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View & Review

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Exercise induction at expression immediate early gene (c-Fos, ARC, EGR-1) in the hippocampus: a systematic review

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ABSTRACT. The immediate early gene exhibits activation markers in the nervous system consisting of ARC, EGR-1, and c-Fos and is related to synaptic plasticity, especially in the hippocampus. Immediate early gene expression is affected by physical exercise, which induces direct ARC, EGR-1, and c-Fos expression. **Objective:** To assess the impact of exercise, we conducted a literature study to determine the expression levels of immediate early genes (ARC, c-Fos, and EGR-1). **Methods:** The databases accessed for online literature included PubMed-Medline, Scopus, and ScienceDirect. The original English articles were selected using the following keywords in the title: (Exercise OR physical activity) AND (c-Fos) AND (Hippocampus), (Exercise OR physical activity) AND (ARC) AND (Hippocampus), (Exercise OR physical activity) AND (EGR-1 OR zif268) AND (Hippocampus). **Results:** Physical exercise can affect the expression of EGR-1, c-Fos, and ARC in the hippocampus, an important part of the brain involved in learning and memory. High-intensity physical exercise can increase c-Fos expression, indicating neural activation. Furthermore, the expression of the ARC gene also increases due to physical exercise. ARC is a gene that plays a role in synaptic plasticity and regulation of learning and memory, changes in synaptic structure and increased synaptic connections, while EGR-1 also plays a role in synaptic plasticity, a genetic change that affects learning and memory. Overall, exercise or regular physical exercise can increase the expression of ARC, c-Fos, and EGR-1 in the hippocampus. This reflects the changes in neuroplasticity and synaptic plasticity that occur in response to physical activity. These changes can improve cognitive function, learning, and memory. **Conclusion:** c-Fos, EGR-1, and ARC expression increases in hippocampal neurons after exercise, enhancing synaptic plasticity and neurogenesis associated with learning and memory.

Keywords: Genes, c-Fos; Hippocampus; Neurons; Exercise.

Indução de exercício físico na expressão do gene precoce imediato (c-Fos, ARC, EGR-1) no hipocampo: uma revisão sistemática

RESUMO. O gene precoce imediato (GPI) exibe marcadores de ativação no sistema nervoso constituídos por ARC, EGR-1 e c-Fos e está relacionado à plasticidade sináptica, especialmente no hipocampo. A expressão do GPI é afetada pelo exercício físico, que induz a expressão direta de ARC, EGR-1 e c-Fos. **Objetivo:** Para avaliar o impacto do exercício físico, realizamos um estudo de literatura para determinar os níveis de expressão dos GPIs (ARC, c-Fos e EGR-1). **Métodos:** A base de dados utiliza literatura *on-line*, PubMed-Medline, Scopus e ScienceDirect. O artigo original em inglês usa as seguintes palavras-chave em seu título: (Exercise) AND (c-Fos) AND (Hippocampus), (Exercise) AND (ARC) AND (Hippocampus), (Exercise) AND (EGR-1) AND (Hippocampus). **Resultados:** O exercício físico pode afetar a expressão de EGR-1, c-fos e ARC no hipocampo, uma parte importante do cérebro envolvida na aprendizagem e na memória. O exercício físico aumenta a expressão do gene c-Fos; sua alta intensidade pode aumentar a expressão de c-Fos, indicando ativação neural. Além disso, a expressão do gene ARC aumentou devido ao exercício físico, onde ARC é um gene que desempenha um papel na plasticidade sináptica e na regulação da aprendizagem e da memória, nas mudanças na estrutura sináptica e no aumento das conexões sinápticas, enquanto o EGR-1 também desempenha um papel na plasticidade sináptica, uma mudança genética que afeta o aprendizado e a memória. De maneira geral, o exercício físico regular pode aumentar a expressão de ARC, c-fos e EGR-1 no hipocampo. Isso reflete as mudanças na neuroplasticidade e na plasticidade sináptica que ocorrem em resposta à atividade física. Essas mudanças podem melhorar a função cognitiva, o aprendizado e a memória. **Conclusão:** A expressão de c-Fos, EGR-1 e ARC aumenta após o exercício físico nos neurônios do hipocampo, para aumentar a plasticidade sináptica, a neurogênese associada ao aprendizado e à memória.

Palavras-chave: Genes fos; Hipocampo; Neurônios; Exercício Físico.

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INTRODUCTION

The group of genes that are activated by neurons is known as immediate early genes (IEG)[1]. IEG is essential in brain function, particularly in the synaptic process. IEG neurons are regulated by cellular and synaptic developmental responses[2]. The expression of c-Fos, ARC, and early growth response 1 (EGR-1)/zif268 represents subsets of IEG genes. These genes are rapidly and selectively controlled in hippocampal learning and memory[3].

