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The Effects of High Intensive Interval Training (HIIT) on Brain-Derived Neurotrophic Factor (BDNF) and Cardiovascular Health: A Review

Yüksek Şiddetli İnterval Antrenmanların (HIIT) Beyin Kaynaklı Nörotrofik Faktör (BDNF) ve Kardiyovasküler Sağlık Üzerine Etkileri: Derleme

Serdar BAYRAKDAROĞLU[1], Nuri TOPSAKAL[2], Özgür EKEN[3]

ABSTRACT

High-intensity interval training (HIIT) programs have lately gained popularity because they produce beneficial adaptations for both inactive and athletes, as well as positive health and performance benefits and time efficiency. Therefore, it was purposed to review scientific research results about the effects of HIIT programs on BDNF and cardiovascular health. Although there are research findings suggesting that HIIT may be an effective strategy for promoting elevation of BDNF concentrations, current research seems to be rather limited and inconclusive. It can be thought that exercise intensity is a factor affecting BDNF activation. In healthy people, there seems to be a positive linear relationship between exercise intensity and BDNF levels of acute exercise. However, further experimental studies are needed to elucidate the effect of HIIT on BDNF in humans with metabolic or cardiovascular diseases. However, it can be suggested that high intensity can be an significant achievement factor to design an effective exercise programs and the HIIT methodology has a critical importance for improving cardiovascular function, particularly in healthy individuals. In conclusion, while existing studies show that high-intensity interval training (HIIT) programs can improve cardiovascular health in some populations, further scientific research is needed to determine the efficiency of this strategy in producing physiological adaptation to exercise.

Keywords: High intensity interval training (HIIT), BDNF, Cardiovascular health

ÖZ

Yüksek şiddetli interval antrenman (HIIT) programları son zamanlarda hem sedanterler hem de sporcular açısından pozitif adaptasyonlar sağlaması, sağlık ve performans açısından olumlu katkılar sunması, zamansal açıdan verim sağlamasından dolayı popülaritesi giderek artmıştır. Bu noktadan hareketle araştırmada HIIT metadolojisinin BDNF ve kardiyovasküler sağlık üzerindeki etkileri hakkında bilimsel araştırma sonuçlarının derlenmesi amaçlanmıştır. HIIT'in BDNF seviyesini arttırmak için etkili bir stratejisi olabileceğini gösteren araştırma sonuçları olmasına rağmen, mevcut araştırmaların oldukça sınırlı ve yetersiz olduğu görülmektedir. Egzersiz yoğunluğunun BDNF aktivasyonunu etkileyen bir unsur olduğu düşünülebilir. Sağlıklı insanlarda, egzersiz şiddeti ile BDNF seviyeleri arasında doğrusal bir ilişki olduğu görülmektedir. Bununla birlikte, metabolik veya kardiyovasküler hastalarda HIIT'in BDNF üzerindeki etkisini açıklamak için daha fazla deneysel çalışmaya ihtiyaç duyulmaktadır. Yüksek egzersiz şiddetlerinin, etkili egzersiz programları oluşturmak için önemli bir faktör olabileceği ve HIIT programlarının özellikle sağlıklı bireylerde kardiovasküler fonksiyonun iyileştirilmesi için kritik bir öneme sahip olduğu söylenebilir. Sonuç olarak, güncel araştırmalar, özel popülasyonlarda uygulanan HIIT programlarının kardiyovasküler sağlık üzerinde olumlu etkilerini rapor etmesine rağmen, bu yöntemin egzersize fizyolojik adaptasyonu sağlamadaki etkinliğini belirlemek için daha fazla bilimsel araştırma sonuçlarına ihtiyaç duyulduğu ifade edilebilir.

