

Mini Review

Hippocampal insulin signaling and neuroprotection mediated by physical exercise in Alzheimer's Disease

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Abstract — Epidemiological studies indicate continuous increases in the prevalence of Alzheimer's Disease (AD) in the next few decades. The key feature of this disease is hippocampal neurodegeneration. This structure has an important role in learning and memory. Intense research efforts have sought to elucidate neuroprotective mechanisms responsible for hippocampal integrity. Insulin signaling seems to be a very promising pathway for the prevention and treatment of AD. This hormone has been described as a powerful activator of neuronal survival. Recent research showed that reduced insulin sensitivity leads to low-grade inflammation, and both phenomena are closely related to AD genesis. Concomitantly, exercise has been shown to exert anti-inflammatory effects and to promote improvement in insulin signaling in the hippocampus, which supports neuronal survival and constitutes an interesting non-pharmacological alternative for the prevention and treatment of AD. This review examines recent advances in understanding the molecular mechanisms involved in hippocampal neuroprotection mediated by exercise.

Keywords: insulin, hippocampus, inflammation, physical exercise.

Introduction

Alzheimer's disease (AD) is the most common form of dementia manifestation¹ and its prevalence increases with aging population². Alzheimer's Disease International³ estimates that dementias reach around 46.8 million people in the world in 2015. Projections indicate that this number will double every 20 years, reaching a 74 million in 2030 and 131 million in 2050³. In 2050, it is expected that at least 100 million of these patients will suffer from AD^{4,5}. In the last year, 818 billion dollars were invested to treat the main forms of dementia. This cost includes hospital expenses, caregivers services and personal expenses, and in 2030, it is estimated a budget of 2 trillion dollars³. Among the reasons to justify this exorbitant cost it is the absence of an effective cure or therapeutic treatment that really slows the progress of AD and other dementias.

Despite significant progress in elucidating the molecular mechanisms involved in neuron survival and the main agents involved in neuronal protection or neuron degeneration in the hippocampus, the scientific community still has big gaps to

translate these findings across species: therapies that work in rodents often do not succeed in humans⁶.

In hippocampal neurons, insulin and growth factors such as BDNF (brain derived neurotrophic factor), IGF-1 and 2 (Insulin-like growth factors 1 and 2) and VEGF (vascular endothelial growth factor) transmit the intracellular signal for neuronal integrity. Under regular physiological conditions, insulin and growth factors act properly to promote neuronal survival keeping the hippocampus functionality. When insulin and growth factors are inhibited to properly exercise its effects we have a favorable condition for the establishment of AD. Changes in insulin and growth factors signaling disrupts neuronal survival contributing to AD pathogenesis. The neuropathology hallmark of AD is characterized by accumulation of β -amyloid, synaptic dysfunction, neuronal inflammation, phosphorylation of tau protein and neurofibrillary tangle formation^{1,6}.

Exercise has been shown to attenuate inflammation in the hippocampus⁷. The insulin sensitizing effects of physical exercise in peripheral tissues are well described in the literature⁸. However, it is more recent the progress to unveil the effects on

the central nervous system (SNC), especially in hippocampal functions and a possible neuroprotective role in AD⁴. Therefore, the objective of this review is to present the molecular aspects involved in the development of AD and the role of physical exercise in the prevention and treatment of this disorder. This study is a narrative mini-review, including relevant work in the author's field of expertise and current literature. Articles that describe the molecular mechanisms of cellular signaling in AD were selected, with special attention to insulin signaling pathway. In addition, were included papers that highlight the relevant role of physical exercise to prevent and attenuate the inflammatory and neurodegenerative process of this disease.

