memories that correlate anticipative cues with reward. compared to those tonic reactions of these neurons control motivation for reacting to these cues [85]. A correct emotional reaction towards stress is necessary for the survival, making it essential that appropriate controlling of the variety of neuronal circuits. Therefore, regulation of these circuits is key for avoidance of the behavioral imbalance.

In the last 20 yrs considerable work has emphasized the key part of ECS in tackling stress modes [86]. The ECS is acknowledged to controlling be accurately the neurotransmitter liberation from different neuron population (for instance - GABA, glutamate, catecholamines as well as monoamines) pointing an elemental mode behind fine tuning neuronal actions along with therefore controlling emotional in addition to stress reactions [86].

### Discussion

Remarkable corroboration reinforces the noticeable implications of ECBs in evoking a promising switch in mood subsequent to acute bouts of exercise. Nevertheless, the close modes reinforcing the ECBs modulated mood elevation subsequent to aerobic exercise have not been completely evaluated. Furthermore, mood elevation caused by exercise gets impacted apart from ECBs liberation, might result from variable psychological as well as environmental factors for instance the setting in addition to the milieu in which exercise takes place [2].

Aerobic exercise stimulates a considerable surge in the ECBs quantities, whose origin takes place from various sources that possess the capacity of seeping from blood brain barrier (BBB), having an influence on a plethora of cerebral regions possessing eCBs. Noticeably, moderate to high intensity exercise stimulates a considerable escalated cortisol liberation, sequentially, inducing an escalated ECBs generation. This ECBs surge mediates a negative feedback regulatory mode on HPA axis, thereby efficaciously controlling stress quantities. Reduction of

the ECBs quantities via physical training that plausibly would lead to physiological adaptation which plausibly diminish the necessary proinflammatory state. Sequentially, exercise training might impact the plasma quantities of ECBs as well as their analogues for instance the manner it influences inflammatory molecules [54].

The escalated ECB quantities plausibly ameliorate sympathetic stimulation, despite the exact mode of actions of this process continues to be evasive, basically aiding in more abrogation of stress. Furthermore, the effectiveness of the ECS stimulates the brain's reward circuitry, basically via the CB1R that have strategic placement, over different cerebral localizations, everyone utilizing unique neurotransmitters.

Despite a plethora of receptors particularness differentiate AEs along with 2-AG, both ECBs generation taking place in reaction to mainly stimulated by increased intracellular calcium quantities [42]. Nevertheless, generation, transport, in addition to deactivation events for AEs along with 2-AG differ over their particular target tissue. A continued enigma in ECB research is regarding the manner lipophilic AEs along with 2-AG pass through their development region, traversing the aqueous environment, reaching variable intracellular membrane regions where its metabolic along with signaling actions take place [87]. Absence of tailored probes as well as approaches regarding tracking in addition to visualization of these bioactive lipids amongst the cellular confinement is the reasons why it is complicated to evaluate the intracellular AEA transport in addition to its organization [87].

While, a plethora of studies have concentrated over walking along with jogging regimens, the effectiveness of resistance exercises has further undergone assessment. Regarding elderly subjects' resistance training illustrated more efficacy in contrast to control situations [5]. Doyne et al. [88], contrasted random enrollment of running versus weight lifting, where their observation was that both actions resulted in reduced depressive symptoms with no statistically significant differences on the cessation of active treatment phase or at the time of 1 yr follow up later [88]. Martinsen et al. [4], however did not find any appreciable variation amongst aerobic actions (for instance jogging or fast walking) in addition to nonaerobic kinds of exercise (inclusive of strength training, coordination as well as flexibility training) [4].

The brain's reward system comprises of a key survival mode. The indulgent actions of aerobic exercise possess key motivational repercussions, escalating the probability of the further engaging in these key actions via positive strengthening effectiveness. The mood elevating part of aerobic exercise possesses an evolutionary importance the survival of species (spp). Nevertheless, all exercise intensities do not possess equivalent efficacy in forming eCBs along with their following psychological well-being actions. Moderate intensity exercise surpasses the escalating greater in addition to escalating lesser intensities regarding this.

Whereas, the exact neurophysiological mode guiding exercise stimulated mood changes as well as reduced anxiety along with depression continue to evade, a unique neural circuits amongst brain's reward system limbic cortex apparently are of considerable importance. The brain's reward system generates a close network constituted by hippocampus, amygdala, VTA, nucleus NAc, PFC in addition to BNST. All these reward circuit constituents possess CBRs as well as liberate plethora of neurotransmitters of which GABA, glutamate, along with dopamine have maximum prevalence. Noticeably, CB1R illustrates a wider organization in contrast to CB2R as well as ECBs, impact CB1R on presynaptic neurons, giving exhaustive modulatory actions on excitatory in addition hampering signaling therefore shaping dynamics of reward processing [77,80]. Endocannabinoids possess a significant part in finetuning VTA-NAc dopaminergic projections, therefore shaping behaviors associated with looking for rewards as well as preventing inimical sequelae.

Subsequent to a continued run, AEs along with 2-AG induce a euphoric state called "runner's high" associated with central actions of circulating ECBs that escalate the self-indulgent signals amongst brain's reward system, generating a tendency for regular aerobic exercise. Furthermore, escalated ECBs quantities at the time of exercise accelerate the Brain derived neurotrophic factor (BDNF); modulating cognitive advantages for instance neurogenesis, synaptic plasticity as well as antidepressant action [1,45].

These central actions in combination of peripheral results for instance improvement of glucose uptake, escalated insulin effects, mitochondrial bio generation reinforces the clinical along with scientific importance of understanding eCBs reactions to exercise, particularly in evaluating intensity of exercise required for evoking these actions [1,45]. Nevertheless, persistence of debates with regards to, essential intensity of exercise for attaining this action [49,89]. Aerobic exercise commands an intensity of minimal 60% VO<sub>2</sub> max for eliciting a cortisol reaction [90].

