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Building resilience with aerobic exercise: role of FKBP5.

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Abstract: *Both preclinical and clinical studies have pointed that aerobic exercise, at moderate doses, is beneficial at all stages of life by promoting a range of physiological and neuroplastic adaptations that reduce the anxiety response. Previous research about this topic have repeatedly described how the regular practice of aerobic exercise induces a positive regulation of neuroplasticity and neurogenesis-related genes, as well as a better control of the HPA axis function. However, limited progress has been carried out in the integration of neuroendocrine and neuroplastic changes, as well as in introducing new factors to understand how aerobic exercise can promote resilience to future stressful conditions. Resilience is defined as the ability to adapt to stress while maintaining healthy mental and physical performance. Consistent findings point to an important role of FKBP5, the gene expressing FK506-binding protein 51 (FKBP51), as a strong inhibitor of the glucocorticoid receptor (GR), and thus, an important regulator of the stress response. We propose that aerobic exercise could contribute to modulate FKBP5 activity acting as a potential therapeutic approach for mood disorders. In this sense, aerobic exercise is well known for increasing the growth factor BDNF, which by downstream pathways could affect the FKBP5 activity. Therefore, our manuscript has the aim of analyzing how FKBP5 could constitute a promising target of aerobic exercise promoting resilient-related phenotypes.*

Keywords: *Anxiety; Depression; Exercise; Glucocorticoid receptor; HPA; Resilience*.

1. Aerobic exercise as a healthy avenue to promote resilience.

Overwhelming evidence exists that lifelong exercise is associated with a longer health span, whereas physical inactivity is the fourth leading contributor to death worldwide [1]. Among its benefits, aerobic exercise not only causes positive effects on physical health, but also on psychological well-being. Hence, those subjects who perform exercise regularly suffer from less depression [2], anxiety [3] and cognitive impairments [4]. Similar results have been found in preclinical studies in which, although running exercise is comparable to other forms of stress in terms of corticosterone release, it induces patterns of neuronal activity that correspond to predictable, controllable and rewarding stimuli, in contrast to negative stressors, such as social isolation or electric shocks [5].

Among the biological mechanisms related to the positive impact of aerobic exercise, several studies have pointed to structural (e.g. increased neurogenesis, synaptogenesis, gliogenesis and angiogenesis) and cellular/molecular (e.g. altered central monoamine neurotransmission and increased growth factor expression) changes which could promote enhanced neuroplasticity and may be capable of buffering the detrimental effects of chronic stress [6]. Hence, the increase of local and systemic expression of growth factors, notably the brain-derived neurotrophic factor (BDNF) has been commonly associated with improvements in the cognitive functioning, as well as in anxiety and depression-related behaviors [7]. Accordingly, the ability of aerobic exercise to enhance BDNF release and function in the synapse, promote dendritic spine integrity, and activate other cellular pathways is a cornerstone for brain processes that are necessary to repair and reorganize neuroplasticity altered during the course of mood disorders [8, 9]. In addition, other growth factors, such as the insulin-like growth factor-1 and the vascular endothelial growth factor, have been shown to play an important role in BDNF-induced effects on neuroplasticity, as well as exerting neuroprotective effects of their own contributing to the beneficial effects of exercise on the brain [10]. On the other hand, exercise appears to have a blunting effect on the hypothalamic–pituitary–adrenal axis (HPA axis) and the sympathetic nervous system. This blunting impact on stress responsiveness seems to contribute to reduce emotional, physiological and metabolic reactivity, as well as increase positive mood and psychological well-being [6]. Finally, other biological target of the aerobic exercise is the immune system. Thus, higher physical activity has been associated with lower inflammatory cytokine responses to a mental stressor, along with a greater parasympathetic control [11]. Moreover, regular exercisers also showed attenuated leucocyte trafficking and adhesion molecule expression in response to a mental stressor compared with less physically active individuals [12].

In summary, these findings are consistent with the concept of *physiological toughening* as a mechanism by which regular exercise can improve stress tolerance by optimizing neuroendocrine and physiological responses [6]. Obviously, the expression of growth factors and neuroplasticity are promising avenues of research with the potential to elucidate the mechanisms of how aerobic exercise works. Concerning this, new lines of research have started to focus on the relationship between FK506-binding protein 5 (FKBP5) gene and BDNF because both are expressed and affect the functioning of brain areas, such as the hippocampus, amygdala and the prefrontal cortex (PFC), involved in the control of the stress response [13, 14]. Genetic studies revealed associations between stressful life events and alterations in the HPA axis that were mediated, in part, by gene × environment interactions involving FKBP5 and BDNF polymorphisms [9, 15, 16]. Consequently, would it also be possible that interactions between genes and eustresors, such as aerobic exercise, could improve the HPA functioning and promote resilient-related behaviors by epigenetic mechanisms?