Anahtar Kelimeler: Yüksek şiddetli interval antrenmanı (HIIT), BDNF, Kardiyovasküler sağlık

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[1] Dr. Serdar BAYRAKDAROĞLU, Movement and Training Science, Gumushane University School of Physical Education and Sports, Department of Coaching Education, bayrakdaroglu85@gmail.com, ORCID: 0000-0002-2166-6675
[2] Assoc. Dr. Nuri TOPSAKAL, Movement and Training Science, Duzce University Faculty of Sports Sciences, topsakal.nuri@gmail.com, ORCID: 0000-0003-1583-107X
[3] Dr. Özgür EKEN, Movement and Training Science, Inonu University/Faculty of Sports Sciences, ozgur.eken@inonu.edu.tr, ORCID: 0000-0002-5488-3158

İletişim / Corresponding Author: Serdar BAYRAKDAROĞLU
e-posta/e-mail: bayrakdaroglu85@gmail.com

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INTRODUCTION

In recent years, some changes have occurred in individuals' daily life behaviors, movements, eating habits and quality of life. As a result of these processes, the incidence of some systemic diseases has increased with inactivity. For this reason, physical exercise has taken the lead among the most important elements for the protection and development of health, and moreover, it has become an important part of life for human beings. It has been reported by scientists that physical exercise improves many parameters related to physical fitness, physical performance and health, and in addition to its physical benefits, it also has psychological positive effects when applied regularly in a planned, structured and repetitive manner. However, some aspects of how and through which physiological mechanisms this effect takes place still remain unclear.[1,2] For this reason, exercise scientists and trainers are constantly researching and trying to develop new exercise methods to improve the performance of their athletes and the health-related parameters of sedentary people. Parallel to this situation, different exercise models have been introduced and a wide variety has been achieved, especially in recent years. In this context, High Intensive Interval Training (HIIT) programs have increased their popularity because they provide positive adaptation for both sedentary and athletes, provide positive contributions in terms of health and performance, take less time and are more efficient compared to traditional aerobic exercise programs. Moreover, HIIT has always been at the forefront of the best fitness trends worldwide in the annual current surveys conducted by the American College of Sports Medicine.[3,4]

In the literature, it is described as a negative situation that HIIT exercises are repeated with the same action, that the exercise becomes routine, that it is excessively tiring, and that all of these create a negative feeling that reduces the enjoyment of the exercise by the participants.[5,6,7] There are studies concluding that these effects increase anxiety, anger, depression and may cause negative mood in exercise participants after HIIT exercises.[8,9] In addition, in cases where exercise participants have pathological disorders, a careful evaluation should be made before performing HIIT exercises, and care should be taken to avoid the negative effects of programming and control on health. When HIIT exercises are performed on healthy exercise participants, a correct periodization should be prepared, and care should be taken to avoid the negative consequences of overload on the cardiovascular, musculoskeletal, endocrine and immune systems.[10,11]

Possible physiological mechanisms affected by HIIT methodology are among the topics discussed and researched in recent years. In particular, it has been shown in many studies in the literature that it affects PGC-1α (Peroxisome proliferator-activated receptor gamma coactivator 1-alpha) receptor activation, which is the main regulator of genetic codes in mitochondria.[3,12,13,14] Activation of PGC-1α increases ATP production. At the same time, with the increase in PGC-1α activation, the effect of MRNA in mitochondria also increases, thus accelerating the mitochondrial adaptation period. In this context, it is known that PGC-1α receptor activation is directly related to exercise intensity. HIIT stimulates this receptor more than endurance training. With HIIT programs, increasing PGC-1α activation in mitochondria provides more energy production and improves the maximal activity level by increasing skeletal muscle oxidation capacity.[3,15] In this context, it is reported that HIIT applied for 6 weeks increases PGC-1α activation by 100%, while HIIT applied for 2 weeks increases it by 25%. In addition, with the increase of PGC-1α receptor activity, the effect of MRNA in mitochondria also increases, thus accelerating the mitochondrial adaptation period. In addition, HIIT affects kinases by accelerating protein kinase and p38 mitogen activation, thus providing phosphorylation by binding phosphate from the ATP molecule to the protein molecule. In addition, it has been

reported that HIIT application improves oxidative capacity, antioxidant defense and endothelial functions.[13,15]

One of the topics discussed recently in the literature is the mechanisms of action of HIIT exercises on BDF and cardiovascular health parameters. Studies in the literature show that a high BDNF response is observed with an increase in lactate levels due to exercise and the importance of high exercise intensities.[16,17] In addition, high exercise intensities are recommended to increase cardiovascular health.[18] Although HIIT has beneficial effects on various cognitive functions[19,20] and motor learning,[21] there is no complete consensus on this issue. In this context, this issue is considered controversial in the literature and it is recommended to conduct scientific evidence-based studies by considering the training status, nutritional status, age variable, general health level and acute training variables of the exercise participant.

