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Research report

Exercise activates the phosphatidylinositol 3-kinase pathway

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Abstract

Physical exercise is known to enhance psychological well-being and coping capacity. Voluntary physical exercise in rats also robustly and rapidly up-regulates hippocampal brain-derived neurotrophic factor (BDNF) mRNA levels, which are potentiated following a regimen of chronic antidepressant treatment. Increased BDNF levels are associated with enhanced activity of cyclic AMP response element binding protein (CREB). So far, relatively little is known about the intracellular signaling mechanisms mediating this effect of exercise. We wished to explore the possibility that exercise and/or antidepressant treatment activate the hippocampal phosphatidylinositol-3 (PI-3) kinase pathway, which mediates cellular survival. In young male Sprague–Dawley rats, we examined the effects of 2 weeks of daily voluntary wheel-running activity and/or tranylcypromine ($n = 7$ per group) on the levels of the active forms of protein-dependent kinase-1 (PDK-1), PI-3 kinase, phospho-thr308-Akt, phospho-ser473-Akt, and phospho-glycogen synthase kinase-3β (GSK3β; inactive form), as well as BDNF, activated CREB, and the phospho-Trk receptor, in the rat hippocampus, and compared these with sedentary saline-treated controls. Immunoblotting analyses revealed that in exercising rats, there was a significant increase in PI-3 kinase expression (4.61 times that of controls, $P = 0.0161$) and phosphorylation of PDK-1 (2.73 times that of controls, $P = 0.0454$), thr308-Akt (2.857 times that of controls, $P = 0.0082$), CREB (60.27 times that of controls, $P = 0.05$), and Trk (35.3 times that of controls, $P < 0.0001$) in the hippocampi of exercising animals; BDNF was also increased (3.2 times that of controls), but this was not statistically significant. In rats receiving both exercise and tranylcypromine, BDNF (4.51 times that of controls, $P = 0.0068$) and PI-3 kinase (4.88 times that of controls, $P = 0.0103$), and the phospho- forms of Trk (13.67 times that of controls, $P = 0.0278$), thr308-Akt (3.644 times that of controls, $P = 0.0004$), GSK-3β (2.93 times that of controls, $P = 0.026$), and CREB (88.97 times that of controls, $P = 0.0053$) were significantly increased. These results suggest that the exercise-induced expression of BDNF is associated with the increased expression of several key intermediates of the PI-3 kinase/Akt pathway, which is known for its role in enhancing neuronal survival.
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1. Introduction

Physical exercise has been shown to improve psychological and cognitive functioning in humans [30,53,58,59,66,67], rats [83,105], and mice [42]. Specifically, in humans, exercise has been shown to decrease anxiety [106], elevate mood and coping skills in response to stress [32], and demonstrate antidepressant activity [31]. Antidepressant medication treatment, which also enhances mood, elevates hippocampal brain-derived neurotrophic factor (BDNF) mRNA [92], trkB [92,113] and cyclic-AMP response element binding protein (CREB) [93,113,128] levels, which are probably, at least in part, mediated by the elevation of norepinephrine (NE) and/or serotonin (5-HT) [35,130] (Fig. 1). In addition, pharmacological activation of brainstem and cortical [39] NE neurons resulted in increased trkB activation [2] and increased BDNF mRNA levels in cultured astrocytes [137].

This laboratory and others have shown that both exercise [60,82,90,91] and antidepressants increase, elevate, and sustain [47,63,97,110–112] hippocampal BDNF mRNA levels more than either of these two interventions alone,

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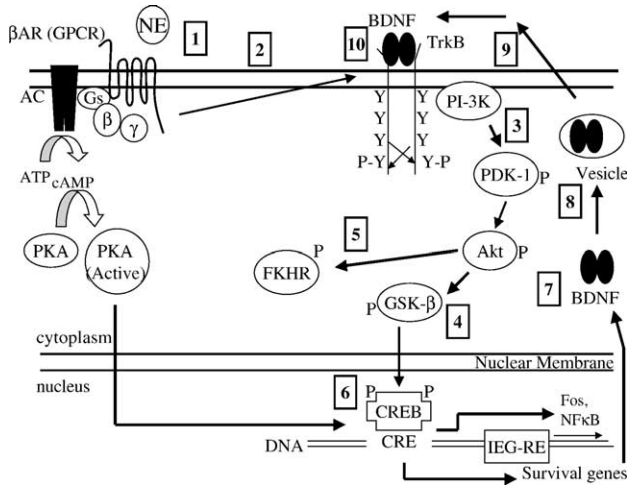

