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Insulin-like Growth Factor 2: Beyond its Role in Hippocampal-dependent Memory

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Insulin-like Growth Factor 2 (IGF2) and Its Signaling in the Nervous System

The insulin-like peptides family is composed of insulin, insulin-like growth factor 1 (IGF1), and insulin-like growth factor (IGF2), together with IGF binding proteins (IGFBP1-IGFBP6) [1]. IGF2 is a single-chain secreted protein of 67 amino acids with important functions in fetal growth and development. IGF2 is the less characterized member of this family, and in mice and rats its expression in the brain occurs during embryonic development and adulthood but declines during aging [2]. Alterations in its expression have an impact both in tissue overgrowth as well as reduce growth observed in the Beckwith-Wiedemann syndrome and the Silver-Russell syndrome, respectively [3]. Despite this, IGF2 is the most abundantly expressed IGF in the central nervous system, where it is highly synthesized in the choroid plexus and meninges in adult rat brains [4]. IGF2 binds with high affinity to the IGF2 receptor (IGF2R), which is also a mannose 6-phosphate (M6P) receptor. The IGF2 receptor is a transmembrane glycoprotein containing a short carboxy-terminal cytoplasmatic tail and a long extracytoplasmic domain containing 15 repeating segments [5]. The IGF2R binds M6P-containing ligand and IGF2 in two distinct sites [5]. This receptor has an important role in the intracellular trafficking of lysosomal enzymes from the trans-Golgi network or the extracellular space to lysosomes and also reduces the bioavailability of IGF2 by targeting it to lysosomes [5]. Unlike IGF1 receptor (IGF1R) and insulin receptor (IR), IGF2R does not have intrinsic tyrosine kinase activity but can recruit G proteins, and even though these G-protein-activated pathways are not well characterized in the brain, PKC and phospholipase C are involved in IGF2 actions in the brain [6] and other cell types [7], respectively. IGF2 can also bind, but with less affinity, to the IGF1 receptor (IGF1R) and the isoform A of the insulin receptor (IRA) [3,8], which may activate the signaling pathway downstream these tyrosine kinase receptors. The activation of this pathway modulates gene transcription and activates multiple downstream Kinases-phosphatases branches, affecting key cellular processes such as protein synthesis, autophagy, apoptosis, and resistance to oxidative stress [9].

IGF2 and Its Role in Hippocampal Physiology and Pathophysiology (Figure 1A)

From the early 1990s, it was already described that IGF2 had neuroprotective functions [10]. Moreover, evidence from the past ten years highlights the importance of IGF2 in brain function and brain diseases. As mentioned before, IGF2 levels are high in the hippocampus, and several groups have demonstrated the importance of IGF2 expression in shaping memory. In rats, it has been demonstrated that the expression of IGF2 is physiologically upregulated during hippocampal-mediated learning, and it is important for memory formation and consolidation [11,12]. Administration of recombinant IGF2 also enhanced memory retention and prevented forgetting, processes that were dependent on the binding of IGF2 to its receptor [11]. Together with memory formation, IGF2 has an important role in the extinction of fear memories in the hippocampus, especially those associated with