The present *CN perspective* has the aim of analyzing the synergistic effects of BDNF and FKBP5, as a still unknown target of aerobic exercise, in promoting resilience to cope with stressful situations.

2. The unknown role of FKBP5 protein in the positive effects induced by aerobic exercise.

In the past decade, FKBP5 (OMIM 602623) has emerged as a promising genetic candidate for investigations of vulnerability to mood and anxiety disorders owing to its involvement in regulating sensitivity of GR [17]. Elevated FKBP5 levels lead to a decreased negative feedback regulation of the HPA axis and GR resistance, which is probably responsible for a dysregulated stress response [18]. Besides, the expression of FKBP51 correlates with plasma BDNF levels in depressed patients [19]. More precisely, the inhibition of GR negatively affects BDNF-induced TrkB phosphorylation and its downstream signaling pathways whereas a short activation of GR is associated with the long-lasting BDNF-delivered mechanisms required for memory consolidation [20].

Additionally, and as we mentioned before, BDNF is involved in the regulation of synaptic plasticity by pre- and post-synaptic mechanisms. Potential downstream targets of BDNF are the Synapsins, a family of presynaptic phosphoproteins, which affect the proportion of vesicles that are available for release [21]. Several studies have found that BDNF increases Synapsin phosphorylation thus enhancing the availability of vesicles and facilitating neurotransmitter release [22, 23]. Interestingly, the presynaptic vesicle protein Synapsin has shown to be an important molecule candidate to modulate FKBP5 reducing the stress responsiveness [24]. It has been found that the expression of FKBP51 and Synapsin is regulated in opposite directions not only in the mouse PFC, but also in the PFC of schizophrenic patients, who are generally known for exhibiting an altered stress-coping behavior [24]. On the other hand, a recent study revealed a critical role of FKBP51 in mBDNF secretion and suggested the involvement of mBDNF in the performance of stress-coping behavior after the administration of the antidepressant S-ketamine [25]. Specifically, and contrary to our expectations, these authors found that the enhancement of BDNF in the extracellular space after S-ketamine administration was absent in FKBP51 deficient mice. This effect could be possible if we consider that this protein plays a double role in mediating responses to stimuli with both positive (*eustresors*) and negative (*stressors*) characteristics [26]. Likewise, the antidepressant effect of paroxetine was related to an enhancement of both BDNF and FKBP5 [19]. Nevertheless, although the mechanism by which FKBP5 is able to modulate mBDNF levels is still unknown, it has been proposed that its interaction with NMDA receptors, as well as with inhibitory synapses in brain regions such as the hippocampus could affect the neuronal activity and consequently BDNF levels [27, 28].

Regarding the direct modulation of FKBP5 by aerobic exercise, we have found in the literature that is a research field scarcely explored. A recent study has found an increase in the gene expression of FKBP5 in relevant limbic areas (e.g. mPFC, insular cortex and hippocampus) after a protocol of wheel-running [29, 30]. It is possible that the enhancement of FKBP5 after running is induced by glucocorticoids (GCs) increase owing to the stressful, but positive, nature of aerobic exercise. Previous studies have found that FKBP5 expression can be produced by GCs and has been shown to be a very accurate measure of GR regulation and signaling constituting an appropriate marker of HPA flexibility [31, 32]. Thus, when GCs enter the cytoplasm, they bind to the GR-chaperone complex, favoring the exchange of FKBP5 for FKBP4, which allows GR translocation to the nucleus and promote the transcriptional activity of many genes involved in the feedback regulation of the HPA axis. Hence, the greater release of GCs caused by the exercise is compensated by the increase of FKBP5 complexes whose exchange to FKBP4 favours the regulation of the stress axis. Therefore, the increased expression of FKBP5 mediated by GCs is considered as an ultrashort, intracellular negative feedback loop that regulates intracellular GR sensitivity [33] (Figure 1). In addition, to understand the paradoxical increase of GCs by exercise, it has been also described that GCs released into the blood eventually reach the mPFC elevating dopamine release, upregulating BDNF [34] and inducing control and coping-related behaviors [35, 36]. In contrast, chronic stress and depression have been associated with an overall reduction in dopamine neurotransmission in areas such as PFC, VTA and nucleus accumbens [37]. In this sense, region-specific effects have been reported by previous research on FKBP5. For example, mice lacking the Fkbp5 gene show stress-induced decline in synapsin expression in the prefrontal cortex but not in the hippocampus, and selective Fkbp5 silencing in the amygdala was shown to confer resilience to restraint stress exposure [32].