Fig. 1. Schematic representation of NE-induced BDNF signaling and the role the PI-3 kinase pathway plays in this signaling. It is well known that both antidepressants and exercise increase NE synthesis and release: (1) NE binds its GPCR (βAR), which then either activates adenylate cyclase (AC) and/or directly transactivates (2) TrkB through small G-protein subunits (Gs, βγ). Phosphorylation of TrkB then activates PI-3 kinase (3), which then phosphorylates Akt, which in turn phosphorylates GSK-3β (4). Akt can also phosphorylate FKHR (5). GSK-3β is one of many kinases (e.g., CaMKII and Ras, not shown for simplicity's sake) capable of phosphorylating CREB (6). CREB phosphorylation can also be achieved by PKA, which was activated by cAMP (shown on the left side of the diagram). Phospho-CREB then transcribes a variety of survival-promoting genes (IEG-RE, Immediate-Early Genes-Regulatory Element), such as BDNF (7), which is then transported through the cytoplasm, packaged into vesicles (8), and exocytosed (9) into the extracellular space so that it can feedback and then bind TrkB, resulting in receptor autophosphorylation (10) to activate the PI-3 kinase pathway (as well as several other pathways) again.

and can prevent (or reverse) deficits in BDNF transcription brought about by acute stress (forced swim [112]). In addition, expression of BDNF and TrkB mRNA levels has been shown to be proportional to running distance [82,136]. Consistently, central administration of BDNF [3,121,122] and over-expression of CREB in the hippocampus [21] have been shown to confer antidepressant-like behavioral and cognitive improvements in rats subjected to various stress and learning paradigms.

Whereas the signaling mechanisms elicited by antidepressant-induced increases in NE and 5-HT are relatively well-known [21,23,35,45,84,104,118], the intracellular signaling mechanisms mediating the exercise-induced increase in these neurotransmitters are relatively unexplored, despite clinical observations that antidepressants and exercise produce similar behavioral and psychological improvements. Recently, exercise has been implicated in the induction of genes related to anti-aging, immune function, neural plasticity, and neuronal signaling [24,48,129]. Other evaluations have revealed significant up-regulation of various signaling molecules, such as calcium-calmodulin-dependent protein kinase-II, mitogen-associated protein kinase (MAP kinase) I and II, phospholipase-c-δ, and CREB, resulting from 7 and/or 28 days of voluntary wheel-running [92].

The MAP kinase [76,102,116,125], PI-3 kinase [11,16,108,116,125,131], phospholipase-*c*-γ (PLC-γ, [11,77]), CaMKII/IV [12,13], and Ras/ERK/RSK [41] represent the major signaling pathways known to be activated by BDNF-induced TrkB activation [102]. In cultured cortical neurons subjected to apoptotic conditions, BDNF has been shown to be anti-apoptotic [7] and neuroprotective by activating the ERK and PI-3 kinase pathways [51]. Consistently, BDNF leads to the phosphorylation of Akt [9], which plays a critical role in controlling the balance between survival and apoptosis [17,44] and is activated by insulin and various growth and survival factors, as well as by other kinases, such as PKA [40]. Akt functions to promote cell survival by inhibiting apoptosis [16,26] through its ability to phosphorylate and inactivate several substrates, including BAD [18], the forkhead transcription factors [15,88], caspase-9 [109], and GSK-3β [25]. Phosphorylation of GSK-3β by PI-3 kinase [28], Akt [25], PKA [38,73], and PKC [4] is pro-survival, whereas active (dephosphorylated) GSK-3β is pro-apoptotic [52]. The GSK-3β pro-apoptotic pathway can be initiated by inhibiting PI-3 kinase or Akt [27].

These intracellular pathways, regulated by neurotrophin/Trk receptor signaling [123], play principal roles in promoting synaptic strength/plasticity [50,56,99,115] and neuronal survival [131]. Thus, in the wake of stress and depression, this enhanced plasticity, resulting from excitatory neural activity elicited by antidepressants [34–36,75] and/or exercise [49,132,133], may promote neuronal recovery and neurogenesis [61,75,87]. The resultant increase in intracellular signaling [5,87] leading to increased BDNF transcription, therefore, regulates synaptic plasticity in an activity (antidepressant and/or exercise)-dependent manner [19].

Intracellular signaling via PI-3 kinase/Akt is but only one pathway that is activated by a variety of trophic factors, such as nerve growth factor, insulin-like growth factor I, platelet-derived growth factor, BDNF [57], or vascular endothelial growth factor (VEGF, [62]). Each of these pathways can contribute to neuronal survival, depending on the conditions, the type of cell, and the survival factor. For example, cerebral ischemia has been shown to induce hippocampal VEGF, phospho-Akt, and PI-3 kinase [62]. And antidepressants have been shown in tissue culture to lead to increased synthesis and release of glial cell line-derived neurotrophic factor from glioblastoma cells and which were regulated by the MAPK pathway [54].

Shown in Fig. 1 is a simplified schematic emphasizing NE-induced G-protein-coupled receptor (GPCR) activation of PKA. Specifically, this pathway is initially activated as a result of increased neural activity brought about by antidepressants and/or exercise. The resulting increased release of NE binds its GPCR, which then activates PKA and subsequent CREB phosphorylation. BDNF is then transcribed, exocytosed, binds trkB, which autophosphorylates, eventually leading to CREB phosphorylation via the PI-3 kinase pathway (among several others) to activate BDNF transcription in a cyclic fashion. It is important to

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