Numerous studies explored neural IEG[4]. One extensively studied gene is the cAMP-responsive element-binding protein (CREB), which plays a crucial role in regulating synaptic development and plasticity[5]. IEG expression is influenced by nerve stimulation; for instance, EGR-1 messenger RiboNucleic Acid (mRNA) depends on N-methyl-D-aspartate (NMDA) glutamate receptors, while c-Fos is independent of nerve stimulation[6,7]. As part of the IEG family, ARC is an effector involved in neural signaling pathways, not a transcription factor. However, the ARC gene is transcribed in response to neuronal activity and synaptic activation of neuron dendrites[8,9].

Several IEGs play a role in encoding transcription factors and transiently enhancing transcription in the rat dentate gyrus following afferent stimulation induced by long-term potentiation (LTP) synaptic plasticity or persistent and long-term potential dependent on the activity of associative memory mechanisms. Among these genes, EGR-1/zif268 is most explicitly linked to LTP because it is induced in all LTP-triggering situations and shows a very high correlation with LTP duration[8,10].

This review aims to elucidate the role of IEG in synaptic plasticity in exercise-induced learning and memory. While many other review articles have discussed IEG in synaptic plasticity, none have specifically delved into the role of exercise-induced IEG genes in synaptic plasticity.

METHODS

We conducted a comprehensive search of online literature databases, including Scopus, PubMed-Medline, and ScienceDirect. The original articles in English were selected using the following keywords in the title: (Exercise OR physical activity) AND (c-Fos) AND (Hippocampus), (Exercise OR physical activity) AND (ARC) AND (Hippocampus), (Exercise OR physical activity) AND (EGR-1 OR zif268) AND (Hippocampus) between 2013 and 2023. Our analysis was limited to experimental studies with exercise interventions, and we included articles in English published between 1987 and 2022 (Figure 1).

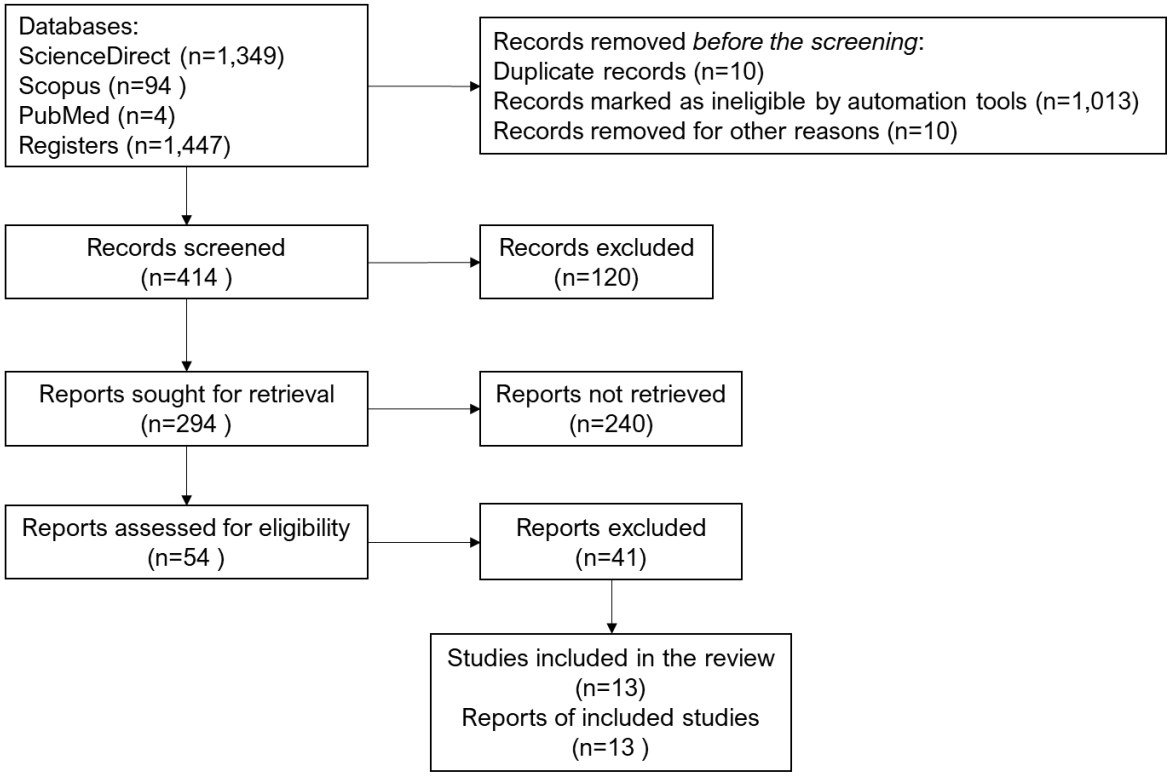

Figure 1. Flowchart of the process of selecting research studies that have been identified and elected based on criteria, research processes, and databases.

