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COMMENTARY

Therapeutic potential of IGF-I on hippocampal neurogenesis and function during aging

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ABSTRACT

In rats, learning and memory performance decline during normal aging, which is paralleled by a severe reduction of the levels of neurogenesis in the hippocampal dentate gyrus (DG). A promising therapeutic strategy to restore neurogenesis in the hippocampus of old rats and their spatial memory involves the use of insulin-like growth factor-I (IGF-I). The peptide exerts pleiotropic effects in the brain, regulating multiple cellular processes. Thus, 4-week intracerebroventricular (ICV) perfusion of IGF-I significantly restored spatial memory and hippocampal neurogenesis in old male rats. Similar results were achieved by ICV IGF-I gene therapy in aging female rats. Thus, the treatment seemed to increase the number of immature neurons in the DG of 28 mo old rats, which was paralleled by an increase in the accuracy of the animals to remember specific patterns, which is known as pattern separation memory. The DG is thought to be the main hippocampal structure involved in pattern separation memory and there is evidence that the level of neurogenesis in the DG is directly related to pattern separation performance in rodents. Summing up, IGF-I emerges as a promising restorative molecule for increasing hippocampal neurogenesis and memory accuracy in aged individuals and possibly, in neurodegenerative pathologies.

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Introduction

Aging is associated with a progressive increase in the incidence of neurodegenerative diseases in both laboratory animals and humans. In particular, cognitive aging and its most devastating expression, Alzheimer Disease (AD), represent a growing medical and socio-economic challenge that calls for vigorous research efforts across the globe to design effective therapeutic interventions.[1] In rats as in humans, learning and memory performance decline during normal aging which makes this rodent species a suitable model to evaluate therapeutic strategies of potential value for correcting age-related cognitive deficits. Some of these strategies involve the administration of neurotrophic factors like insulin-like growth factor-I (IGF-I). What follows, will focus on the evidence pointing to IGF-I as a promising neuroprotective molecule for improving spatial memory and hippocampal neurogenesis in the aging brain. Other, lesser restorative effects of IGF-I on the morphology of the old hippocampus will be briefly mentioned.

IGF-I as a physiologic neuroprotective molecule

There is clear evidence that IGF-I plays a physiologic role in neuroprotection. Thus, IGF-I is strongly induced in the central nervous system (CNS) after different insults such as ischemia,[2] cortical injury[3] and spinal cord lesions.[4] In situations involving cytotoxic damage in the hippocampus, the microglia of this region dramatically increases production of IGF-I and IGF-I binding protein 2, which suggests a neuroprotective role of these molecules in the CNS.[5] Also, the neuroprotective effect of physical exercise in rodent models of ataxia, domoic acid-mediated hippocampal damage and inherited Purkinje cell degeneration (pcd mouse model) was reported to be mediated by circulating IGF-I.[6] Several lines of evidence demonstrate the relevance of IGF-I for neuronal survival. Thus, *in vitro* studies have shown that IGF-I increases cell survival in primary hypothalamic cell cultures.[7] It has been also documented that IGF-I stimulates differentiation of rat mesencephalic dopaminergic (DA) neurons.[8] A protective effect of IGF-I has been reported

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in immortalized hypothalamic cells exposed to reduced glutathione-depleting agents,[9] in human DA cell cultures exposed to the toxin salsolinol[10] and in human and rodent neuronal cultures exposed to toxic doses of DA.[11]

IGF-I-gene delivery promotes corticospinal neuronal survival after adult brain injury.[12] Combined with pAKT, IGF-I signaling promote hippocampal CA1 neuronal survival following injury to dendate granule cells.[13] Conversely, adult-onset deficiency in growth hormone and IGF-I decreases survival of dendate granule neurons.[14]

