

## ARTICLE

# THE EFFECT OF EXERCISE AND DRUGS ON COGNITIVE FUNCTION AND BDNF PROTEIN

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## ABSTRACT

Exercise is an effective factor that can promote the cognition function of brain like spatial and object recognition tasks. Thus, exercise can act in different part of the nervous system, such as stimulating neurons augmentation and increasing cell survival. The effect of exercise can change the dentate gyrus function that it causes cognitive improvement and has effect on object recognition, specific neurogenic and neurotrophic. In this manner, exercise influences cognition, BDNF and cell proliferation in particular. Results have revealed that nerve revival is enhanced by treadmill training which leads to enhancement of BDNF mRNA expression in motoneurons. Brain-derived neurotrophic factor (BDNF) which is a member of the neurotrophic factors has a critical role in the observance and survival of neurons, synaptic integrity and synaptic plasticity. Stress also modulates BDNF expression. Drug addiction is a disorder that has been defined as the need to search and take drugs. Absence of drugs causes the addicted drug-users lose self-control, and negative emotional (called withdrawal syndrome) appears. The purpose of this review is to show exercise effects on the nervous system and BDNF which is an important protein. It also reveals the influences of drugs on BDNF and the effects of exercise, addiction and BDNF on the process of learning and memory.

## INTRODUCTION

Exercise is physical activity that is programmed, repetitive and purposefully in the sense that leads to amelioration or fortification of one or more parts of physical fitness is an objective [1]. Exercise increases the neurogenesis, learning and memory enhancement. There are many evidences that suggest BDNF as the variable which improves learning and memory through exercise [2]. Stress elevates the level of glucocorticoids that causes them to have an effect on BDNF expression. For instance, corticosterone (CORT) treatment of rodents decreases the expression of BDNF in the hippocampus [3, 4]. BDNF level in limbic structure and serum is enhanced by administration of anti depressions [5, 6]. Drugs have a moderating role in BDNF level. while drugs can increase the measure of BDNF in some parts of the brain, they can decrease the level of this neurotrophine in other parts [7, 8].

Exercise increases the level of endorphins and can have euphoria effects. It also observed that exercise can reduce the tendency to addiction [9]. It has been revealed that the increase in the level of exercise in rats is accompanied by decrease in self-administration [10]. Similarly, the teens who exercise have less tendency to smoke and use drugs [11]. In this review, we consider the corresponding effects of exercise and addiction on cognition function of brain. Also we talk about BDNF (an important protein), has a critical role in cognitive acts like learning and memory. In this manner, we focus on cellular changes that cause increase in the level of BDNF via exercise, addiction pathway and its effect on learning and memory. Physical activity in our daily life can improve health. A positive relation between exercise and health has been reported by the department of health and human services (HHS). Exercise is divided in two general types: 1) aerobic exercise, 2) anaerobic exercise, and each of them has an effect on different types of muscles. Evidences have revealed that the effects of exercise are depended on intensity, species, sex and the method of learning.

### Exercise can change nervous system operation

Exercise can increase skeletal muscle activity; however, the physiological effects of exercise are only on muscles but also they influence all body systems as well as nerves system. Exercise is also necessary for activities of daily living, and one of the most serious consequences of disease is the limitation of exercise capacity. The brain receives almost the same absolute blood flow at rest and at exercise [12]. But How Exercise influences brain? It is clear that physical activity can increase brain health and plasticity of neurons [13, 14]. Exercise can improve cognition functions [15, 16], function of hippocampus such as learning and memory [17, 18], and increase natural operation of hippocampal in rodents like long term potentiation, neurogenesis, the level of growth factor and dendritic spine [18, 19]. Also exercise can increase the number of cholinergic neurons [20] and the stabilization of information as long-term memory [15, 21-23]. Wheel running as a voluntary exercise has shown that it can increase the firing rate of hippocampal cells and synaptic plasticity [24].