Studies in animals that involved exercise interventions and included neurocognitive impairment were considered. However, we excluded systematic reviews, literature articles, and simplified and expanded abstracts published in proceedings and book chapters. Studies related to neurodegenerative diseases, such as Huntington's disease and diabetes mellitus, were also excluded.

RESULTS

A total of 13 articles were selected for the systematic review whose authorship, year of publication, study population, techniques used, and prominent results are shown in Table 1[11-23].

Outcomes

C-Fos, ARC, and EGR-1/zif268 are induced in neurons during neural activity in the hippocampus, including Morris' water maze[24-27]. Physical activity upregulates neurotrophins and neuropeptides[28-30] in long-term hippocampal potentiation (LTP)[31]. Molteni et al. (2002) showed in research that physical exercise increases hippocampal gene expression, including IEGs, associated with neuronal plasticity[32] (Figure 2).

c-Fos expression during exercise

c-Fos is one of the first neuronal transcription genes whose induction is activity-dependent[33] due to cAMP and Ca2+ stimulation by activating the CREB complex[34]. Increased c-Fos expression is an indicator of neural activation, as demonstrated by behavioral training in learning[35], cognitive performance[36,37], and memory formation[38].

Physical exercise induces c-Fos expression in the rat hippocampal central nervous system, contributing to neuroplasticity[35,39], increased neural activity[40], and spatial memory coding[41]. c-Fos expression also plays a role in autonomic and somatomotor control and extends to other parts of the brain[42]. Additio ally, physical exercise increases the c-Fos expression through serum insulin-like growth factor-I (IGF-I) as a neuroprotective factor[43].

Previous studies showed that physical exercise can improve cognitive function by increasing hippocampal neurogenesis[44]. This is supported by evidence from voluntary wheel running exercise, which maintains a stable level of neurogenesis through increased progenitor cell differentiation, mediated by elevated c-Fos levels in the dentate gyrus of rats[45]. Alongside c-Fos, the expression of EGR-1/zif268 and ARC also increases, further promoting neurogenesis activity in the hippocampal granule cell layer[46]. Voluntary running exercise induction also boosts c-Fos expression through Akt phosphorylation in the female rat hippocampus, enhancing adult hippocampal neurogenesis for cell survival, even in rats with Huntington's disease[19]. The expression of c-Fos also increases after treadmill exercise induction, influencing learning and spatial memory[18]. Cold water swimming is associated with increased activation of hippocampal interneurons and a higher number of new neurons in the dentate gyrus[16].

Grinspun et al. research in 2019[47] explained that running wheel exercise improves memory, as evaluated by increased c-Fos immunoreactivity in the tuberomammillary nucleus (TMN). Similarly, treadmill exercise is shown to benefit several neurodegenerative diseases, such as Alzheimer's, by increasing c-Fos expression in the hippocampus in mice after streptozotocin (STZ) injection, reducing long-term memory deficits[48]. In rats with diabetes induced by STZ injection, subsequent treadmill exercise can enhance neuroplasticity and spatial memory by upregulating the expression of the c-Fos nerve gene in the hippocampus[49]. Increased c-Fos expression resulting from physical exercise and therapy aims to boost neural activity, learning, and memory, even in children born to alcoholic mothers during pregnancy, thus countering the effects of alcohol poisoning on postpartum mothers and their babies[50]. Swimming exercise has been found to mitigate isoflurane-induced memory impairment by increasing the expression of c-Fos, a CREB-binding protein (CBP), which elevates hippocampal histone acetylation and activates more neuron cells during memory formation, ultimately improving memory impairment[20].

Exercise intensity plays a significant role in c-Fos expression. High-intensity treadmill exercise increases c-Fos expression and brain-derived neurotrophic factor (BDNF) levels in the hippocampus, thereby enhancing memory through heightened neuroplasticity in both the hippocampus and prefrontal cortex[21]. Foley et al. study also demonstrated that the induction of c-Fos mRNA expression at high intensities significantly increases c-Fos mRNA activation in the hippocampus, affecting the pattern of potential brain activation compared to low-intensity exercise[51]. Low-intensity acute and long-term treadmill exercise, performed at a speed of 10 m/min over four weeks, induces c-Fos expression by increasing the density of c-Fos+ cells in various brain regions, including the striatum, primary somatosensory and secondary motor cortex, hippocampal subregion, nucleus hypothalamus, and lateral periaqueductal grey. This positive correlation with BDNF expression suggests that long-term exercise has

Table 1. Bibliographic sources identified, type of exercise, technique used, sample, intervention, and outcomes.

