

# The Impact of Early Growth Response 1 (Egr1) on Hippocampal Synaptic Plasticity and Cognitive Function: Narrative Review

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**EGR1 (Early Growth Response 1) gene expression is a molecular response that occurs in the brain as a result of synaptic activity and environmental stimuli. Early growth response 1 (EGR1) expression can be affected by several factors, including exercise or physical training. This review aims to determine the effect of EGR 1 expression on hippocampal synaptic plasticity function. Literature search using data-based Pubmed, Science Direct, and Scopus online. The data used is from the year 1978 until the year 2022. Searched using English keywords such as EGR 1 and hippocampus. Animal and human studies show that physical exercise can increase the expression of the EGR1 gene in the brain. This enhanced EGR1 expression is associated with increased synaptic plasticity, which includes changes in the strength and connectivity of synapses between neurons. Synaptic plasticity refers to the ability of the nervous system to change the strength and efficiency of communication between neurons. Physical exercise has been shown to increase synaptic plasticity by increasing dendritic growth and continuity, increasing neurogenesis (the formation of new neurons), and increasing synaptic connections between neurons. Physical exercise can increase EGR1 expression and synaptic plasticity. Increased EGR1 expression and synaptic plasticity induced by physical exercise are associated with improvements in cognitive functions, including memory, learning, and thinking ability. There is evidence that exercise can increase EGR1 expression and synaptic plasticity in the brain, especially in the hippocampus, to improve cognitive function.**

**Keywords:** EGR 1; Hippocampus; Synaptic plasticity.

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Early Growth Response 1 (EGR1) is a gene that plays a role in cognitive processes. Different members of the Egr family of transcriptional regulators have distinct functions in cognitive processes, with Egr1 being required specifically for long-term memory, while Egr3 is primarily

essential for short-term memory<sup>1</sup>. EGR 1 in the central nervous system is a mediator of the interaction of genes with the environment and how environmental stimuli trigger rapid responses and lasting neural adaptations to neuronal function and plasticity<sup>2,3</sup>. EGR1 is activated by several external

stimuli, such as growth factors, and cytokinin stimuli<sup>4,5</sup>. When activated, the EGR1 protein binds to a specific DNA region called an early growth response element (ERE) located in the promoter of a target gene<sup>6</sup>.

After EGR1, mRNA levels are characterized by their rapid upregulation within minutes. It is not related to protein synthesis, which is activated by general intracellular signaling pathways such as the triphosphoinositide kinase (PI3K) pathway or the mitogen-activated kinase (MAPK) pathway and can be triggered by various stimuli<sup>2,6,7</sup>. Despite their extensive and overlapping nature, each EGR 1 differs in its activator, downstream regulatory pathway, target, and expression pattern<sup>1,2,6,8</sup>. Early growth response 1 (EGR1) underlies brain activity, including neurotransmission, synaptic plasticity, and learning and memory processes. In this article, We emphasize the function of EGR1 in both physiological states of the CNS. Before analyzing the genes, pathways, and biological processes that are targets of EGR1 in the CNS, we provide a summary of the variables that regulate its expression.

## METHOD

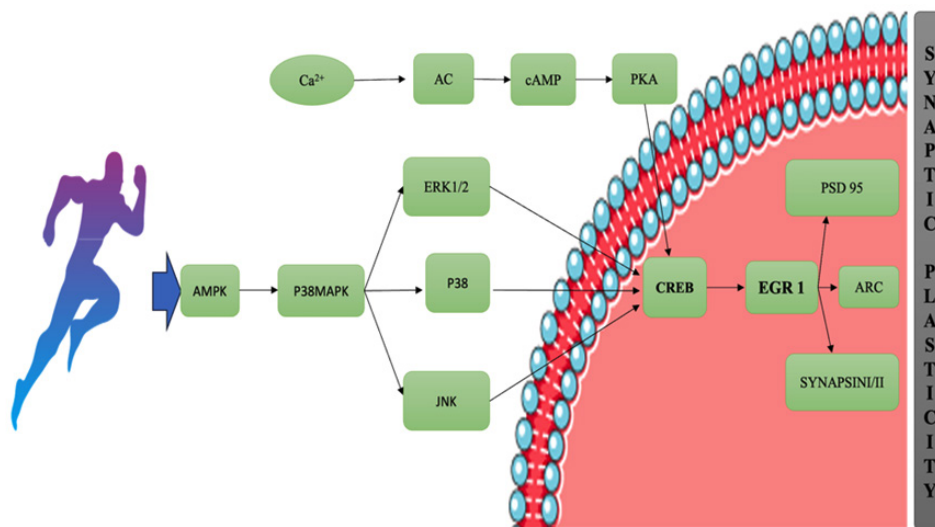
Literature search using data based Pubmed, Science direct and Scopus online. The

data used is from year 1978 until year 2022. Searched using English keywords such as EGR 1 and hippocampus.

