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INVITED REVIEW

Fat cell-secreted adiponectin mediates physical exercise-induced hippocampal neurogenesis: an alternative anti-depressive treatment?

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Abstract

Psychological depression is drawing accumulating attention nowadays, due to the skyrocketing incidence worldwide and the enormous burdens it incurs. Physical exercise has been long recognized for its therapeutic effects on depressive disorders, although knowledge of the underlying mechanisms remains limited. Suppressed hippocampal neurogenesis in adult brains has been regarded, at least partly, contributive to depression, whereas physical exercise that restores neurogenesis accordingly exerts the anti-depressive action. Several recent publications have suggested the potential role of adiponectin, a protein hormone secreted by peripheral mature adipocytes, in mediating physical exercise-triggered enhancement of hippocampal neurogenesis and alleviation of depression. Here, we briefly review these novel findings and discuss the possibility of counteracting depression by modulating adiponectin signaling in the hippocampus with interventions including physical exercise and administration of pharmacological agents.

***Key Words:** hippocampus; adult neurogenesis; physical exercise; voluntary wheel running; depression; neural progenitor cell; adipocyte; adiponectin; adiponectin receptor; AMP-activated protein kinase*

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Maintenance of generating adult-born neurons in the hippocampal dentate gyrus has been considered preventive to the occurrence of depressive disorders (Sahay and Hen, 2007), given that multiple anti-depressive treatments, including antidepressants, electroconvulsion, physical activities and vagus nerve stimulation (Banni et al., 2012) are unexceptionally capable of enhancing this process, whereas maneuvers which eliminate adult hippocampal neurogenesis (*e.g.,* irradiation) concurrently abolish the therapeutic effects (Santarelli et al., 2003). As a long-recognized remedy against depression, physical exercise has been demonstrated to promote hippocampal plasticity from a variety of aspects, including neurogenesis, dendritic complexity and synaptic plasticity (Eadie et al., 2005); this is also reinforced by our previous observation that voluntary running decreases depression-like behaviors and improves hippocampus-dependent spatial learning and memory through restoring hippocampal neurogenesis and increasing dendritic plasticity (Yau et al., 2011). Although physical exercise elicits various beneficial biological changes, its capacity to induce the production of neurotrophic factors that nourish and protect neurons in the central nervous systems (*e.g.*, brain-derived neurotrophic factor) is putatively regarded as the principal mechanism mediating its anti-depressive action.

Very recently, a new member called adiponectin has joined

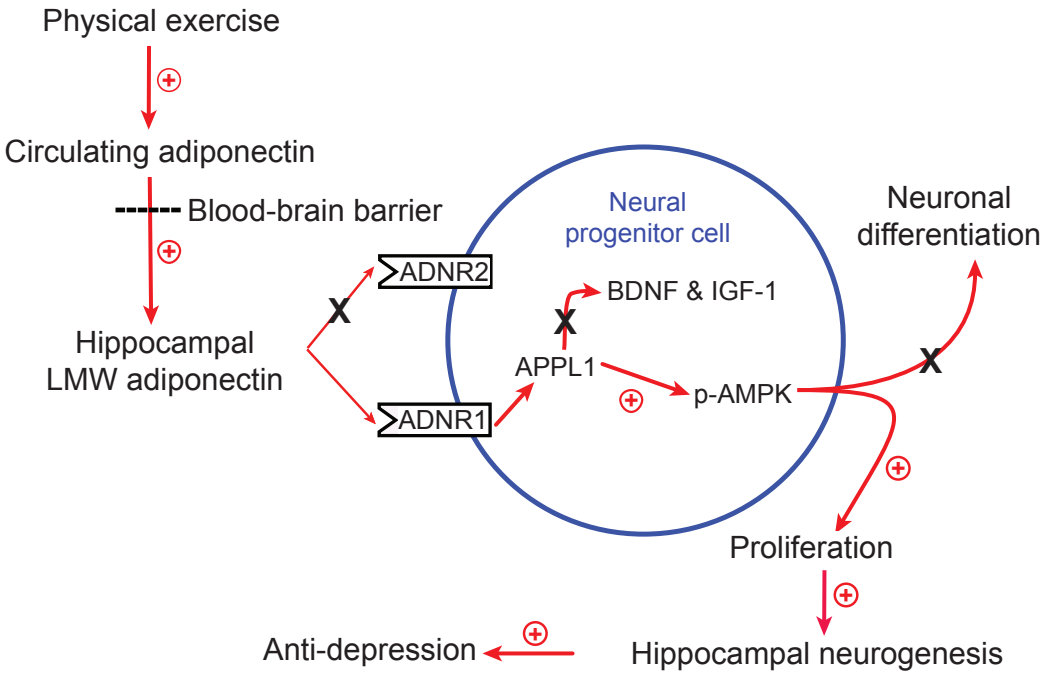

Figure 1 Schematic diagram illustrating the potential mechanism mediating the anti-depressive action of physical exercise.
As shown in this cartoon, physical exercise initially raises circulating adiponectin levels. The low-molecular-weight (LMW) form of adiponectin passes through the blood-brain barrier, and accumulates in the hippocampus to activate adiponectin receptor (ADNR) 1 expressed by neural progenitor cells. Following the relay of adapter protein containing PH domain, PTB domain and leucine zipper motif 1 (APPL1), the phosphorylated AMP-activated protein kinase (p-AMPK) is increased, subsequently initiating the downstream proneurogenic cascade that enhances hippocampal cell proliferation without affecting neuronal differentiation. The enlarged population of adult-born neurons changes the activity of neural circuits and enables the antidepressant effects elicited by physical exercise. Brain-derived neurotrophic factor (BDNF) and insulin-like growth factor (IGF-1) do not seem to directly crosstalk with this adiponectin-stimulated proneurogenic pathway.

this neurotrophic family as a key molecule modulating the antidepressant effects of physical exercise (Yau et al., 2014). Adiponectin is released into the bloodstream after synthesis by mature adipocytes, and possesses anti-diabetic, anti-inflammatory, anti-atherogenic and cardio-protective properties (Kadowaki and Yamauchi, 2005). Resembling physical exercise, adiponectin is able to promote glucose utilization in the skeletal muscle and suppresses glucose production in the liver. Besides its well-known influence on metabolism, a few reports also suggest that adiponectin functions in the brain, such as altering hypothalamus-controlled food intake and energy expenditure, as well as protecting neurons against different insults (Thundyil et al., 2012).