### KEY WORDS

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Exercise promotes operation of spatial learning and memory tasks [16, 17, 25], and thus it can modify LTP in brain [26]. In this regard, the voluntary exercise increases LTP in medial PP to dentate gyrus synapses [27]. Exercise instigates cell proliferation, enhances neuronal survival, and has a strong effect on neurogenesis [28]. The effects of exercise can fundamentally improve neuronal survival [29, 30]. So exercise has potent effect on cognition, BDNF, and cell proliferation [31]. Running increases neurogenesis fourfold and enhances operation in cognition tasks like Morris water maze [32, 33]. Also Physical activity is accompanied with increase in glutamate activity by enhance in expression of NMDA receptors [26, 34]. How can exercise improve neurogenesis and cell survive? During exercise, Glutamate, as an excitatory neurotransmitter, is released from presynaptic terminal axon and can activate the receptors in postsynaptic terminals. After that,  $Ca^{++}$  is released and the signaling begins. Firstly, transcription of gene that is related to synaptic plasticity and neuronal survival like neurotrophin factors, chaperon proteins and antioxidant enzyme are increased. Then, they reform the energy metabolism of mitochondria and correction of free radical production. Finally,  $Ca^{++}$  is released from endoplasmic reticulum. Exercise can increase the functional ability of the brain via actions in synapses and neural stem cells [33]. Also, evidence shows that exercise can increase the expression of BDNF mRNA in hippocampus [21, 35-39]

BDNF plays an effective role in mediating the beneficial effects of exercise on cognitive functions like learning and memory as well as long term potentiation [17, 40]. Exercise, as an external factor can change the operation of nervous system. This alteration is accompanied by an increase in cognition function and behavior. It is repeatedly distinguished that exercise has influence on brain especially hippocampus and can increase the amount of neurogenesis, neurotrophins and LTP. Also it has been shown that increase in glutamate via exercise can activate the cellular cascade that causes improvement in synaptic plasticity. Exercise can enhance level of BDNF that has critical role in learning and memory.

### **Influence of exercise on learning and memory**

Physical activity has an effect on brain function. It is distinguished that exercise can improve learning and memory through increase in neuronal plasticity, and change the level of large numbers of genes that are important in memory. These processes are associated with changes in neuronal activity, synaptic structure and the concentration of neurotransmitters [41]. Physical activity has revealed increase in the cognition in both object recognition [42, 43] and spatial tasks [44], improvement of neurogenesis, and neurotrophic changes in the dentate gyrus of rats [31, 45-47]. Aerobic exercise can improve spatial memory and can invert age-related decline in hippocampal volumes [48]. Physical activity also results in physiological changes and increases cell proliferation in hippocampal [17, 18, 24]. Hippocampal synaptic function is important in learning and memory [49]. Hippocampus is the brain region where cell proliferation continues throughout life in the adult mammals like human [50, 51]. Exercise improves neurogenesis and increases dendritic spine density in the Hippocampus [52, 53].

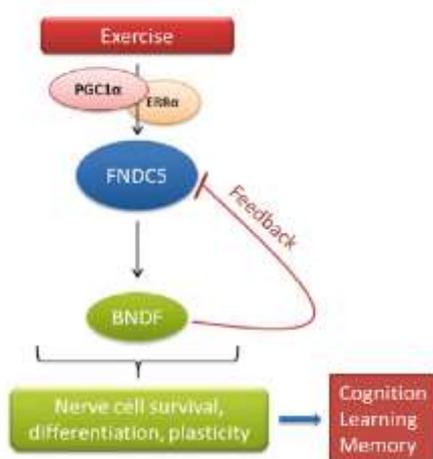
BDNF is thought to mediate changes in hippocampal synaptic plasticity and so it seems that voluntary exercise induced BDNF may affect learning and memory by mediating changes in neuronal plasticity [37, 54]. Exercise through changes in brain function can affect cognition and behavioral function. Just as defined in researches, physical activity improves neuronal plasticity and synaptic function. Hippocampus (an important area for learning and memory) function is influenced by exercise. Possibly positive effect of exercise on hippocampus is caused by the release of brain derived neurotrophic factor (BDNF).

### **How can exercise increase the level of BDNF?**

Physical activity can increase brain function like learning and memory, and has an effect on hippocampus via changes in BDNF concentration. BDNF is one member of Neurotrophins -(NTs)- are an important signaling molecules which play a critical role in the growth and development of central and peripheral nervous systems [55, 56]. This molecules contains nerve growth factor (NGF1) [57] and brain derived neurotrophic factor (BDNF) which are synthesized in central and peripheral nervous system, vascular endothelium, immune cells [58-60] as well as neurotrophins 3(NT-3) and neurotrophins 4 and 5 (NT-4/5) [61]. They promote the growth, proliferation, migration and survival of neurons; regulate neurotransmitters like synthesis and secretion and modulate the development of synaptic plasticity. Also they modulate immune cells [62-64].