## RESULT AND DISCUSSION

Nearly three decades ago EGR 1 was first discovered to be cloned to be regulated by nerve growth factor (NGF) in the presence of a protein synthesis inhibitor while screening the cycloheximide<sup>9</sup> in mouse PC12 cells. The process of cloning and characterization of this protein is carried out simultaneously in different groups in different cell lines stimulated by growth factors, which explains its alternative name: EGR1<sup>10</sup>, NGFI-A<sup>9</sup>, Krox -24<sup>11</sup>, TIS8<sup>5</sup>, and Zif268<sup>12</sup>. The screening strategy identified EGR3, EGR4 and EGR2, which together with EGR1 form the EGR family<sup>6,8</sup>.

All EGRs among species in the region contain three cysteine-2-histidine-two-zinc-finger (C2H2) DNA-binding domains and are homologous, indicating similarities in the DNA sequences recognized by each EGR protein and thus can overlap. In the purpose and function of EGR1, EGR2, and EGR3, but not EGR4, exhibit interaction domains with the transcriptional co-repressors NGFI-A-1/2 (NAB1 and NAB2), in addition, exerting negative control on transcriptional activity. Upregulation of EGR<sup>13</sup>, EGR1, EGR2 and



**Fig. 1.** Exercise triggers the release of neural activity factor, intracellular signaling pathways, AMPK, cAMP, MAPK, or AKT are activated<sup>4</sup>

EGR3 proteins may lead to suppression of their transcriptional role, partly supported by *in vivo* experimental evidence<sup>14,15</sup>.

EGR1 is common in humans and many other animal species. This gene is located on chromosome 5 at the 5q31 locus. The EGR1 protein acts as a transcription factor, a molecule that regulates gene expression by binding to DNA and regulating the activity of target genes. Thus, it is imperative to align the amino acid sequences of all human, rat, and mouse EGR protein due to different regulation, transcriptional regulation, reactivity, neural function between EGR protein and protein interactions<sup>8</sup>.

EGR1 expression is undetectable in the nervous system of both embryos<sup>16,17</sup>, during postnatal development and its expression continues to slowly increase until adulthood, namely on postnatal day 17 in the mouse brain<sup>18</sup>. The gradual increase in EGR1 expression, closely corresponds to the period of maximal N-methyl-D-aspartate (NMDA) response and coincides with the time of synaptic formation in the CA1 and hippocampal cortical regions, increasing long-term inducibility (LTP)<sup>18</sup>. Establishing a link between EGR1 expression and synaptic plasticity. In adulthood, EGR1 is widely expressed throughout the brain, which tends to control cognition, including the hippocampus<sup>6,19,20</sup>. Thus, EGR1 plays a crucial role in learning and memory, as its activity increases in brain regions involved in cognitive function.

#### **EGR 1 And Synaptic Plasticity**

The dentate hippocampus is an integral part of the brain involved in memory formation and storage. EGR 1 is critical in regulating tooth learning<sup>15</sup>. The signaling process of EGR1 expression and signal transmission to neuronal synapses involves several complex steps. The EGR1 signaling pathway is triggered by an external stimulus, such as new learning or interesting stimuli. This stimulus activates neurons in the brain and triggers a series of biochemical and electrochemical changes in the cells<sup>4</sup>. An external stimulus causes a change in the membrane potential of neurons, which triggers the release of neurotransmitters at presynaptic synapses. These neurotransmitters bind to receptors on the postsynaptic cell membrane and initiate signaling through signaling pathways. When a neurotransmitter binds to a receptor, it

activates the receptor. Receptors are composed of protein subunits and have a central function in transmitting signals to the cell. Activation of the receptor triggers a series of biochemical and molecular changes in the cell. EGR1 expression is often accompanied by MAPK signaling pathway and the protein kinase A (PKA) pathway<sup>4</sup>.

Activation of the receptor triggers the activation of MAP kinase, which is responsible for the phosphorylation and activation of the Ras protein. Ras then activates a series of protein kinases, including MEK (MAPK/ERK kinase) and ERK (extracellular signal-regulated kinase). ERK then translocates to the cell nucleus and phosphorylates a transcription factor such as Elk-1, which interacts with the early growth response element (ERE) in the EGR1 gene promoter to initiate gene expression<sup>4</sup>. Activation of the receptor can also trigger activation of the PKA pathway. PKA phosphorylates transcription factors such as CREB (cAMP response element binding protein). Phosphorylation of CREB triggers interactions with transcriptional co-activators, including EGR1. This CREB-EGR1 complex binds to the ERE region of the EGR1 gene promoter to amplify the gene<sup>21</sup>.