No	Author	Animal population	Type of exercise	Techniques used	Results	Importance
1	Sable et al.[11]	Long-Evans Rat (n=28), Two groups (Exercise, Sedentary) DF-Exercise (n=7) DF-Sedentary (n=7) WD-Exercise (n=7) WD-Sedentary (n=7)	Treadmill: 25 m/min, three times/week for 30 min, six weeks	Tissue extraction and Western blotting	↑Protein BDNF, ARC, P-STAT3 in hippocampal	Exercise on Daniel Fast (DF) rats on spatial and neuroprotective working memory (WM) is more effective than on rats fed with the Western diet (WD)
2	O'Leary et al.[12]	Male Sprague Dawley Rat; Adult (8 weeks-old) and adolescent (4 weeks-old). n=41 (adolescent=20, adult=21) Two groups (Exercise) and (Sedentary control)	Running wheel Open field arena, diameter (90 cm) for seven weeks. Adult running; 3.96 km/day Adolescence running 3.43 km/day	qRT-PCR	↑Ekspresi mRNA ARC, Synaptophysin, BDNF, PSD-95, CREB, TLX, and DCX	Exercise initiated by adolescent rats (4 weeks) can increase mRNA expression as a marker of neural plasticity in the Hippocampus, whereas Exercise in adults does not increase gene expression. However, synaptophysin gene expression in the amygdala increased in adult rats (aged 8 weeks).
3	Sun et al.[13]	Sprague Dawley Rat; N=40 Pregnant Rat Disruptor di-(2-ethylhexyl)-phthalate (DEHP), Postnatal (days 22–56) Two groups (Sedentary, Exercise), Postnatal (days 57–65) (open field test, test, Morris Water Maze).	Treadmill. 8 m/min, 30 min/day, seven days/week for four weeks	Western Blott Ellisa	↑BDNF, NMDAR, ARC, and synaptophysin Protein Expression at Hippocampus.	Exercise on rats exposed to Disruptor di-(2-ethylhexyl)-phthalate (DEHP) postnatal days 22–56 and days 57–65 can restore learning and memory disorders.
4	Tsuchida et al.[14]	Adult male C57BL/6J Mice (4 weeks-old) n=56. At 8 weeks of age, mice; Two groups: Treadmill (n=16) and Rotarod (n=40).	Treadmill (15 m/min (T15) 30 min/day and Rotarod 30 rpm (R30)); diameter of the rod 3.2 cm for five days.	Immunohistochemistry	↑Protein c-Fos.	At an exercise intensity of 15 m/min (T15), it is more effective in increasing hippocampal nerve activation than in rotarod exercise at 30 rpm (R30).
5	Meireles et al.[15]	Male Wistar Rat (n=76); aged 2 and 22 months. Divided into five groups (Sedentary, Aerobic, Acrobatic, Resistance, and Combined)	Treadmill; Low intensity 5 m/min. Resistance training climbing (height 1 m, inclination of 85°) Acrobatic horizontal ladder (100 cm in diameter, 3 cm spaced rungs) Combined exercise modalities; 20-min exercise sessions, three times a week on alternate days, for 12 weeks	Chip	↑mRNA Promoter BDNF, c-Fos, and DNA methyltransferase 3a (Dnmt3a)	Exercise starting at the age of 22 months (aging) has an impact on cognitive decline. Resistance, acrobatic, aerobic, and combined modalities were able to enhance epigenetic (H3K9ac, H3K4me3, H4K8ac) and repressive (H3K9me2) marker mechanisms and aversive memory performance in aged mice
6	Schoenfeld et al.[16]	Adult male C57BL/6 Mice (n=24) (6 weeks of age) Divided in two groups (Exercise=12 and Sedentary=12)	Running wheel (swimming) 5 min, six weeks	Immunohistochemistry	Exercise ↑ protein c-Fos, ARC	In central dentate gyrus, exercise increased the number of new neurons and reduced anxiety behavior. In contrast, in the dorsal dentate gyrus, sedentary and exercised rats showed increased gene expression (c-Fos, ARC). (Interventioh rats experiencing stress while swimming in cold water

Continue...