IGF-I and neurogenesis

The generation of neurons in the adult mammalian brain requires the activation of quiescent neural stem cells (NSCs). This activation and the sequential steps of neuron formation from NSCs are regulated by a number of stimuli, including growth factors like IGF-I which exerts pleiotropic effects on the brain. Although IGF-I expression is relatively high in the embryonic brain its levels drop sharply in adult brains except in neurogenic regions like the hippocampus, subventricular zone (SVZ) and olfactory bulb (OB).[15] IGF-I can cross the blood-brain-barrier by binding to the IGF-IR (IGF-I Receptor) on endothelial cells and later it is picked up either by astrocytes to be transferred to neurons or directly by neurons.[16]

The IGF-I/IGF-IR system regulates the differentiation and maturation of neurons generated from NSCs and progenitors both during embryonic development and in the adult brain largely via the PI3K/Akt pathway.[17] In igf-I and igf-IR KO mice, a reduction in the number of neurons during embryonic development and postnatal-adult neurogenesis in the SVZ, OB and hippocampus has been described.[18] Transgenic conditional mice that overexpress igf-1 exhibit an increase in the number of neurons in the hippocampus.[19]

Therapeutic potential of IGF-1 for neuroprotection

Direct IGF-I infusion has been used to protect different brain regions. For instance, studies in 6-hydroxydopamine-lesioned rats suggest that IGF-I mediates the neuroprotective effect of estrogen on nigral DA neurons.[20] In a rat model of cerebellar ataxia (induced by 3-acetylpyridine (AC)), subcutaneous (sc) or intracerebro-ventricular (ICV) administration of IGF-I restored motor coordination and partially rescued inferior olive neurons from the toxic effect of AC.[6] Continuous infusion of IGF-I in the lateral ventricle, partially restored reference and working memory in 32- as compare with 4-month old male rats.[21] Furthermore, IGF-I has been reported to protect hippocampal neurons from the toxic effects of amyloid peptides.[22] Interestingly, IGF-I treatment of mice overexpressing a mutant Aβ amyloid peptide markedly reduced their brain burden of Aβ amyloid.[23]

A novel approach for IGF-I delivery involves the use of IGF-I-producing human neural progenitor cells (hNPC) which were transplanted into a rat model of Parkinson Disease (PD) generated by nigral injection of 6-hydroxydopamine (6-OHDA), a dopaminergic toxin, 7 d prior to the hNPC treatment. The results showed that the treatment reduced asymmetric rotation as well as DA neuron loss and increased overall survival of hNPC.[24]

A recent study showed that subcutaneous injection of IGF-I coupled to polyethylene glycol in *pmn* mutant mice, a model with typical dying-back motoneuron degeneration, prolonged survival, protected mice against late stage weight loss and significantly maintained muscle force and motor coordination.[25]

Gene therapy for IGF-I

Gene therapy for IGF-I has shown promising results in the brain of aging rats. Thus, a recombinant adenoviral vector (RAd-IGFI) harboring the gene for rat IGF-I was used to implement IGF-I gene therapy in the hypothalamus of senile female rats, which display tuberoinfundibular dopaminergic (TIDA) neurodegeneration and, as a consequence, chronic hyperprolactinemia. Restorative IGF-I gene therapy was implemented in young (5 mo.) and senile (28 mo.) female rats, which received a single intrahypothalamic injection RAd-βgal (a control adenoviral vector expressing β-galactosidase) or RAd-IGFI and were sacrificed 17 d post-injection. In young animals, neither vector modified serum prolactin levels but in RAd-IGFI-injected senile rats a nearly full reversion of their hyperprolactinemic status was recorded. Morphometric analysis revealed a significant increase in the total number of tyrosine hydroxylase (TH) positive cells in the hypothalamus of experimental as compared with control senile animals.[26] These results suggested, although did not prove, that IGF-I may

have a neurogenic action on hypothalamic DA neuron populations in senile animals. Interestingly, IGF-I gene therapy did not affect DA neuron population in the hypothalamus of young rats. The neurogenic and astrogenic activity of IGF-I in the hypothalamus was subsequently demonstrated in vivo in adult rats.[27] A point of concern, regarding the administration of IGF-I peripherally, stems from the mitogenic activity of the peptide. Exposure to high circulating levels of IGF-I may lead to breast or prostate hyperplasia and eventually tumors. If the peptide is injected ICV or in brain structures, tumorigenic risk is minimized.