After activation of signaling pathways, transcription factors such as Elk-1, CREB, and EGR1 move to the cell nucleus. In the cell nucleus, these factors interact with the ERE region of the EGR1 gene promoter. This interaction triggers the transcription and synthesis of EGR1 mRNA. The newly synthesized mRNA is then translated into the EGR1 protein in the cytoplasm of the cell. The EGR1 protein is then transported back to the cell nucleus where it functions as a transcription factor. After returning to the cell nucleus, the EGR1 protein binds to the ERE region of the target gene promoter. It modulates the transcriptional activity of target genes involved in memory formation and storage<sup>15</sup>.

EGR1 expression and regulation of its target genes influence synapse modification. This can include structural changes, such as the increase or elimination of synaptic spikes, as well as changes in the release of neurotransmitters and the sensitivity of the receptor<sup>15</sup>. Through these steps, the EGR1 signaling pathway influences gene expression and synaptic modifications that promote

learning and memory processes in neurons. However, it is important to remember that these explanations are descriptive and the complexity of signaling mechanisms can vary depending on the context and type of stimulus.

### **EGR 1, Synaptic Plasticity and Exercise**

Physical exercise can influence gene expression through complex signaling pathways<sup>22</sup>. Intense and regular physical exercise can provide the body with external stimulation. This stimulation can occur during aerobic activity or other stressful activities that affect the nervous system<sup>23</sup>. Physical exercise activates the nervous system, especially the autonomic and central nervous systems<sup>24</sup>. This activation releases neurotransmitters and peptides that play a role in nerve signal transmission<sup>25</sup>.

During physical exercise, muscle activity increases, which can activate the AMPK. Biochemical changes in AMPK cells can be triggered by phosphorylation of transcription factors such as CREB. Physical exercise can also trigger MAPK pathways, such as the ERK (extracellular signal-regulated kinase) pathway. Activation of the MAPK pathway can trigger the phosphorylation of transcription factors involved in EGR1 expression, such as Elk-1. Activation of transcription factors such as CREB and Elk-1 can interact with the early growth response elements (ERE) of the EGR1 gene promoter. This initiates the process of transcription and synthesis of EGR1 mRNA. The newly synthesized EGR1 mRNA is then translated into EGR1 protein in the cytoplasm, then functions as a transcription factor after the EGR1 protein is transported to the cell nucleus. When the EGR1 protein returns to the cell nucleus, it binds to the ERE region of the target gene promoter. This gene functions to regulate target genes involved in regulated physiological responses and adaptation to physical conditions exercise<sup>4</sup> (Figure 1).

Physical activity can trigger the expression of the EGR 1 gene to increase blood flow and neurotrophic factors, such as brain-derived neurotrophic factor (BDNF) which plays a role in nerve growth and development<sup>26</sup>. This neurotrophic factor can stimulate EGR1 expression in the hippocampus, which regulates synaptic plasticity, an important mechanism for learning and memory<sup>15</sup>. Exercise can also have neuroprotective

effects on the brain, including the hippocampus. Increased expression of EGR1 may play a role in protecting and restoring brain function disrupted by oxidative stress or cell damage<sup>27,28</sup>.

Exercise can increase EGR1 gene expression in the brain as a whole. This may occur because physical activity increases blood flow and neurotrophic factors, such as BDNF, which can stimulate EGR1 expression in neurons<sup>23,26</sup>. Regular exercise has been shown to protect nerves and improve nerve health. Several studies in which EGR1 expression can promote neuroprotection and recovery of impaired neuronal function<sup>23</sup>. Exercise can also increase neural plasticity, namely the ability of the nervous system to adapt and make new connections between neurons<sup>29</sup>. Although direct studies have not examined the effect of exercise on EGR1 expression in plastic neurons, higher EGR1 expression may play a role in the regulation of plastic neurons and the formation of new synaptic connections<sup>30,31</sup>.

EGR1 expression, and neurological health greatly requires further research to understand the precise relationship between exercise. Variables such as exercise type, duration, intensity, and individual characteristics can also affect cognitive function. A recent study and a more comprehensive review of the literature may provide additional information on the effect of exercise on EGR1 expression in neurons.

## **CONCLUSION**

The expression of EGR1 can enhance synaptic plasticity in the brain, leading to improved cognitive function. Exercise is also a factor that can influence EGR1 expression.

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### **Conflict of Interest**

The authors declare that they have no conflict of interest.

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