The aim of the research in this review is to present information based on scientific research results about the effects of HIIT methodology on BDNF and cardiovascular health. In this context, the data obtained from the researches available on the subject in the literature were used and scientific research findings were used. "Pubmed", "Scholar Google", "Ovid", "Sciencedirect", "Wiley Interscience", "Web of Science" databases were used to search the researches carried out in the literature on the subject without any year limit. In the research, as inclusion criteria; Randomized, randomized controlled, experimental, reviews, and case report studies were used to explain possible BDNF and Cardiovascular health response mechanisms after acute and chronic HIIT training. This review was carried out using results from original studies (studies with ethical approval) previously published in the literature. Therefore, this study is free of ethical approval.

What is the High İntensive İnterval Training (HIIT) ?

HIIT is an exercise model that has been widely preferred by both coaches and exercise scientists recently. HIIT is used for loads at maximal (peak) oxygen uptake level with relatively short rest intervals. Loading times can last from 3-5 seconds to a few minutes, followed by several minutes of rest intervals.[3,22] Despite the short duration of HIIT and the shortness of the total exercise time, it is thought that HIIT has physiologically similar efficacy compared to continuous training at moderate intensity.[23] This is due to HIIT workouts burn more calories than conventional workouts particularly following training. In this context, due to the nature of HIIT exercises, EPOC tends to be higher overall, adding approximately 6 to 15% more calories to overall exercise energy expenditure. HIIT programs can be carried out in all exercise styles, including cycling, walking, swimming, water training, elliptical cross-training, and many group exercise classes.[24,25] Studies in the literature have shown that HIIT can enhance aerobic and anaerobic fitness, blood pressure, cardiovascular health, insulin sensitivity (helps exercise muscles utilize glucose for energy more easily), thyroid metabolism,[26] cholesterol profiles, muscle mass. It is thought to have positive effects on the preservation and reduction of body weight.[3,27]

What is the Brain-Derived Neurotrophic Factor?

BDNF was first demonstrated in 1982 as the second member of the neurotrophin family, noted to contribute to the survival of a subpopulation of dorsal root ganglion neurons. Later, it was isolated from pig brain by Yves-Alain Barde and Hans Thoenen in 1989 and its biochemical structure was revealed.[28,29,30] It is known as the gene responsible for producing a protein named brain-derived neurotrophic factor, which is found in the brain and spinal cord. However, BDNF is highly distributed in the mammalian brain. However, BDNF is one of the most studied neurotrophins in research. This protein plays a major role in the growth, maturation (differentiation) and repair of brain cells (neurons). Its prominent functions

include neurogenesis, neuroprotection, control of neuronal and glial improvement, modulation of both short- and long-term synaptic transmission, which is important for cognition and memory, but its deficiency is thought to negatively affect these activities.[30,31]

It is reported that BDNF have effects on specific neurons in the central and peripheral nervous system, helping to stimulate the survival of existing neurons, growth and differentiation of new neurons and synapses. There is also evidence that nociceptive sensory neurons migrate to both their peripheral and central terminals.[32,33] BDNF, which is of great importance for learning and memory development, is active in the hippocampus, cortex and forebrain in the brain. BDNF is also expressed in motor neurons and skeletal muscle.[34,35]

Does HIIT Affect Brain Neurotrophic Factor?

