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Editorial

Taking Advantage of Neuronal Wnt and BDNF Signaling: Neuroprotective Mechanisms and Effects of Physical Exercise and the Potential for Ginko Biloba in Aging and Disease

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It is well known that running exercise promotes hippocampal neurogenesis in young animals [1-5] and that brain-derived neurotrophic factor (BDNF) mediates this effect [6]. BDNF is a putative neuronal survival protein that has been shown to play a pivotal ameliorative role in development, learning and memory and trauma and disease, such as mood disorders [6-10]. Thus, it has also been shown that the intracellular signaling mechanisms underlying this ameliorative effect of BDNF are shared by both exercise and pharmacotherapeutic interventions, such as antidepressant medications used for the treatment of mood disorders [6,11]. Much of the recovery process as a result of antidepressant and/or running exercise is a result of putative BDNF-induced dendritic arborization and/or axonal extension [12-14], synaptogenesis [15] and neurogenesis [9,16].

In addition, *in vitro* application of norepinephrine to embryonic hippocampal neurons increases hippocampal BDNF and two critical cell survival signaling pathways, PI-3K/Akt and MAPK, and phospho-cyclic adenosine-monophosphate binding protein (CREB) [17]. The application of norepinephrine to neurons in culture provided us with a viable tissue culture model that mimics the sympathetic nervous system-activated release of norephinephrine and epinephrine that occurs during physical exercise. Thus, norepinephrine-induced increase in BDNF has neuroprotective effects on neuronal survival when cells were stressed, deprived of certain critical nutrients [18,19]. This increase in hippocampal BDNF was brought about activating the phosphatidylinositol-3'-kinase (PI-3K)-Akt pro-survival pathway, which led to increased CREB phosphorylation.

There is evidence that running exercise-induced Wnt signaling mediates hippocampal neurogenesis in young animals through an up-regulation of BDNF [10]. Whether this also occurs in aged animals is still unknown, as the evidence for this is extremely sparse [20]. With general aging, there is a down-regulation of axonal growth, cytoskeletal assembly and transport, signaling, lipogenic uptake pathways and concomitant increase in immune/inflammatory lysosomal, protein/lipid degeneration, cholesterol transport, TGF and cAMP-mediated pathways [21]. In cognitively impaired aged rats, there is down-regulation of Wnt, insulin and its influences in lipid and glycogen pathways, and G-protein-coupled receptor (GPCR) signaling [21]. However, Miranda., *et al*. [22] investigated the communication between neural progenitor cells and astrocytes. They applied survivin, a chromosomal passenger protein (*aka* Birc5), to neural progenitor cells. Age-associated changes in neural progenitor cell proliferation reveal a decrease in neural progenitor cell with age, indicating that astrocytes in the neurogenic niche regulate changes in Wnt signaling via survivin regulation within neural progenitor cells [22]. That is, Wnts secreted from neighboring astrocytes regulate survivin expression and proliferation of adult neural progenitor cells [22]. And predictably, impaired Wnt signaling leads to decreased neurotrophin-induced neuroprotection and concomitant pathology [23].

Much of our understanding about Wnt signaling comes from studying crosstalk between astrocytes and neural progenitor cells [24]. *In vivo*, astrocytic Wnt3/3a expression and release decreases with age [25]. Moreover, in young and aged astrocytic cultures expressing Wnt3 shRNA, there was increased tubulin III and synapsin I expression, indicating that astrocytic Wnt3a causes a neurogenic effect on adult hippocampal neural stem cells in an age-dependent manner and that such cells are primed for increased growth and neurotransmitter release.

These neural stem cells will eventually become granule cells in which the *Prox1* promotor will be regulated, which remains highly active throughout the maturation of the granule cell and may be responsible for specifying the neuronal phenotype [26]. Furthermore, Okamoto., *et al*. [24] found that the doublecortin (dcx) genes activate the dcx promotor, which contains two L1 sequences regions with Wnt signaling regulatory sites. At the *Neurod1* promotor, binding of acetylated histone A3, β-catenin, and CREB gradually decreases with aging, indicating that the aging process controls the repressive chromatin state. It is possible that physical exercise may decrease this repression.

Aging specifically compromises Wnt pathway signaling [25], whereas exercise increases Wnt3 expression, thereby reversing the decline in neurogenesis brought on by age [24], as well as genes downstream of it [27,28]. In addition, although either an enriched environment or Wnt7/7a application had the same effects on neurogenesis [29], it is possible that the running component of such a stimulating environment was the crucial ingredient in eliciting neurogenesis [30].

Recent studies have shown that Ginko biloba also has neuroprotective effects in a rat model of depression [31] and stroke [32]. Such neuroprotection may occur through activation of the transcription factor CREB [32,33] and the promotion of neurogenesis [34]. Such findings naturally beg the question regarding the potential benefits to be derived from natural medicines. Many of the drugs in use today, such as morphine, digitalis and vinblastine, are alkaloids – derived from natural compounds. However, each of these is a single molecule with a specific pharmacologic profile. For natural plant extracts, such as Ginko biloba, comprehensive detailed studies should be carried out on its main active ingredients, such as bilobilide [35] and quercetin [36]. There is much potential in the ability of such molecules to be medically beneficial [35,36] if more progress can be made to thoroughly characterize each chemical or at least, each putative active ingredient. Only through a thorough understanding of the molecular and genetic mechanisms of such molecules [37,38] can light be shed on how the extract works as a whole. And when combined with physical exercise, pathology-induced clinical functional loss can be delayed even more than when only one or the other intervention alone is employed.

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