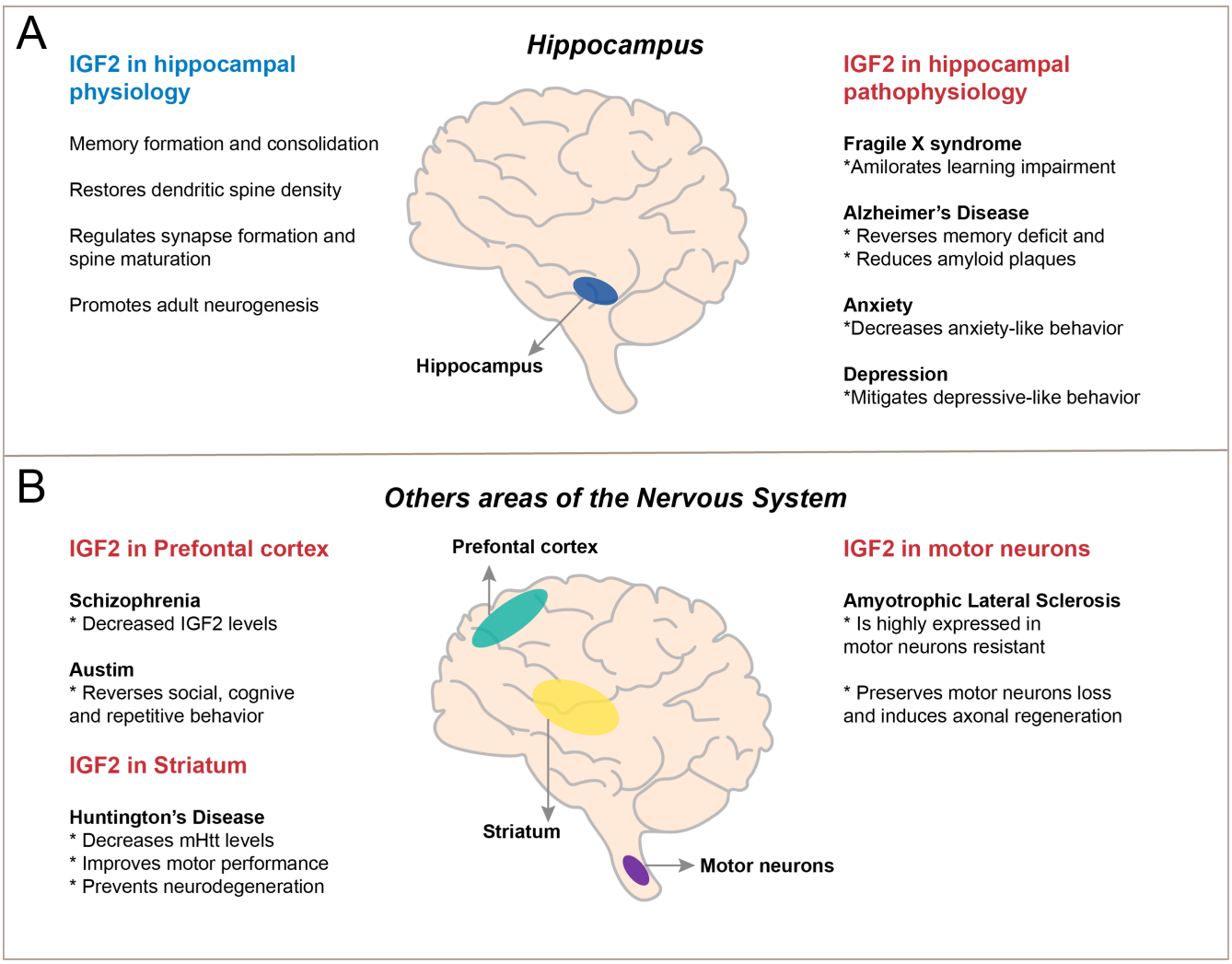

Figure 1: IGF2 functions in the nervous system. (A) The most described roles of IGF2 in the central nervous system are confined to the hippocampus, where its expression is key for hippocampal physiology, such as adult neurogenesis, spine maturation and synapses formation, and an important role in memory formation and consolidation (left panel). Also, IGF2 treatment has shown positive effects in ameliorating different behavioral abnormalities under pathophysiological conditions (right panel). **(B)** Recent findings have shown that IGF2 has also important functions beyond the hippocampus, where its overexpression has evidence important effects in several diseases affecting the prefrontal cortex, striatum, and motor neurons.

anxiety and mood disorders [13]. Contrary to memory formation, extinction of fear memory was dependent on IGF1R activation [13]. These functions could be explained in part by the fact that IGF2 acts as a regulator of synapse formation and spine maturation in hippocampal neurons, which is mediated by the activation of the IGF2R [14]. In line with these results, it has been observed that intranasal administration of IGF2 ameliorated learning and memory impairments in a mouse model of Fragile X syndrome [15]. Moreover, in aged mice and rats, the hippocampal expression of IGF2 is decreased, and adeno-associated viral vector (AAV)-mediated overexpression of IGF2 or recombinant administration of this peptide in the hippocampus restored hippocampal-dependent memory and dendritic spine density impairments [16,17]. Furthermore, IGF2 expression is also decreased in the hippocampus of Alzheimer's disease patients and a mouse model of this disease, and AAV-mediated overexpression of IGF2 in the hippocampus of transgenic aged mice reverses memory deficit and restored spine density [16]. Interestingly, IGF2 overexpression reduced amyloid-β plaques in the hippocampus of transgenic mice [16,18], which was mediated by the IGF2R [16].

Interestingly, it has been described an important role of IGF2 in the modulation of anxiety and depressive-like behavior, phenotypes that are also associated with hippocampal function [19]. Treatment of a mouse model of depression with dicholine succinate decreased anxiety-like behavior in treated mice, which was accompanied by increased hippocampal IGF2 expression [20]. When IGF2 is ablated in the placenta of wild type mice, this is associated with increased anxiety in their progeny in adulthood [21]. Moreover, in a rat model of depression, IGF2 levels were decreased in the hippocampus, and this phenotype was reversed when IGF2 was overexpressed in this brain area [22]. In line with these findings, treatment of depressive-like mice with the antidepressant ketamine induces an increase in the expression of IGF2 in the hippocampus [23].