Although circulating BDNF activation in response to physical exercise has recently been investigated by exercise and health scientists in the literature, the underlying mechanisms of action are still not fully understood.[36] However, increased synthesis and release of BDNF during exercise is thought to modulate peripheral energy metabolism, particularly as a part of the hypothalamic response.[37]

Although findings from animal studies provide strong evidence that both acute and chronic exercise lead to increased BDNF concentrations in the brain, limited human studies show chronic exercise-induced increases in hippocampal, basal ganglia, and prefrontal cortex volumes. In addition, studies in the literature have reported that exercise triggers acute increases in serum or plasma BDNF concentrations in humans.[20,38,39] In particular, exercise intensity is thought to be a factor affecting BDNF activation. In this context, Ferris et al. (2007) reported a significant correlation between BDNF serum concentrations and blood lactate levels,[20] while Winter et al. (2007), on the other hand, reported that 40 minutes of moderate-intensity work with blood lactate concentrations <2mmol did not have a significant effect on serum BDNF concentrations, and sprints up to 2x3 minutes of exhaustion increased BDNF concentrations.[39] In healthy population, there seems to be a lineary connection between exercise intensity and the positive short-term influence of acute exercise on BDNF levels (BDNF levels mostly found following high intensity workout protocols).4[0]

Effects in Animal Studies

In recent years, different perspectives have emerged on the possible mechanisms and possible effects of the HIIT philosophy. In particular, the acute or chronic effects of HIIT on BDNF parameters are among the topics discussed by researchers. Although potential effects of HIIT on brain function have been reported, the current evidence is rather insufficient. In this context, in studies carried out on animals; Afzalpour et al. (2015) showed that the modalities of HIIT (95-100% VO2max) and continuous exercise (80% VO2max) applied for 6 weeks on rats were determined by brain-derived neurotrophic factor (BDNF), glial cell line-derived neurotrophic factor (GDNF), hydrogen peroxide (H_2O_2) and the effects on tumor necrosis factor alpha (TNF-a) were compared. As a result, both HIIT and continuous exercise showed increases in H_2O_2 level and TNF-a concentration in the brain, and it was reported that BDNF and GDNF concentrations increased significantly more in HIIT condition than in continuous exercise.[41]

In addition, it has been shown that H2O2 and TNF-a concentration are positively correlated with both BDNF and GDNF concentrations. In another study, Almeida et al., (2013) revealed that animals who did intensive physical activity had higher synthesis of BDNF than those who did not.[42]

In study of Freitas et al., (2018), there was a decline in oxidative damage and an increase in enzymatic, non-enymatic activity, cytokine levels and BDNF levels in male Wistar rats.

As a result, six weeks of HIIT has been shown to have a positive effect on reducing hippocampal oxidative stress by reducing lipoperoxidation and inflammatory markers, as well as increasing antioxidant defenses and BDNF content.[43]

Effects in Human Studies

In human studies, Slusher et al. (2018) examined the effect of HIIT on plasma and serum BDNF response. In a controlled study of thirteen healthy male volunteers, it was reported that a single low-volume HIIT protocol performed 2 weeks apart significantly increased prefrontal cortex-dependent executive function and increased serum BDNF levels.[44] Saucedo Marquez et al. (2015), on the other hand, compared the continuous exercise protocol at 70% of VO2max and the HIIT protocol at 90% of VO2max on healthy people in terms of the potential to affect BDNF levels (both protocols lasted 20 minutes). Although similar BDNF kinetics were observed in both protocols and maximum BDNF concentrations were reached towards the end of the program, higher serum BDNF activation was observed in the HIIT protocol compared to continuous exercise. At the same time, researchers reported that HIIT modality could be an effective strategy for raising BDNF levels and potentially improving brain health.[40] In this regard, the efficiency of HIIT modalities is attributed to the fact that they are conducted over an individual's aerobic threshold and are believed to result in considerable blood lactate accumulation.[23] Researching the effect of a short-term (4 weeks, 3 days a week) HIIT protocol on serum BDNF concentrations in healthy young women, Rentería et al. (2020) conducted a study on 17 female volunteers with a mean age of 22, a mean body mass index of 24.2, and a mean body fat percentage of 25.8. in the study, they randomly divided the volunteers into the control (n=8) and HIIT groups (n=9). Researchers have shown that 12 sessions of HIIT increased circulating BDNF concentrations in healthy young women, although there was no change in physical performance or fat percentage.[45]