BDNF is the most abundant neurotrophin in the central nervous system and has major role in neuroplasticity [65-67] in pathology of psychiatric diseases [68]. The concentration in brain BDNF is associated with change in serum BDNF [69]. Pre-pro-BDNF is a precursor of BDNF. Pro-BDNF then is division into mature BDNF [70]. Mature BDNF is connected with two trans-membrane receptors that are located in dendrites. One of them is tropomyosin-related kinase B (TrkB) receptor which dose the majority of the known functions of BDNF and has high-affinity with this neurotrophin. The other receptor is pan neurotrophin p75NTR which interacts with the precursor pro-BDNF [71]. After their contiguity, the intracellular signaling cascades are activated by autophosphorylated tyrosine kinase and N-methyl-D-aspartate (NMDA) receptor currents [67]. When BDNF and TrkB rebounded to each other, three intracellular pathway will be activated: phospholipase C (PLC), phosphatidylinositol 3-kinase (PI3K), and mitogen-activated protein kinase [MAPK, or extracellular signal related kinase (ERK)] [72-74]. Exercise can increase expression of BDNF. But how does it happen?

One possible way that voluntary exercise can increase the level of BDNF is via increasing histamine acetylation and diminish DNA methylation in promoter IV and means increase in BDNF expression and this enhance of BDNF is clear in different region of brain especially hippocampus [9, 21]. Another way that exercise can increase BDNF is via PGC1 $\alpha$ . PGC1 $\alpha$  is produced through exercise in skeletal muscles and make some major beneficial metabolic of physical activity [75]. PGC1 $\alpha$  has an important role in brain that accompanied by neurodegeneration [76, 77]. Voluntary exercise increases the concentration of PGC1 $\alpha$  in different area of brain. It is distinguished that , the PGC1 $\alpha$ - depend myokine, FNDC5, is release from muscles through exercise and cause positive operation of exercise [78, 79] FNDC5 is a glycosylated type I membrane protein and is delivered into the circulation after proteolytic cleavage. Irisin is the secreted form of FNDC5 that contain 112 amino acids [79, 80] and there is positive relation between physical activity and Irisin [81, 82]. Also FNDC5 is expressed in the brain [83-85]. The level of FNDC5 in brain region like hippocampus is increased via endurance exercise. It is observed that PGC-1 $\alpha$  and FNDC5 compose BDNF expression in the brain. The other way that exercise can change the level of BDNF is through norepinephrine levels[86], and IGF-1 measure.they can crossing the blood-brain barrier, have also been discussed as exerciserelated inducers of BDNF [87].



**Fig. 1:** The hippocampal PGC-1 $\alpha$ /FNDC5/ BDNF pathway in exercise [88]

### Exercise and brain neurotransmitter

Exercise can increase the concentration of dopamine and via this way can activate the reward pathway[89-91]. Also exercise can decrease the level of glutamate in striatum [92] forced exercise like running on treadmill can improve the calcium in serum. Calcium can penetrate the blood brain barrier and activate synthesis of dopamine [93]. Physical activitylike force running enhance the concentration of tyrosine hydroxylase that is the rate limiting enzyme in dopamine synthesis [89, 93-96]. Voluntary exercise in rodents is also accompanied bydopaminergic neurons activation in the ventral tegmental area (VTA) [97]. Also distinguished that, voluntary exercise (wheel running) in rats can increase the level of dopamine in nucleus accumbens (NA) [98] and can improve the levels of Fos-B and tyrosine hydroxylase mRNA in the NAc, and decreased gathering of dopamine D2-receptors [99-101]. Chronic high levels of exercise may lead to an upregulation of dopamine D1 receptor-signaling [102-104]. It is probable the reason for euphoria after exercise is due dopamine release. Also exercise can decrease the concentration of glutamate.

Addiction is one of the major problems of societies, and can cause decrease the level of health and active people in countries. Exercise via increasing the rate of self-reliance in young person and also via activating the pathways that increase the euphoria can decrease the tendency of youth to use abuse drug.

### Could exercise decrease the tendency for using drug?

Exercise like abuse drugs can enhance the amount of euphoria [105, 106]. It was distinguished that physical activity decrease drug self-administration [107]. Also voluntary exercise (wheel running) diminished the oral consumption of a liquid amphetamine solution [108]. In other studies have shown running wheel reduce intravenous self-administration of cocaine and decreased responding maintained by methamphetamine [109], it was interesting that, even the physical activity was not exist, the diminish of using drug was continuously happen [110].