Hippocampal Insulin Signaling

Insulin exerts intracellular signaling by binding to the insulin receptor (IR). The IR is composed of two α -subunits and two β -subunits connected through disulfide bonds. Insulin binding to α -subunit induces receptor conformational change and activates the tyrosine kinase activity of the β -subunit. The β subunit has an intrinsic tyrosine kinase activity, having the ability to phosphorylate itself and other tyrosine substrates. Tyrosine phosphorylation of major insulin receptor substrates (IRS-1 and IRS-2) by IR creates binding sites for the enzyme phosphatidylinositol-3 kinase (PI3K), activating it. Once activated, PI3K converts the membrane phospholipid phosphatidylinositol 4,5biphosphate to phosphatidylinositol 3,4,5-trisphosphate. This conversion mediates the activation of the protein kinase B (PKB/Akt) through the 3-phosphoinositide dependent kinase (PDK). The protein kinase B PKB/Akt signaling coordinates diverse cellular responses^{8,9}. One of the main actions of this protein in the hippocampus is to promote neuronal survival. Akt enhances phosphorylation of FOXO transcription factor (forkhead box transcriptional factor family) and promotes its extrusion from the cell nucleus for subsequent proteasomal degradation. The FOXO presence in the nucleus acts as transcription factor of pro-apoptotic proteins and contributes to degenerative process¹⁰.

In addition, Akt is responsible for inactivating protein of GSK3- β (glycogen synthase kinase 3 β). When activated in hippocampal neurons, GSK3- β promotes the phosphorylation of tau protein a major contributor to AD. By reducing the ability of insulin to propagate its intracellular signal, the continuous activation of GSK3- β promotes hyperphosphorylation of tau protein⁹ and the subsequent formation of neurofibrillary tangles. All this mechanism results deleterious effects on synaptic dysfunction and cognitive impairment¹.

The accumulation of β -amyloid oligomers is another pathogenic aspect of AD. These oligomers are main component of senile plaques seen in brains with AD. The β -amyloid protein is a peptide originated from cleavage of amyloid precursor protein (APP) by gamma-secretase enzyme¹¹ and leads to neurotoxicity. Several studies have provided evidence between insulin metabolism and β -amyloid accumulation. The hyperinsulinemia may increase the extracellular concentration of β -amyloid protein by increasing its release from neurons and modulation of gamma-secretase enzyme activity¹². Other findings have

shown that increased insulin concentration in the extracellular medium competes with β -amyloid protein as substrate of the insulin degradation enzyme (IDE). This protein may degrade insulin or β -amyloid protein. By promoting the degradation of insulin instead of β -amyloid protein, this mechanism hits the neuron in two different ways. First, by reducing the degradation of β -amyloid protein and second, by reducing the binding of insulin IR and, thus, its ability to spread its neuroprotective signal intracellularly¹².

Inside the cell, the phosphorylation of IRS 1 and 2 also activates the mitogen activated protein kinase (MAPK) cascade of Ras/MEK/ERK¹³, triggering multiple cell responses. The ERK phosphorylation leads growth, differentiation and proliferation of hippocampal neurons, being essential for neuronal survival and neurogenesis¹⁴ through the activation of cytosolic proteins and transcription factors in the nucleus¹⁵. The main target protein phosphorylation of ERK (extracellular signal-regulated kinase) is CREB (cAMP response binding protein). This protein function in hippocampus results the formation of long-term memory and increases synaptic plasticity¹⁶. These modifications generate activity-dependent responses of synaptic transmission efficiency (functional plasticity) and changes in the structure and number of synaptic connections (structural plasticity)¹⁷.

Understanding insulin signaling is important to understand the connection between the mechanisms underlying inflammation and the reduced action of this hormone. Moreover, this accumulated knowledge involving the insulin signal transduction in the hippocampus has allowed the understanding of the effect of exercise to cooperate in mitigating the disease.