Cabral et al. (2016) compared the effects of HIIT modalities of the same intensity but different volumes on BDNF responses on 10 physically active male volunteers. They reported that BDNF level increased immediately after exercise in both protocols and BDNF concentrations returned to baseline levels after 60 minutes. In a study examining the long-term effects of HIIT on serum BDNF levels, participants were subjected to a three-months whole body exercises and the protocol was effective in the increase of serum BDNF concentrations.[46] In addition, the output source of BDNF was not clear.[47] In a controlled study examining the effects of HIIT (10 × (60s VO_2max 90%) and continuous exercise (22 minutes, VO_2max 70%)) protocols on 10 volunteers with type 1 diabetes, it was reported that HIIT and continuous exercise increased serum BDNF levels. It has been reported that it produces a dose response.[48] However, a recent study performed in a protocol of HIIT, resistance training, or a combination of both, examined neurotrophic factor responses in a group of 18-30 year old physically inactive overweight adults. Although acute resistance training and combined exercise have been shown to increase neurotrophic factors in physically inactive overweight adults, HIIT protocol has not been shown to produce a good stimulus to increase peripheral BDNF.[49] Giacomet et al., (2019) evaluated the effect of a single HIIT session on creatine kinase (CK), BDNF, and global histone H3 and H4 acetylation levels in obese postmenopausal women. In conclusion, they reported that a single HIIT session is not an effective strategy to modulate histone acetylation status, CK and BDNF levels in postmenopausal obese women. However, one of the paradoxical issues is the kinetics of exercise-induced BDNF changes during exercise.[50] In this context, some existing data obtained from studies conducted in the literature report that values of BDNF have reached to maximum levels following nearly

10-20 minutes of moderate or intense exercise and then show a slight decrease.[40]

HIIT: Cardiovascular Health

The human cardiovascular system is one of the topics that have been researched by scientists for many years. Today, researches are carried out to understand the cardiovascular system in order to protect health and maintain it throughout life, and the mechanisms of action of the cellular and molecular function of this system are tried to be brought to light. Because this system is part of a larger system of organs and tissues. At the same time, the cardiovascular system undertakes the task of regulating blood distribution in processes such as thermoregulation, digestion, metabolic processes and exercise adaptation. For this reason, cardiovascular health is one of the most important issues in order to increase the quality of life. During exercise, many interrelated cardiovascular changes (heart rate, stroke volume, cardiac output, blood pressure, blood flow) can occur in the human body.[51] In this context, American Heart Association (AHA) and American College of Sports Medicine (ACSM) recommend that total of 150 minutes of moderate-to-moderate-intensity aerobic exercise for adults, at least 30 minutes in 5 times a week, for general cardiovascular health. The other recommendation is that combination of vigorous exercise or moderate-intensity aerobic exercise for a total of 75 minutes, at least 25 minutes 3 times a week.[52] Although the benefits of regular physical exercise in terms of cardiovascular health are known in the studies carried out in the literature, one of the issues that has been discussed in recent years is the mechanism of action of HIIT methodologies.