Norepinephrine release in the frontal cortexwas decreased during exercise [111]. The norepinephrine is important for both cocaine-primed rein- statement and stress-induced in rodents [112, 113]. The catecholamines, can decrease the amount of glutamate, but promote the reply of this amino acid to drug administration [114]. Changing in glutamate signaling pathway has an important role in mediating drug searching and relapse after chronic drug exposure [115]. Exercise increases the concentration of exogenous opioid peptides in plasma. Opioid plasma can bind with opioid receptors [116-119]. Exercise

through increasing the amount of endogenous opioids can decrease the sensitivity to exogenous opioids [120, 121]. Also physical activity can decrease self-administration of morphine and heroin via changing the central opioid receptor populations. Exercise has effect on cyclic adenosine monophosphate (cAMP)/protein kinase A (PKA) signaling. This signaling mediated cocaine administration upregulates D1 and reinforcing effects of dopamine agonists are certainly correlated with their ability to stimulate cAMP production. When the PKA is active directly, self-administration of cocaine was increased and inhibition of PKA decreases cocaine self-administration and subsequent drug-seeking behavior during reinstatement [122, 123]. The mice which have regular treadmill in daily planned have lower levels of transcripts encoding adenylate cyclase subtypes and activating polypeptides in the striatum relative to controls. Exercise modulate dopamine cAMP-regulated neuronal phosphoprotein [124], A target of PKA that is essential for drug reinforcement [125]. Exercise palliate the positive reinforcing effects of different classes of abuse drugs [9] and may function as an alternative non-drug reinforce that competes with the drug and decrease vulnerability. Miller et al, showed that mice that received both exercise and methamphetamine are less interested in self-administration compare the sedentary rats [126]. Also the mice with running wheel have been reduced the use of alcohol consumption under 2-bottle free access conditions [127]. It has shown wheel running reduced rates of utilization of cocaine self-administration where under non-concurrent conditions [128]. In human study, teens who have regular exercise in the daily schedule are less likely to use cigarettes and illicit drugs than less active groups, and regular exercise from childhood to adulthood reduces the tendency towards smoking and use of illicit drugs like marijuana [131-129, 11, 10]. Exercise be an appropriate substitute for drugs. Because exercise, as well as drug, increases the activity of signaling pathways of dopamine. This increase will reduce damage caused by drug use [9]. Thoren et al, have shown that physical activity and exercise could be remedy for patients with addiction disorder because rhythmic exercise could activate the central opioid systems [132]. Generally, exercise with different way, can act as an efficacious way for treatment of using drugs. Firstly, exercise can decrease the tendency of using drugs, and it was observation in many researches that athlete teenagers have less interest in using drugs. Secondary, physical activity can active the signaling pathways to cause euphoria.

**Addiction and neurocirculation of drug abuse**

Generally, there are three explanations for drug abuse: (1) Forced to search and consumption of drugs (2) Loss of control by limiting drugs, and (3) After drug discontinuation and lack of access to drugs is intense emotional states, like anxiety, dysphoria and irritability [133]. Addiction is now understood as a pathological of natural rewards. The reward center is the mesocorticolimbic system, including the ventral tegmental area, nucleus accumbens, amygdala, and hippocampus [134].

The euphoria through using drug is due to a dopamine surge in the mesolimbic pathways. For example using or injecting Opioids produce a dramatic euphoric. When addictive drugs are injected, they can decrease the thresholds of reward stimulation in brain [135]. All drugs of abuse activate the dopamine system in brain, like mesolimbic, ventral tegmental and ventral striatum area neurons on nucleus accumbens [136-139]. Also the dopamine projections in Ventral tegmental area such as the prefrontal cortex and amygdala are other forebrain areas play a critical role in shaping drug-taking behaviors [140]. And also the central nucleus of the amygdala (CeA) has akey function in the acute reinforcing actions of drugs of abuse [141].

**Table 1:** Drugs and their mechanism

Drugs	Effects in brain	Mechanism
Cocaine and amphetamines	Active the dopaminergic pathways in NA and amygdala and enhance the level of dopamine [142]	Have direct actions on dopamine terminals [142]
Opioids	1) In VTA (ventral tegmentom area) and amygdala with direct or indirect actions through interneurons can active the opioids receptors 2) They can increase the amount of release DA with act on VTA and NA 3) Activate elements independent of the dopamine system [142] 3) Reduce the inhibitory GABA release on dopamine [143] 4) Via increase the level of norepinephrine, play a role in rewarding effects [144]	1) Increase the release of dopamine  2) Has a effects on internurons [142]