Table 1. Continuation.

No	Author	Animal population	Type of exercise	Techniques used	Results	Importance
7	Keloglan et al.[17]	Male Wistar Rat; 3 weeks-old; Postnatal days (PNDs) 21–34. n=32 Control (C) n=8; Social Isolation (SI) n=8; Exercised (E) n=8; Social isolation + Exercise (SE) n=8.	Treadmill: direct current shock (0.1–0.15 mA), 20-60 min/days, five days per week, four weeks	RT-PCR	Exercise ↑NMDAR, mRNA Cdk5r, ASCL1. BDNF, Cdk5r, ARC, c-Fos	Long-term treadmill training enhances learning-related genes and neurogenesis without increasing cognitive behavior in socially isolated mice. Exercise can alter brain development, function, and development due to neuropsychiatric disorders.
8	Zielinski et al.[18]	Male C57BL/6J Mice; n=40 Normal sleep + Sedentary, Normal sleep + Exercise, Sleep restriction + Sedentary, and Sleep restriction + Exercise	Treadmill 18–21 m/min, 60 min/day, six days/week, 11 weeks and 5% grade.	Immunohistochemistry.	↑Protein c-Fos, BDNF	Exercise increased memory recall with increased c-Fos positive cells
9	Ransome and Hannan[19]	Female and male R6/1 HD transgenic mice, (12 weeks-old); Female wildtype (n=18) and R6/1 HD (n=18) 7 weeks of age control littermates; (n=9 wildtypes; n=9 R6/1 HD), run/enriched littermates (n=9 wildtypes; n=9 R6/1 HD)	Voluntary running 90 min, 7 days, 4 weeks	Immunofluorescence Immunohistochemistry	↑Protein c-Fos	Running induced Akt phosphorylation in the hippocampus of female wildtype mice, which was not reflected in R6/1 HD mice. Running in adult rats caused neurogenesis in the hippocampus
10	Zhong et al.[20]	Male C57BL/6 Mice; n=294, groups of 12–20 mice	Swimming, water depth 5–15 cm. 5 min, four times/session, every session 30 min, five days/week, four weeks	Immunohistochemistry	↑Protein c-Fos, histone acetylation, CREB) - binding protein (CBP)	There was increased hippocampal acetylation of H3K9, H4K5, and H4K12, an increased number of c-Fos-positive cells one hour after CFC training, and less memory impairment and increased histone acetylation and (CREB)-binding protein (CBP) in rats that underwent exercise regular swimming
11	Cefis et al.[21]	Wistar Rat, 10-week-old; n=69 Two groups: SED (sedentary), Exercise (EX12, EX18)	Treadmill Low-intensity exercise (12 m/min, EX12), High-intensity (18 m/min, EX18), 30 min/day, one week	Western Blotting	↑Protein c-Fos, BDNF, Synaptophysin	High-intensity exercise (E18) improves memory performance compared to low intensity (EX12) and sedentary.
12	Tsai et al.[22]	6-week-old Mice; n=30 Four groups: 1-day single-bout (Acute Exercise); Without Exercise (Basal); Exercise for one hour (E1h); and Exercise for one hour and rest at the home cage for two hours (E1hR2h)	Treadmill - Acute exercise; 10 m/min, 60 min - Long-time exercise: 10 m/min for 20–60 min/day, five days/week, four weeks	Immunohistochemistry Western Blott	↑Protein c-Fos	Acute exercise caused increased c-Fos+ cell density in the ventral hip hippocampal CA1 region, primary somatosensory cortex, other hippocampal subregions, and striatum Long-term exercise increased c-Fos+ cell density in the striatum, primary somatosensory, primary and secondary motor cortex, hippocampal subregion, hypothalamic nucleus, and lateral periaqueductal gray
13	Belviranlı and Okunda[23]	Female Wistar rats (aged 3 months) and (aged 20 months); n= 30 Four groups: Control (Yc, n=8); Young Exercise (Yt, n=8); Aged control (AC, n=7); and Aged Exercise (AT, n=7).	Running wheel, 90 days	Western Blott	↑mRNA BDNF, FNDC5, PGC-1α, mTOR, ARC, c-Fos, ERK, SIRT, dan FOXO	Exercise training improved spatial learning and memory in aged rats

Abbreviations: DF, Daniel Fast; WM, working memory; WD, Western diet; BDNF, brain-derived neurotrophic factor; CREB, cAMP-responsive element-binding protein; mRNA, messenger RiboNucleic Acid; Yc, Young control; Yt, Young Training; AT, Aged Training; CFC, contextual fear conditioning.