Inflammation and Insulin Resistance

The low-grade inflammation is a molecular process that reduces the capacity of insulin to propagate their intracellular signal, culminating in a state of insulin resistance. Compensatory body's response to reduced insulin action consists of the chronic conditions of hyperinsulinemia¹⁸, providing the basis for the establishment of Diabetes Mellitus Type 2 (DM2). It was found that the AD has features in common with DM2, leading some researchers to announce the AD as Diabetes Type 3. The insulin resistance and decrease of growth factors are closely associated with typical neurodegeneration in AD⁹. During inflammation, hippocampal levels of pro-inflammatory cytokines such as TNF- α (tumor necrosis factor alpha) and β -IL1 (interleukin 1 β) are elevated⁷. One factor that is highly related to increased cytokines is aging^{7,19} and this process is denominated "Inflammaging"^{20,21}. This condition has high prevalence in the elderly population and AD carriers³. The cytokines bind to their receptors trigger the inflammatory pathway through the JNK protein (c-Jun N-terminal kinase) and IKK (I kappa B kinase) activation. Both proteins disrupt insulin signaling and exacerbate inflammation by increasing the transcription of inflammatory genes²².

JNK is a serine kinase activated by TNF- α binding to the receptor or through the activation of TLR-4 receptors (Toll-like receptor 4)²¹. When activated by these pathways, the JNK promotes phosphorylation of IRS-1 serine³⁰⁷ turning off key steps

of its signaling cascade and constituting a major mechanism of insulin resistance²². JNK also acts as activator of the transcription factor AP1 leading to the transcription inflammatory genes and cytokines production²². The *post-mortem* brains from AD patients showed increased phosphorylation of IRS-1 in the serine³⁰⁷ residue and JNK expression, just as like in T2DM patients²³. Other studies have shown that both oligomers of β -amyloid protein²³ as a high fat diet activate JNK phosphorylation in hippocampal neurons²⁴. Both findings led to increased IRS-1 serine³⁰⁷ phosphorylation and tau protein levels. This mechanism brings a strong association between AD and obesity due to the reduction of insulin signaling in neuronal survival. Although the aging process is associated with increased inflammation, this situation is even worse in the obese elderly.

The other mediator of insulin resistance is IKK. When activated by the signaling cascade of TNF- α and TLR-4, the IKK cleaves the NF- κ B/I κ B complex¹⁹. This complex disruption releases the transcription factor NF- κ B (nuclear factor kappa B), which migrates to the nucleus and initiates transcription proteins such as TNF- α , IL1- β and iNOS^{7,19,22}. In addition, IKK is also capable of promoting IRS-1 serine³⁰⁷ phosphorylation in hippocampal neurons upon activation by oligomers of β -amyloid protein²³. The aging contributes to increased activation of NF- κ B transcription factor in hippocampus and may be one of the factors by which AD is mainly related to elderly population⁷.

The numerous events that lead to activation of inflammatory signaling involve formation and clearance of several different proteins. The crucial organelle for this machinery is the endoplasmic reticulum (ER). This structure is a major regulator of inflammation feedback. This important site is responsible for the proper synthesis and protein folding²². This organelle is also highly sensitive to disturbances in cellular homeostasis and ER malfunction increases the concentration of misfolded proteins, altering the normal functionality of these proteins. This state of unbalance of protein folding is denominated endoplasmic reticulum stress²⁵. The circulating lipids has a powerful effect of endoplasmic reticulum stress, linking the excessive consumption of this macronutrient and obesity²⁵. As cellular response to restore the level of unfolded proteins properly there is a mechanism denominated UPR (unfolded protein response). This mechanism consists in the activation of proteins IRE1 (inositol-requiring enzyme 1), PERK (protein kinase (PKR) -like endoplasmic reticulum kinase) and ATF6 (activating transcription factor 6). This regulation reduces the overall transcription of inflammatory agents and increase the synthesis of chaperones, restoring the proper function of endoplasmic reticulum²². However, with persistent ER stress, the UPR ultimately triggers cellular defense mechanisms by inflammation and programmed cell death (apoptosis) in last case. This role process involves the previous described proteins JNK and NF- κ B.