The HPA axis portrays a key target of ECBs, selectively controlling the HPA axis in addition to sustenance of regulation of cortisol quantities, specifically prominent in aerobically trained subjects as well as acute exercise setting. Psychological stress impacts overtime negative feedback loop via limbic structures on the HPA axis. Nevertheless, this mode behind effectiveness continues to be restricted, along with common unregulated psychological stress might not possess the capacity of ameliorating escalated cortisol quantities, plausibly resulting in hypertension in addition to other conditions correlated with escalated cortisol quantities. At the time of aerobic exercise, the upsurge of ECBs possesses the capacity of directly hampering the HPA axis via CB1R with existence in the hypothalamic PVN, pituitary gland along with adrenal gland as well. Indications point that AEs along with 2-AG, possess key part in the feedback event [95].

Exercise positively influences conducting cognitive acts impacting brain's reward system as well as eliciting a feeling on being contented [91,92]. By modulation of a plethora of signaling mediators exercise efficaciously influences mood along

with nociception impacting immune system working by the side of exhaustive whole body energy metabolism[91-95. Endocannabinoids modulate central as well as peripheral actions of exercise aiding in psychological well-being[96].

### Future Directions

More research that needs further evaluation for generating tailored exercise protocols applicable for a variable demographic group, incorporating age, gender, familial as well as social circumstances i) getting into the actions of intermittent aerobic exercise over the ECBs along with its impact over mood enhancement possesses considerable importance. The problems numerous adults encounter regarding sustenance of moderate intensity aerobic exercise regimens makes it imperative to gain greater insight over the influence of rest time periods amongst exercise plausibly prolonging exercise time periods ii)deeply probing the part of sprinting, pacy runs, or greater intensity, lesser time periods exercises has a probability for healthy adult subjects in addition to subjects suffering from mood problems .This is specifically germane for younger population along with the ones possessing considerable physical fitness iii) assessment of actions of recreational team sports unexplored arena. Tackling the motivation intimidating botherations specifically amongst adults is key.

Team sports for instance football, hockey or basketball might act as good outlets, nevertheless, their being intermittent along with probable influence over mood enhancement makes it mandatory for further evaluation iv) contrasting the effectiveness of home bound exercise for instance treadmill running or stationary cycling with outdoor actions are intriguing topics. Acknowledging restricted time, specifically women, professionals who are busy, inferring if indoor actions give unquestionable advantages are necessary.v) Assessing if a subject's preferential mode of exercise is cycling/swimming yields a greater robust reward reactions in contrast to alternate non preferential ones might yield considerable understanding .Given the variations of preferences of subjects, the crosstalk amongst mode of exercise as well as rewarding results possesses repercussions regarding sustenance in addition to sticking to same .A considerable degree of commitment is required for unveiling this unresearched arena systematically. The close interactions of aerobic exercise, ECBs along with psychological well-being stimulate finding attractive interventions which might be having the capability of transformation of the lives of those fighting numerous health problems.

### Conclusions

Communication amongst aerobic exercise as well as the ECBs with regards to stress implicates the exercise triggered escalated ECBs quantities, plausibly aiding in the stress relief actions of the physical activity. Multiple aspects of the crosstalk amongst aerobic exercise, ECS, in addition to psychological well-being continue to be not clarified . However physiologically important understanding gained from the research make it mandatory to pay interest & endeavors to solve i) Subsequent to an aerobic exercise session the blood quantities of AEAs illustrate an upsurge with the degree of escalation dependent on

the intensity of exercise. Noticeably moderate intensity aerobic exercise evokes a considerable escalated AEAs quantities . On the other hand, post aerobic exercise plasma quantities of 2- AG continue to be a topic of debate. ii)The euphoria feelings usually correlated with running yield these part reasons for escalated AEAs quantities. Usually, a single bout of aerobic exercise is associated with sustenance of decreased anxiety state as well as physiological arousal continues for 2-4 hrs iii) escalated ECBs quantities in the form of sequelae to exercise is further a key for aiding in accelerating BDNF, therefore promoting cognitive escalation, neurogenesis, synaptic plasticity in addition to antidepressant action as well .iv) the ECS 's key part in modulating the actions of aerobic exercise basically implicate the CB1R activation, whereas CB2R is restricted in mood enhancement, CB1R being the main player iv) Noticeably, considerable psychological escalation have been found in subjects feeling moderate depression subsequent to performance of exercise on a regular basis. Nevertheless, change in subjects possessing canonical spectrum of depression along with anxiety are not much v)Existence of CB1R is observed amongst hypothalamic PVN in addition to anterior pituitary gland. Acute aerobic exercise mediates negative feedback amongst the HPA axis by escalating AEAs as well as 2- AG vi) The ECS has a key part in signaling rewarding actions.

Endocannabinoids modulate these actions through crosstalk amongst CB1R's having organization over variable region of limbic cortex .Next to dopaminergic neurons, the close canvass of reward processing is further significant based over cholinergic, glutamatergic, along with GABAergic neurons .The limbic centers involved are inclusive of VTA, -NAc, PFC in addition to BNST . Noticeably ECBs possess a key part in finetuning the VTA -NAc dopaminergic pathway involved, thereby impacting the behaviors regarding getting rewards or preventing inimical sequelae. These advantages of ECBs & exercise might be extrapolated in the treatment of chronic musculoskeletal pain inclusive of osteoarthritis, chronic low back pain, rheumatoid arthritis, as well as fibromyalgia [97].

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