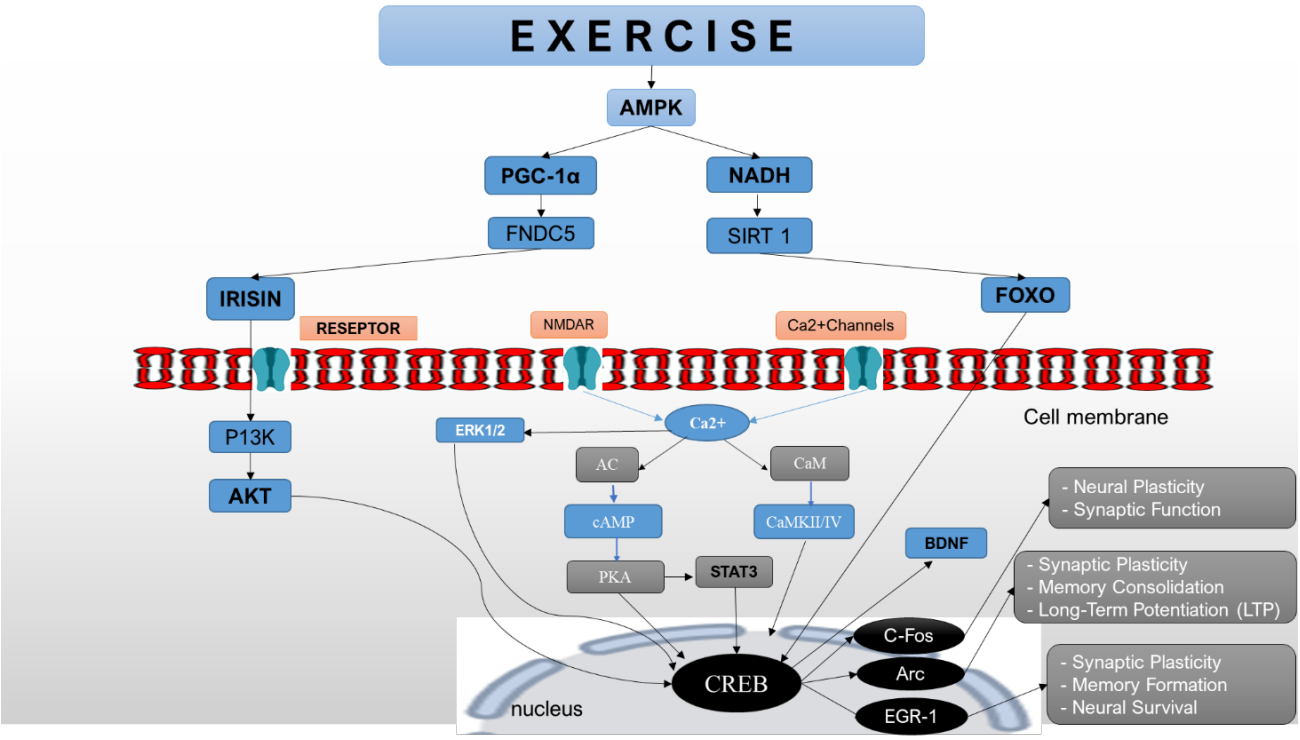

Figure 2. C-Fos, ARC, EGR-1 expression during exercise: physical exercise triggers physiological changes in the body by myokine expression in the muscles. Activation of membrane receptors in the brain: the neurotransmitters released bind to specific receptors in the brain, including in the hippocampus. This activation causes a cascade of intracellular events. Opening signaling pathways: the binding of neurotransmitters to their receptors initiates signaling pathways within hippocampal neurons. The cyclic adenosine monophosphate (cAMP) pathway is involved, CaMkII/IV. The cAMP pathway: activation of the cAMP pathway triggers a cascade of intracellular reactions, activating protein kinase A (PKA). PKA is an enzyme that phosphorylates and activates other proteins in gene expression. Once activated, PKA translocates to the nucleus of hippocampal neurons, where it phosphorylates and activates transcription factors such as CREB. Gene expression: CREB binds to a specific DNA sequence called the cAMP response element (CRE) in the promoter region of the target gene. This binding initiates a transcription of these genes directly to the start gene (c-Fos, ARC, EGR-1). Exercise stimulates neurotransmitter release, activates signaling pathways, phosphorylates transcription factors, and leads to c-Fos, ARC, and Egr-1 expression in the hippocampus. The activation of this gene indicates increased neural activity, synaptic plasticity, and cognitive benefits associated with exercise.

a broader regional and temporal impact on the brain than acute exercise[22]. Moderate-intensity treadmill exercise has proven more efficient in activating hippocampal nerves than rotarod exercise[14].