Together with its important functions in the hippocampus, IGF2 has a key role in the maintenance of brain neural stem cells (NSCs), which are present in the subventricular zone of the lateral ventricles [24] and the subgranular zone of the dentate gyrus, a region of the hippocampus [25]. It has been shown that IGF2 promotes NSCs self-renewal and stemness in the subventricular zone, which is mediated by IRA, a high-affinity receptor for IGF2 [26,27]. Importantly, IGF2 is highly expressed in NSCs of the dentate gyrus, where it promotes adult neurogenesis both *in vitro* and *in vivo* [28,29], an important function of IGF2 that could be therapeutically exploited. The generation of new neurons plays important roles in brain tissue maintenance and function [30], and this process is affected in a variety of brain diseases, including neurodegenerative diseases, mood disorders, epilepsy, and even during aging [31,32]. In conclusion, IGF2 has important functions for brain physiology and in counteracting some of the phenotypes observed in a diverse group of brain diseases.

IGF2 and Its Functions Outside the Limits of the Hippocampus (Figure 1B)

Contrary to the vast literature regarding IGF2 function in the physiology and pathophysiology of the hippocampus, only a few reports have linked IGF2 to the amelioration of other nervous system-related diseases that are not linked to hippocampal function. For example, IGF2 is downregulated in the prefrontal cortex of patients with schizophrenia [33], and also hypomethylation of an enhancer within the *IGF2* gene has been observed in the prefrontal cortex neurons of schizophrenia patients [34]. Moreover, IGF2 serum levels were decreased in Chinese schizophrenic patients, which were correlated with negative cognitive symptoms in patients [35]. Also, in a mouse model of autism, the systemic injection of IGF2 reversed social, cognitive, and repetitive behaviors [36]. In the peripheral nervous system, it has been shown that IGF2 is highly expressed in resistant motor neurons in amyotrophic lateral sclerosis (ALS) and that the overexpression of IGF2 in human spinal motor neurons of ALS and spinal muscular atrophy patients protected motor neurons from degeneration [32]. Furthermore, AAV-mediated delivery of IGF2 into muscles of ALS transgenic mice preserved motor neurons and induced axonal regeneration and extended mice life-span [32].

We recently published the impact of IGF2 overexpression in the context of Huntington's disease (HD). HD is an autosomal dominant neurodegenerative disorder caused by a polyglutamine expansion mutation in the Htt protein [37]. Although the mutated huntingtin (mHtt) is present in all cell types, medium spiny neurons (MSNs) of the striatum and cortical pyramidal neurons are particularly affected in HD [38]. These alterations trigger a plethora of motor, cognitive, and psychiatric symptoms, which finally causes the death of affected patients. In our study, first we demonstrated that IGF2 overexpression decreases the intracellular levels of mHtt and $polyQ_{79}$, a peptide used to mimic mHtt aggregation *in vitro* [39]. This decrease was not due to the activation of macroautophagy or the ubiquitin-proteosome system, but instead, mHtt/$polyQ_{79}$ was secreted to the extracellular space under IGF2 administration [39]. The secretion was dependent on the IGF2R and actin cytoskeleton remodeling and was through microvesicles and exosomes [39], but we cannot rule out other possible mechanisms mediating mHtt/$polyQ_{79}$ secretion, as described by others [40].

After our interesting results of the significant reduction of mHtt aggregation observed in cells overexpressing IGF2, we developed a strategy to deliver IGF2 into the brain of HD mice using the stereotaxic injection of AAVs to then assess the impact on mHtt levels. For this purpose, we used three different animal models of HD. First, we used an animal model of HD to monitor mHtt aggregation based on the local delivery into the striatum of a large fragment of mHtt of 588 amino acids containing 95 glutamine repetitions fused to monomeric RFP ($Htt588Q_{95}$-RFP) [41]. We observed a significant decrease in mHtt aggregates and monomeric forms in the striatum of these mice, which was accompanied by increased DARPP-32 levels, a marker of medium spiny neurons viability[39]. Given these positive results, we also evaluated the effect of IGF2 expression in the striatum of adult YAC128 mice, a mouse model that expresses full-length mHtt with 128 tandem glutamines using an artificial chromosome that contains all endogenous regulatory elements [42]. Besides, we observed a significant reduction of full-length mHtt levels in the striatum, with a near 80% decrease on average [39]. Moreover, we investigated the effect of IGF2 delivery into the ventricle of newborn pups, since stereotaxic injections only transduce a restricted area of the striatum restricting