IGF-I gene therapy and neurogenesis in the dentate gyrus (DG) of old rats

It is well-established that neurogenesis in the DG declines significantly with aging in both female and male rats. This change seems to be causally associated to a decline in spatial memory. Thus, it has been reported that the accuracy to remember the escape hole in the Barnes maze declines with age in female rats, a change that is paralleled by an age-related reduction in the numbers of doblecortin (DCX) neurons in the DG.[28] In 28 months old male Brown Norway X Fischer 344 rats, a significant reduction in the number of newly generated cells was reported in the DG as well as a 60% reduction in diferentiation of newborn cells into neurons.[29] In the same study it was demonstrated that ICV administration of IGF-I peptide to old animals, signifcantly restored neurogenesis in the DG through an approximately 3-fold increase in neuronal production, without having any effect on progenitor differentiation to neurons or on survival of newborn cells. Lichtenwalner *et al.*[29] administered the IGF-I peptide via repeated ventricular osmotic minipump implants (for 28 days) to old rats. In order to improve this experimental approach, the gene for IGF-I was delivered ICV using an adenoviral vector. The decision to use an adenovector for ICV gene delivery was based on the fact that adenoviral vectors are highly selective for ependymal cells which were efficiently transduced by RAd-IGF-I, an adenovector harboring the gene for rat IGF-I, thus significantly increasing IGF-I levels in the cerebrospinal fluid (CSF).[30] This way it was possible to efficiently transduce the ependymal layer, thus increasing CSF levels of IGF-I in old female rats even 18 d after vector injection.[31] With this approach it was observed that IGF-I gene therapy significantly improved spatial memory accuracy as compared with control counterparts. In the DG of the old rats submitted to IGF-I gene therapy it was observed a higher number of immature neurons than in the old controls. Since IGF-I gene therapy increases the neurogenic activity in the DG of old rats[31] an increased neurogenesis may induce an improvement of pattern separation, which is defined as the ability to separate the components of memories into distinct complex memory representations that are unique and therefore allow an accurate discrimination of similar patterns. The DG is thought to be the main hippocampal structure involved in pattern separation memory[32] and the level of neurogenesis in the DG is directly related to pattern separation performance in rodents.[33] Furthermore, a number of studies in rodents, primates and humans have shown that DG is a region particularly vulnerable to the effects of aging and that hippocampal aging is associated with an impairment in pattern separation function which is likely to be due in large measure to age-related reduction in DG neurogenesis.[34] It is of interest that IGF-I gene therapy in old female rats also increased hippocampal astrocyte branching and reduced their numbers in the hippocampal stratum radiatum.[31] In an earlier study, an age-related reduction in length and complexity of hippocampal astrocyte processes in female rats was reported.[28] Reduced branching in aged astrocytes may impair the ability of these cells to provide trophic support to neurons. Therefore, the finding that IGF-I gene delivery to the brain of old rats restores complexity (but not length) of glial processes in the hippocampus, suggests that this effect may contribute to improving neuronal function in the region.

Concluding remarks

It is well-established that IGF-I has pleoitropic actions on the CNS, including neurogenesis and neuroprotection. Current evidence suggests that overexpression of the peptide in the aging rat brain is able to improve the accuracy of spatial memory, acting at least in part via a neurogenic action on the DG and through a reduction of hippocampal age-related astrogliosis and microglial reactivity. The reported restorative effects were achieved after a relatively short exposure of the CNS to IGF-I (less than a month). A longer exposure of the brain to

the peptide could effect additional restorative actions on spatial memory in old rodents.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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