In summary, these mechanisms (JNK, IKK and ER stress) are the major agents of low-grade inflammation and insulin resistance. Activation of these pathways in the hippocampus results in reduced ability of insulin to exerts its neuroprotective effect and the consequences are accumulation of β -amyloid oligomers, hyperphosphorylation of tau protein and neuronal apoptosis, creating favorable conditions for the genesis of AD.

The next step is to discover how exercise works in this context to reduce the expression and activity of inflammatory and apoptotic proteins.

Neuroprotection Mediated by Physical Exercise

The effects of exercise on insulin signaling pathway have been intensively investigated in the last few years. On peripheral tissues, exercise stimulates the glucose uptake independent of insulin via activation of protein kinase activated by AMP (AMPK) and mTOR (mammalian target of rapamycin)²⁶. In addition, the exercise reduces the activation of serine kinase JNK and IKK²⁷, attenuating the subclinical inflammation and the deleterious effects pro-inflammatory cytokines on the insulin signal transduction. However, physical exercise exerts different effects on the CNS. Several beneficial results demonstrated that physical exercise improves synaptic plasticity and cognition^{13,28}, regulates the production and degradation of neurotransmitters^{29,30} and increases angiogenesis³¹ and neurogenesis³². Although the molecular mechanisms responsible for these events are not completely understood, there are strong evidences showing the exercise mediating the production and sensitivity to growth factors such as BDNF, IGF-1, IGF-2 and VEGF^{1,28,32,33}.

Diegues and colleagues¹³ conducted an elegant study in which investigated the molecular mechanisms of physical training in diabetic Wistar rats. After induction of diabetes by administration of Alloxan, these researchers have found impaired performance in Morris water maze (spatial memory test) in sedentary diabetic rats compared to diabetic animals subjected to physical training (6 weeks of swimming, 1 hour daily for 5 days per week and the animal supporting load corresponding to 90% of the anaerobic threshold). Further analysis in hippocampus showed increased IGF-1 receptor expression and phosphorylation of Akt-1/2 isoforms in trained groups. The sedentary diabetic rats, however, presented increased β -amyloid phosphorylation. Furthermore, the exercise reduced both the expression of APP and the phosphorylation of tau protein, which is consistent evidence about the neuroprotective effects of exercise on hippocampal neurons and prevention of AD.

The hippocampal neuroprotection mediated by exercise has been under investigation of Um and colleagues³⁴. In this remarkable study, Tg-NSE / hPS2m mice (transgenic model of AD) performed physical training for 3 months on a treadmill (5 days per week with a daily 60 minutes and speed of 12 m/min). Analyzing hippocampal samples, they found reduced expression of β -amyloid protein, Cox-2 (cyclooxygenase 2) and caspase-3 (pro-apoptotic protein) in trained animals. These alterations were concomitant to reduced JNK and tau phosphorylation and increased ERK phosphorylation, CREB, PI3K, Akt and GSK3- β , all involved in insulin signaling pathway. They also found reduced apoptotic state of hippocampal neurons in mice trained through a TUNEL assay to detect DNA fragmentation typical of apoptotic process. In addition, they have found a substantial increase of BDNF expression. These results demonstrate in mice the powerful effect of exercise training to reduce or even reverse the inflammation and apoptosis of hippocampal neurons present in AD.