Today, HIIT with its various forms is considered as one of the most effective methods that improves the cardiovascular system, metabolic functions and thus the physical performance of athletes. In this context, it has been shown that spending a few minutes (at 90% VO_2max) is the best stimulant for athletes' maximal cardiovascular system and peripheral adaptation.[3] HIIT not only improves physiological parameters and performance, but also attracts the attention of sports science by characterizing the training protocol that includes keeping the performance of athletes above 90% of VO2max for a long time.[23] It is accepted by exercise scientists that exercise intensity should be close to VO2max in order to strengthen large motor units and increase cardiac output. In this context, HIIT is reported to be a good alternative to traditional endurance training for healthy exercise participants.[3] Examining the effects of short-term HIIT training on cardiovascular function and cardiovascular fitness on active athletes, Astorino et al. (2012) reported that the HIIT training model significantly improved cardiovascular function and VO2max levels.[53] On the other hand, Gormley et al., (2008) reported that exercise intensity affects cardiovascular health in healthy young populations, and higher exercise intensities are more effective in improving cardiovascular functions.[54] However, one of the issues that has been discussed recently is the mechanisms of action of HIIT modalities on special populations with cardiovascular disease. In this regard, results of studies in individuals who had problems with heart and coronary artery show that HIIT is related with greater enhancement in exercise tolerance and compliance, heart rate control, VO^{2max}, cardiovascular and muscle function compared with moderate-intensity continuous exercise.[55,56] Moreover, studies in the literature have shown that HIIT programs improve VO^{2max}, ventilatory threshold, cardiovascular function and motor performance in stroke individuals.[57] In addition, systematic reviews and meta-analysis studies in the literature support that HIIT is superior to traditional moderate-intensity continuous exercise to improve VO^{2max} in both healthy young and middle-aged individuals and people with cardiometabolic diseases.[58,59] Fisher et al., (2015) compared the effects of 6 weeks of HIIT and continuous moderate-intensity training (MICT) to improve body

composition, insulin sensitivity, blood pressure, blood lipids, and cardiovascular fitness in sedentary obese young men. As a result of the study, it was reported that while both exercise groups led to similar improvements in cardiometabolic risk factor, MICT led to a greater improvement in overall cardiovascular fitness.[60]

However, despite all these evaluations and important research results, one of the issues frequently discussed by researchers is the question of how safe HIIT programs are on special populations. In this context, the largest available dataset evaluating the safety of HIIT in the studies conducted in the literature was obtained from the study conducted by Rognmo et al., (2012) on 4846 cardiac rehabilitation patients. Before participating in the study, all volunteers underwent a full medical screening and cardiopulmonary exercise test. While 2 non-fatal cardiac deaths were detected in 46,364 hours of supervised HIIT, 1 fatal cardiac arrest was detected in 129,456 hours of supervised MICT.[61] In this context, he emphasizes that the risk of both approaches is low. However, the risk of sudden cardiac death and acute myocardial infarction has been reported to increase after vigorous activity in susceptible individuals, including structural heart disease and its congenital complications.[62] Therefore, it is important to pay attention to the guidelines of the American College of Sports Medicine and the American Heart Association for identifying high-risk patients and performing pre-exercise screening in such individuals.[62,63] Therefore, attention should be paid to the programming of these exercise modalities. In addition, coaches must be qualified and experienced regarding this exercise method. Moreover, it is expected that the exercise fitness level of the individuals to whom these exercise modalities will be applied will be good. It is a common view that especially inexperienced individuals' or newcomers should not exercise at these limits. It is another reality on which there is consensus that experienced or professional people would be more suitable for the HIIT modality. For these reasons, training participation prerequisites must be determined before HIIT is programmed.[64]

CONCLUSION AND RECOMMENDATIONS

Recent development in exercise physiology studies have significantly contributed to knowledge related to cellular and molecular mechanisms underlying exercise adaptation. In this context, we can say that HIIT modalities applied in healthy individuals may be an important factor for the improvement of cardiovascular functions. On the other hand, more scientific evidence-based studies are needed in terms of whether HIIT modalities are safe in special populations and to develop optimal exercise responses and adaptations. However, there is a noticeable lack of a standardized and consistent approach to prescribing HIIT protocols. In healthy people, exercise intensity stands out as a factor affecting acute BDNF activation. HIIT may induce elevations in BDNF concentrations, but more research is needed before we can say that it may be an effective strategy. However, there is no complete consensus for the influence of HIIT on BDNF in individuals with metabolic and heart diseases. More scientific evidence, on the other hand, is required to explain the effect of high-intensity interval training (HIIT) on cardiovascular health and BDNF levels.

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