In addition to exercise intensity, the type of exercise also significantly influences c-Fos expression in the hippocampus, especially in treadmill and rotarod exercises. Immunohistochemical examination of c-Fos as a nerve activation marker revealed that treadmill exercise at 15 m/min (T15) significantly increases c-Fos expression in all hippocampus subfields, including CA3, CA1, and the dentate gyrus. In contrast, 30 rpm rotarod exercise (R30) does not result in increased c-Fos expression[14].

The duration of exercise in voluntary wheel running over 25 days is found to increase the survival of new neurons and affect c-Fos expression. Longer exercise duration has a greater impact on the rate of neurogenesis, as it leads to increased differentiation of hippocampal progenitor cells in adult rat models[52]. The expression of c-Fos induced by physical exercise is influenced by exercise intensity, type, and duration, with higher intensity and longer durations resulting in increased c-Fos expression in the hippocampus[53,54].

Increased c-Fos expression in the rat hippocampus due to treadmill exercise was observed across all age groups. The cornu ammonis (CA) region showed the highest increase in c-Fos expression with treadmill exercise in 4-week-old rats, while in the dentate gyrus, the highest increase was observed in rats aged 62 weeks. This suggests that age is a crucial factor in regulating c-Fos expression in the hippocampus, as it appears to be age-dependent when induced by exercise[55].

Expression ARC during exercise

ARC is one of the most characteristic molecules that play a key role in memory formation. This gene encodes

proteins involved in synaptic functions related to serotonin, glutamate, and dopamine, distinguishing it from c-Fos and EGR-1[56-59]. ARC expression is regulated by EGR-1[60] and its mRNA is transported to dendrites[61,62], making it a marker of neural activity[56,63].

Under certain conditions, mRNA ARCs can form in postsynaptic dendrites independently of presynaptic axons[64,65]. ARC acts on both new and established synapses, playing a crucial role in mechanisms related to synaptic plasticity, such as long-term potentiation (LTP) and long-term depression (LTD)[3,66]. ARC encodes an F-actin-associated (ARC)[10,67] growth factor that contributes to dendritic reconfiguration[62,68]. Therefore, both the ARC and EGR-1 genes, albeit to varying degrees, influence changes in neural tissue and play more specific roles than c-Fos[69].

Chronic aerobic exercise improves working memory and can be evaluated as a neuroprotective measure due to increased ARC and BDNF expression in the hippocampus. This effect was observed in rats subjected to a Western diet combined with a plant-based Daniel Fast (DF) intervention[11]. The expression of ARC induced by physical exercise is influenced by age, with physical exercise during adolescence increasing the expression of genes related to synaptic plasticity and cognitive function in the hippocampus, including synaptophysin, BDNF, PSD-95, CREB, ARC, TLX, and DCX. However, physical exercise in adulthood does not affect the expression of these genes, suggesting that exercise during adolescence is more effective in enhancing cognitive function[12]. This finding was supported by Sun et al. research in 2021[13] whose research explained that treadmill exercise can improve neuroplasticity in male rats exposed to (2-ethylhexyl)-phthalate DEHP before birth, leading to memory and spatial learning deficits during late adolescence. Exercise during childhood and adolescence can restore gene expression and improve learning and memory deficits[16]. In old age, wheel running exercise increases the expression of genes such as BDNF, FNDC5, PGC-1α, mTOR, ARC, c-Fos, ERK, SIRT, and FOXO. This can help counter cognitive dysfunction associated with aging, which is characterized by decreased expression of genes and proteins like PGC-1α, FNDC5, and BDNF in the hippocampus[23].

Expression EGR-1 during exercise

EGR-1, known by various names such as zif268, NGFI-A, Krox 24, or ZENK[70,71], is a transcription factor whose expression is induced by various factors, including injury, stress, cell differentiation, and extracellular signals such as growth factors, neurotransmitters, and peptides[72-74]. EGR-1 expression exhibits a distinct pattern in the brain compared to c-Fos[68-75]. It plays a crucial role in mediating the expression of multiple genes involved in neural processes, ranging from growth control to changes in synaptic plasticity[76-78]. EGR-1 is relatively highly expressed during neural activity[72,79], particularly in the hippocampus[3,80] and the dentate gyrus[7]. Its role in learning and memory is attributed to its modulation of synaptic plasticity, including the remodeling of dendrites, and synapses, and the formation of new synaptic connections[69].