The high fat diet consumption and obesity are one of the main cause of ER stress. Feeding Sprague-Dawley rats with high fat diet for 8 weeks was sufficient to induce obesity and ER stress in hippocampus³⁵. A study conducted by Cai and colleagues³⁵ supported this fact, revealing increased IRE-1 and eIF2a phosphorylation/total extract protein ration in obese rats. Physical training treadmill (8 weeks, 5 days per week with 40 minutes daily and speed of 18m/min) have shown a powerful tool in this scenario. Physical exercise recovered the ERK and CREB phosphorylation in high fat animals in comparison to sedentary chow-fed animals. In fact, the trained chow-fed animals showed the highest levels of ERK and CREB phosphorylation among all groups studied. Obesity increased expression of apoptotic proteins (caspase-12, CHOP and Bax) and reduced Bcl-2(anti-apoptotic) content. However, it was significantly restored in the obese trained group in comparison to obese sedentary group, but not to levels of lean animals. While physical exercise contributed to reduction of ER stress, these results demonstrate that the losses caused by obesity are not fully restored. This gap can be an important target for development of more efficient protocols of physical training. Further, reinforcing the importance of weight control and reduced intake of saturated fats to prevent the degeneration of hippocampal neurons.

The activation of the transcription factor NF- κ B appears to have close relation to aging and the AD development. Aged Wistar animals (20 months) showed increased activation of NF- κ B in hippocampus compared to young animals (3 months)⁷. In the same study, it was investigated the effect of two weeks of exercise on a treadmill (20 minutes per day to 60% of the estimated intensity of maximum consumption of animal oxygen) on the activation of NF- κ B in the hippocampus, and there was no significant difference between young animals that were or not subjected to exercise. However, in older animals (20 months), physical exercise was able to reduce the NF- κ B activation in the hippocampus 1 hour after the last exercise bout. In this particular study, Wistar rats were not induced obesity, diabetes or DA, leading us to believe that exercise may attenuates the effect of aging⁷. Future studies shall be conducted to investigate the effects of exercise on the NF- κ B activation in the hippocampus of animals at different ages.

Recent results indicate that physical exercise promotes increased phosphorylation of AMPK in the hippocampus^{36,37}. AMPK is an essential regulator of autophagy leading degradation and inhibition of poorly folded proteins. This mechanism prevents and stops the ER stress contributing for the cell function. The pharmacological activation of AMPK in cell culture was able to promote the degradation of β -amyloid protein³⁸. However, further researches need to investigate the AMPK activation mediated by physical exercise *in vivo*.

The effects of exercise on insulin signaling and neuroinflammation are truly relevant in the hippocampus. Physical training reduces the expression of β -amyloid (34) and tau phosphorylation¹³, classic hallmarks in development of AD. The increased signal transduction of the insulin pathway of key proteins in the hippocampus, as Akt and ERK, is an indication that there is direct positive effect on neuronal survival. Furthermore, the insulin signaling acts on inflammation, reducing the JNK

phosphorylation, NF- κ B activation and transcription of both pro-inflammatory and pro-apoptotic proteins. For all these actions, it is possible that the exercise is still an underestimated method, but promising method for prevention and treatment of AD. In the same context, Figure 1 shows an original and schematic illustration of the effects of exercise, which promote neuroprotection in the hippocampus.