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Alcohol	<ol style="list-style-type: none"> <li>1) Has a direct or indirect effect on GABAA (g-aminobutyric acid) in VTA, NA and amygdala</li> <li>2) Enhance the release of dopamine and opioids peptides in VTA, NA and central nucleus of amygdala [142]</li> </ol>	<ol style="list-style-type: none"> <li>1) Activated the GABA receptors</li> <li>2) Increase the release of dopamine</li> </ol>
Nicotine	<ol style="list-style-type: none"> <li>1) Activates nicotinic acetylcholine receptors in the VTA, nucleus accumbens, and amygdala, either directly or indirectly, through actions on interneurons [142]</li> <li>2) Excitatory glutamate transmission in the VTA [145]</li> </ol>	Increase the activity of nicotinic acetylcholine receptors [142]
Cannabinoids	<ol style="list-style-type: none"> <li>1) Active the CB1 receptor in VTA, NA and amygdala</li> <li>2) Increase the release of dopamine in VTA and NA [142]</li> </ol>	<ol style="list-style-type: none"> <li>1) Activated the CB1 receptors</li> <li>2) Increase the release Dopamin with unknown mechanism [142]</li> </ol>

Evidences have shown that two major neurotransmitter that have a critical role in reward pathway are dopamine and peptides of opioid. Also the corticotropin releasing factor, norepinephrine, and dynorphin are the major neurotransmitters in amygdala that is associated with negative reinforcement.

### Addiction and learning and memory

In learning pathway, the dopaminergic cells in ventral tegmental area (VTA) release dopamine into prefrontal cortex (PFC), amygdala and nucleus accumbens. The addictive drugs use these cells to affect the learning pathway [146-148]. It has been observed that, the addicted animals learn better due to glutamatergic projections from PFC to the Nucleus accumbens emerges [149-151]. Addictive drugs operate the release of dopamine in the nucleus accumbens (NAC) [152], but different drugs can increase the level of dopamine in different ways. Addictive drugs can increase the strength of excitatory synapses on dopaminergic neurons in the VTA in rodents [153]. Also addictive drugs can increase the level of dopamine release with different mechanism [137, 147, 154]. And as mentioned earlier, dopamine plays an important role in learning process [146]. Research has shown that addictive drugs can release dopamine every time the drug is used but in normal condition there is a tolerance development of released dopamine in biological. But, in chronic users, this tolerance occurs and increases the dose. Dopamine is an important influence on the synthesis of proteins that cause physiological changes. Further, it was found that dopamine plays a role in gene expression of BDNF. The evidences have shown that normal expression of the dopamine D3 receptor in nucleus accumbens can increase BDNF from dopamine neurons in both during development and in adulthood [155].

On the other hand, when the periods of abstinence of drugs is increased the level of BDNF changes [156-158], the stimulating BDNF receptors in the amygdala, VTA or NAc promotes [159-161], and microinjection of BDNF into the PFC can reduce of drug demand [162]. On the other hand, it was found in additional research that BDNF and TrkB signaling are enhanced in the nucleus accumbens after short and long term of cocaine administration. This increase is not observed in the core region of NAc, VTA and hippocampus [163]. It is interesting that the level of BDNF in the VTA, NA and amygdala, progressively are increased during drug consumption [156]. Also the evidences have shown that chronic exposure to opiates addictive drugs can decrease neurogenesis and alter synaptic transmission in the hippocampus and decrease long-term potentiation (LTP) in hippocampus- a form of synaptic plasticity that be a mechanism for learning and memory [164-167]. On another hand, research showed chronic exposure to morphine increases the level of BDNF protein in the hippocampus and serum in the sedentary morphine-dependent rodents and human [168-171]. Chu, Zuo et al. Found that morphine reduces the amount of BDNF in the VTA, and BDNF levels in ventral tegmental area will increase the morphine withdrawal [172] it was observed that, after long-term withdrawal from self-administered of heroin the expression of BDNF mRNA is enhanced [173].

### CONCLUSION

According to the recent studies, we can conclude that exercise can change the brain BDNF level by cellular and molecular pathways in different areas of the brain. BDNF has a significant role in learning and memory. Exercise also can elevate learning and memory activities. Addiction that is defined as a pathological behavior or repeated use of a substance, forces the addict to use drug or do something by affecting on reward pathway. Evidences suggested that the brain neurotransmitters are released by drugs which effect on learning and memory pathways. Recent studies investigate the effect of drugs on BDNF,

and this review has shown that drugs have different impression on the level of BDNF in various region of brain. Exercise can be considered as a factor for the prevention of addiction. It is mentioned in many articles that when exercise is accessible, the level of self-administration is less than non-exercise group. As well as, Adults who do exercise regularly have a less tendency to use cigarette and illicit drugs. Due to the growing trend of drug abuse in today's society, it is suggested that the exercise should be institutionalized in young people and teenagers.

#### CONFLICT OF INTEREST

There is no conflict of interest

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#### FINANCIAL DISCLOSURE

None

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