This study supports the role of EGR-1 in learning and memory formation, affecting neural and cognitive functions. EGR-1 functions as a transcription factor that regulates numerous identified target genes. In contrast to c-Fos, which primarily targets genes related to vesicular transport and neurotransmitter release, EGR-1 targets genes that often depend on clathrin or actin processes[81,82].

Physical exercise also influences EGR-1 expression, with different durations of exercise affecting EGR-1 expression in the hippocampus[83]. However, research on the effects of exercise on EGR-1 expression is still limited, and conclusive findings on its impact in the hippocampus cannot be drawn at this time.

DISCUSSION

The review analysis above demonstrates that environment and exercise influence the expression of EGR-1, ARC, and c-Fos genes in memory formation and storage. C-Fos gene expression serves as an indicator of neuronal activity. When neurons are active, the c-Fos gene becomes activated, leading to increased production of c-Fos protein. This protein plays a crucial role in neuroplasticity, involving structural and functional changes in the brain. Its role in the hippocampus has been investigated in mice, where c-Fos is involved in neurogenesis and the significance of the AP-1 transcription factor in c-Fos development[84]. The activation of the c-Fos gene and protein occurs rapidly after stimulation and depends on the type and timing of the stimulus. C-Fos requires the participation of other genes, such as c-Jun, for its expression during heterodimer formation. C-Fos dimerizes with the c-Jun protein to form the AP-1 factor, which promotes the transcription of various genes. While the production and removal of c-Fos are part of cellular homeostasis, overexpression can lead to increased cell proliferation[85].

Similarly, ARC expression is influenced by physical exercise in the hippocampus. When we engage in physical exercise, synaptic activity in the hippocampus increases, facilitating communication between neurons.

This heightened synaptic activity triggers the expression of the ARC gene. The primary role of ARC protein is in the process of neuroplasticity. When the ARC gene is activated, ARC proteins are produced and move to the synapses, where neurons communicate. ARC protein acts as a bridge between synaptic signaling and structural changes in neurons, regulating synaptic changes and promoting the formation and maintenance of new synaptic pathways[86].

In the context of the hippocampus, exercise-induced c-Fos and ARC gene expression may facilitate synaptic changes that support learning and memory. The ARC protein also plays a role in memory consolidation, converting short-term memory into long-term memory. Additionally, both c-Fos and ARC proteins are involved in the storage and reactivation of existing memories[66,87]. Therefore, increased ARC gene expression due to physical exercise can influence neuroplasticity in the hippocampus, including memory formation and maintenance. Research has also demonstrated that a deficiency in the ARC gene can impair cognitive performance and memory, underscoring the critical role of this gene in brain function[88].

ARC expression is regulated by EGR-1[60]. EGR-1 is a transcription factor involved in gene regulation in cells, and its activation can affect the expression of genes involved in synaptic plasticity, learning, and memory in the hippocampus. EGR-1 gene expression plays a pivotal role in the brain's response to physical exercise in the hippocampus. EGR-1 is a transcription factor activated by external stimuli, including physical exercise. Physical exercise is shown to increase EGR-1 gene expression in the hippocampus. During physical exercise, there is an increase in synaptic activity and the release of neurotransmitters in the hippocampus, resulting in an external stimulus that triggers the activation of the EGR-1 gene[46].

The primary function of the EGR-1 protein is to regulate the expression of other genes in response to stimuli. The EGR-1 protein acts as a transcription factor, binding to the promoter of the target gene and regulating the production of that protein. In the context of the hippocampus, exercise-induced increased expression of the EGR-1 gene influences other genes involved in synaptic plasticity, neurogenesis, and cognitive function[82].

Although numerous studies demonstrated a relationship between physical exercise, c-Fos, ARC, EGR-1 gene expression, and hippocampal function, this area remains a subject of ongoing research. In particular, research into the effect of exercise on EGR-1 gene and protein expression is still limited. Therefore, further research is needed to understand the impact of physical exercise on EGR-1 gene expression, hippocampal function, and other factors such as the type of exercise, intensity, and duration, which can also influence the brain's response.

In conclusion, the expression of IEG genes, including c-Fos, EGR-1, and ARC, in hippocampal neurons increases after being induced by exercise. This beneficial process in synaptic plasticity is associated with learning, memory, and neurogenesis.

AUTHORS' CONTRIBUTIONS

UR: conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft. HG: conceptualization, data curation, formal analysis, investigation, methodology, writing – original draft, writing – review & editing. NS: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, writing – original draft, writing – review & editing. IS: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, writing – original draft, writing – review & editing. STP: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, writing – original draft, writing – review & editing. SA: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, writing – original draft, writing – review & editing. LAF: conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, writing – original draft, writing – review & editing.

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