In the latest study, we investigated the potential correlation among physical exercise, adiponectin, hippocampal neurogenesis and antidepressant-like effects (Yau et al., 2014). Overexpressing adiponectin after intracerebroventricular injection with recombinant adenovirus replicated the beneficial effects of physical exercise in sedentary C57BL/6J mice, including the enhancement of hippocampal neurogenesis and the proportional reduction of depression-like behaviors, which supports the causal relationship between these two parameters. The reported antidepressant-like property is in accordance with a prior publication that adiponectin-haploinsufficient mice with reduced adiponectin levels show a greater susceptibility to depression after exposure to chronic social isolation-elicited stress, while intracerebroventricular administration of recombinant adiponectin directly mitigates such a defect (Liu et al., 2012). Next, we examined the potential consequence of adiponectin deficiency to physical exercise-triggered benefits using adiponectin-knockout mice. Although the basal hippocampal cell proliferation, neuronal differentiation and depressive state remained comparable in both strains, physical exercise-stimulated hippocampal neurogenesis and anti-depressive activity were absent after knocking out adiponectin. Notably, this was unlikely due to the discrepancies of locomotor function or hippocampal levels of brain-derived neurotrophic factor and insulin-like growth factor, as the changes between adiponectin-knockout and wild-type runners were similar. In contrast, the elevated hippocampal adiponectin content following the 2-week voluntary wheel running was only observed in wild-type mice, suggesting this adiponectin increase might serve as the enabling step; in particular, the expression profiles of adiponectin receptors (ADNRs) and their adapter protein containing PH domain, PTB domain and leucine zipper motif 1 (APPL1) were unchanged. Since socially-defeated mice exhibit a shortened duration of interaction that parallels the circulating adiponectin reduction (Liu et al., 2012), we further explored whether the low-molecular-weight trimeric

adiponectin could be permeable to the blood-brain barrier. Reintroduction of the trimeric adiponectin into adiponectin-knockout mice by tail vein injection resulted in the appearance of adiponectin in the cerebrospinal fluid. Hence, adiponectin potentially enables the crosstalk between the peripheral adipose tissues and the brain.

For an in-depth mechanistic research, we assayed the hippocampal lysates and found that the running-stimulated phosphorylation of AMP-activated protein kinase (AMPK) was compromised after knocking out adiponectin. Of note, this signaling pathway can be activated by adiponectin (Kadowaki and Yamauchi, 2005) and is also known to promote hippocampal neurogenesis (Kobilo et al., 2011). Neurogenesis originates neural progenitor cells (Sahay and Hen, 2007). We isolated these primary cells from hippocampi of adult wild-type and adiponectin-knockout mice and proved that ADNR1, ADNR2 and APPL1 were expressed at similar levels compared with that in the murine neuroblastoma cell line N2a. Applying the trimeric adiponectin accelerated propagation in all of the three cell preparations, whereas down-regulating ADNR1, rather than ADNR2 diminished such a proneurogenic effect. Collectively, our data have substantiated the notion that adiponectin increase in the hippocampus following physical exercise activates ADNR1 to enhance the phosphorylation of AMPK in NPCs, subsequently enhancing hippocampal neurogenesis and lowering depressive severity (**Figure 1**).

The above-mentioned animal work has been in agreement with clinical studies, including that, (1) the low-molecular-weight adiponectin is detectable in the human cerebrospinal fluid (Taylor and Macqueen, 2010); (2) the reduction of serum adiponectin levels occurs in the major depressive patients (Leo et al., 2006), which could be restored by antidepressants (Narita et al., 2006); (3) diabetic patients with declined adiponectin levels often have a higher incidence of depression (Taylor and Macqueen, 2010). Interestingly, peroxisome proliferation-activated receptor-γ (PPARγ) agonists that increase the production of adiponectin coincidentally exert antidepressant-like effects (Sepanjnia et al., 2012). Likewise, vagus nerve stimulation, a non-pharmacological approach for treating drug-resistant depression, is known to induce neurogenesis (Biggio et al., 2009) and increase N-palmitoylethanolamide, an endogenous ligand of PPARα in the adipose tissue (Banni et al., 2012). Thus, it is possible that such antidepressant-like effects may be mediated by adiponectin signaling through enhancing the endogenous secretion of adiponectin.

Being a severe prevalent disabling disease, depression has caused an inestimable cost worldwide. Unfortunately, the lack of breakthrough in developing novel pharmaceutical agents owing to the poor understanding on the pathogenesis of depression has been lasting for decades, and the medicinal drugs currently applied in clinical therapy frequently cause side effects and sometimes turn out to be ineffective. The current research unveils a previously-unidentified role of adiponectin as the mediator conveying the proneurogenic and anti-depressive effects of physical exercise, accordingly shedding a light on treatment of depressive disorders through manipulating adiponectin levels in the brain with physical exercise or other adiponectin-secretion stimulants, such as PPAR agonists.

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