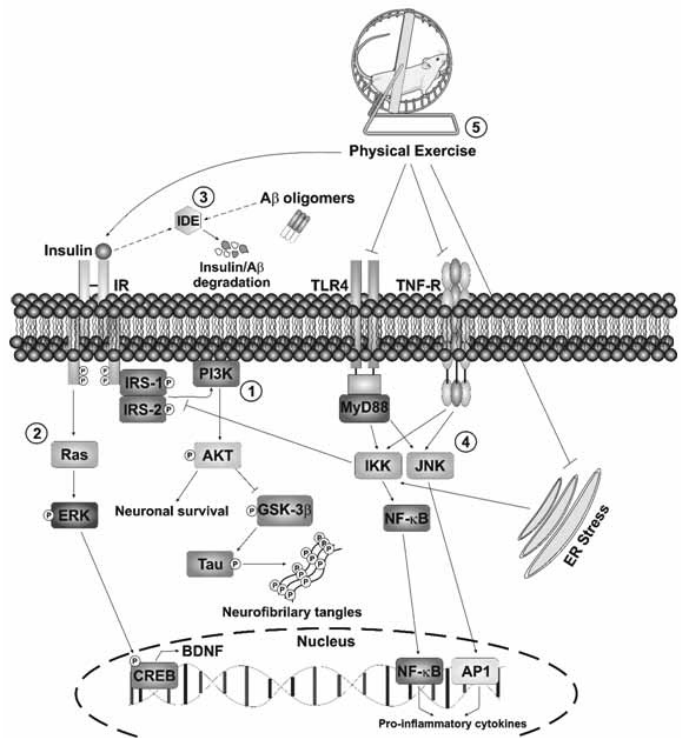


Figure 1. In hippocampal neurons, binding of insulin to the IR active routes of PI3-K/Akt and MAPKs. 1) PI3K/Akt activation leads to inhibition of GSK3 beta activity, reducing phosphorylation of tau protein, a protein strictly involved in AD. This pathway also promotes neuronal survival by an antiapoptotic effect through FOXO phosphorylation and deactivation. FOXO is an important transcriptional factor of genes involved in apoptosis and it is active when dephosphorylated. 2) The MAPKs pathway (Ras/ERK) induces CREB phosphorylation and activation, increasing the transcription of BDNF, an important growth factor. 3) The IDE is a major degradative enzymes β -amyloid. Higher levels of circulating insulin competes as substrate for degradation by IDE, favoring the concentration of β -amyloid. The hyperphosphorylation of tau protein and β -amyloid accumulation are typical characteristics of brain with Alzheimer's disease. 4) Pro-inflammatory mechanisms, such as activation of JNK and IKK enzymes by TNF- α , TLR-4 and Endoplasmic Reticulum Stress, reduce the ability of insulin to propagate their intracellular signal and contribute to the pathogenesis of Alzheimer's disease. 5) On the other hand, physical exercise has been shown to be effective in attenuating inflammation and restoring the insulin signaling in hippocampal neurons and proved to be an interesting alternative for the

treatment of AD. AD, Alzheimer disease; IR, insulin receptor; IDE, insulin degrading enzyme; IRS-1/2, 1/2 substrate insulin receptor; PI3-K, phosphatidylinositol 3 kinase; Akt protein kinase B; GSK3- β , glycogen synthase kinase 3 beta; ERK, extracellular signal-regulated kinase; CREB: cAMP response element binding protein; BDNF, brain-derived neurotrophic factor TLR4, toll like receptor 4; TNF-R, tumor necrosis factor receptor; IKK, I kappa B kinase; JNK, c-Jun N-terminal kinase; NF-kB, nuclear factor kappa B; AP1, activator protein 1 transcriptional factor; ER, endoplasmic reticulum. This figure is original and made by the authors with the purpose of illustrate the molecular mechanisms involved in AD.

In a recent meta-analysis³⁹, it was estimated that physical exercise could reduce the risk of AD development by up to 45%. Despite the limitations of performing this measurement due to different exercise protocols used, the studies showed that variables related to physical exercise as type, frequency, intensity, duration and progression could produce different physiological and metabolic responses. Although that is very well established that physical exercise promotes beneficial effects in AD, there is no consensus on which dose between volume, intensity or type of exercise is better to treat⁴⁰. Nevertheless, it is accept that both moderated or high-intensity as resistance and strength training promotes neuroprotective effects⁴⁰.

The greater challenge of the scientific community in the future is overcome the difficulties of translation between species in studies of AD. Elucidate the mechanisms involved in neuroprotection mediated by exercise will help our understanding in the AD and the understanding of each result may provide the missing information that we need to treat or prevent this disease.

Conclusion

Exercise has been shown to promote neuronal survival and protection, especially in the hippocampus. This important structure responsible for learning and memory functions is severely affected by AD. The positive effects of exercise are known to reduce low-grade inflammation, increase insulin sensitivity and augment the expression of growth factors in hippocampal neurons.

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