the analysis of motor function. This route of AAV delivery generates a global spreading of viral particles throughout the nervous system. We demonstrated that IGF2 expression significantly reduces the total levels of mHtt in the brain of YAC128 animals, which was accompanied by an improved average of motor performance over time [39]. Finally, we used a third model, the R6/2 mice, a transgenic HD model that expresses exon 1 of human huntingtin containing ~150 CAG repeat [43], which allows the visualization of intracellular mHtt inclusions. Using immunohistochemistry and immunofluorescence analysis, we observed a strong reduction in the content of mHtt-positive inclusions upon AAV-IGF2 administration. These results strongly support the fact that the artificial enforcement of IGF2 expression in the brain reduces mHtt levels in the striatum of different HD models.

One of the most important conclusions drawn from our results is that IGF2 delivery into the striatum has neuroprotective effects and improves motor performance in HD mouse models, adding to the shortlist of publications in which IGF2 has neuroprotective effects outside the hippocampus. What is also important is that IGF2 could be studied in HD models to alleviate other symptoms found in HD patients, which are modeled by HD mice. Motor symptoms in HD patients are usually used to diagnose the disease. However, studies both in humans and in animal models highlight the fact that cognitive, mood, and psychiatric disorders appear before motor symptoms, which in patients have been observed 4-10 years before the onset of motor phenotypes [44]. These disturbances include impulsivity, irritability, anxiety, and depression. In YAC128 mice, cognitive disorders precede motor abnormalities and present similar symptoms and progression of cognitive deficits found in patients [45]. Among the psychiatric disorders present in HD patients and mouse models of HD is anxiety, which can be evaluated using different batteries of behavioral tests [44]. It has been previously described that symptomatic YAC128 mice display increased anxious behavior compared with WT mice [46-48]. Interestingly, the hippocampus is a core brain structure in the genesis of anxiety [19], and alterations of neurogenesis in the hippocampal dentate gyrus have been directly associated with anxious behavior. Furthermore, it has been shown that YAC128 mice have decreased hippocampal cell proliferation and neuronal differentiation [49]. As described previously, several studies highlight the important role of IGF2 in hippocampal neurogenesis. IGF2 is upregulated in neural stem cells that will divide and form new neurons in the dentate gyrus of the hippocampus [28], and also participates in synapse formation and spine maturation in hippocampal neurons [14]. These findings strongly suggest that overexpression of IGF2 in the hippocampus of HD mouse models would have a positive impact in decreasing anxiety in these mice. Moreover, the effect of IGF2 delivery in other brain areas typically involved in anxious behavior, such as the amygdala, medial prefrontal cortex, among others needs further investigation.

The hippocampal function has widely been associated with memory formation ref. The YAC128 mouse model shows impaired learning and memory starting at 8 months of age, which progressively worsen [45]. This phenotype has been attributed to reduced hippocampal dentate gyrus neurogenesis, as previously described [49]. Using our YAC128 mouse model, we did not observe impaired spatial learning and memory, which could be caused by the different genetic background of the mice used in this study. Several investigations have demonstrated the importance of IGF2 in memory enhancement and consolidation[11], and its effect in reversing memory deficits and hippocampal synaptic alterations in mouse models of AD [50]. Therefore, we speculate that IGF2 expression in mice would recover learning and memory in HD mouse models.

Concluding Remarks

Over the past 10 years, important evidence has highlighted the important function of IGF2 in brain physiology and in pathophysiological conditions. Several findings have demonstrated the crucial function of IGF2 in hippocampal memory formation and extinction, neurogenesis, and spine and dendrites formation. Beyond the hippocampal boundaries, IGF2 has shown to be neuroprotective for motor and striatal neurons under pathological conditions. It is clear that the neuroprotective effects of IGF2 must be studied in other brain areas affected in different brain diseases, which we speculate would have beneficial effects in other cognitive symptoms beyond hippocampal-dependent memory. Anxiety, obsessive-compulsive behaviors, addictions, depression, and other cognitive disabilities could be targeted by the treatment with IGF2. Given that IGF2 crosses the blood-brain, it appears as an interesting candidate for potential translational applications, where its route of administration can be non-invasive for patients and it could reach all brain areas or other organs affected by one of the many diseases present in humans. Although IGF2 has been the less studied member of the IGF peptide family for years, it is time for us to focus our attention on this soluble factor that has been shown to be an important actor in many brain conditions.

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