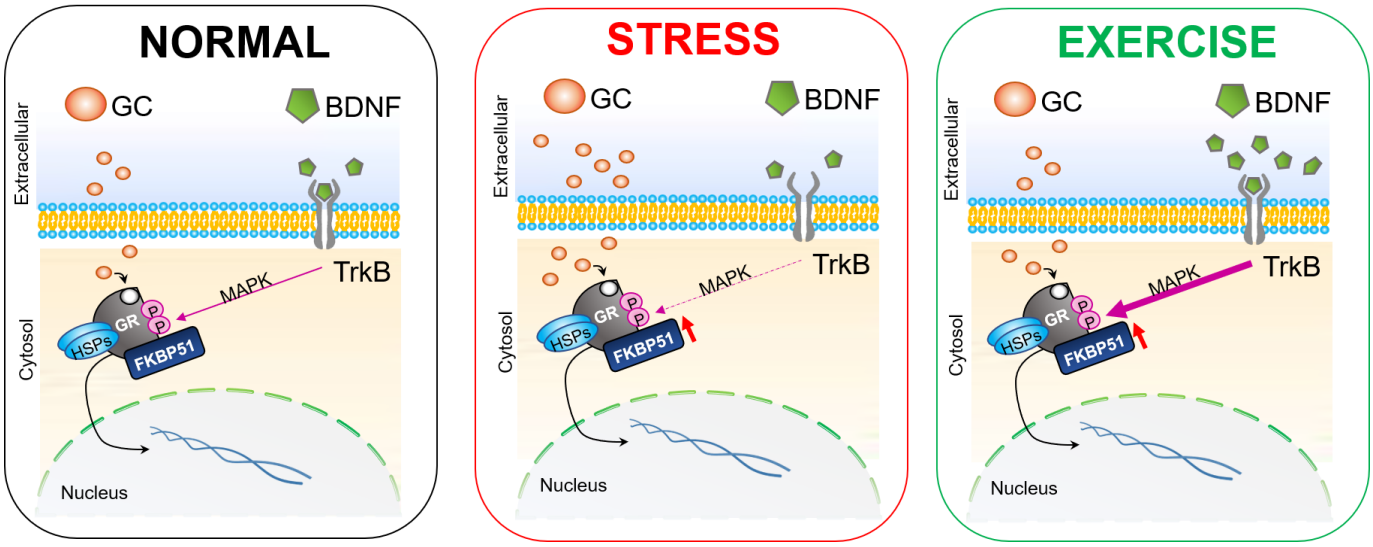

Figure 1. Hypothetical mechanisms of the action of stress and exercise in the BDNF- and FKBP5-mediated GR phosphorylation signaling pathway. Aerobic exercise increases BDNF expression, which in turn promotes GR phosphorylation through the serine residues by mitogen-activated protein kinase (MAPK) signaling pathway [38]. Hence, exercise could boost MAPK signaling enhancing the level of the activated form of this transcription factor as previous studies have found after only a week of voluntary running [39]. In consequence, activation of a TrkB-MAPK pathway could trigger GR phosphorylation and the expression of genes involved in resilience-related neuroplasticity.

CONCLUSION

Most people are confronted with stressful situations at some point in their lives and do not develop mental disorders as a result. This ability to deal with and overcome adversity involves the complex construct of resilience. Several resilience-promoting avenues have been described, being the performance of regular physical activity one of them. It exerts antidepressant and anxiolytic-like effects by toughening the physiological and neuroendocrine mechanisms involved in the negative feedback of the HPA axis. Hence, we propose a scarcely explored pathway mediated by increased exercise-induced GCs and BDNF, which through its action on the FKBP5 chaperone could result in the transcription of genes involved in resilient behavior to cope with future stressors. Thereby, studies with animal models carrying mutations targeting BDNF-sensitive GR phosphorylation sites could be an adequate approach to analyze the physiological and behavioral importance of these modifications, as well as the pleiotropic effects of FKBP5 depending on the stressor applied.

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CONFLICT OF INTEREST

Authors declare no conflict of interest.

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