The Insulin-like Growth Factor-1 Axis and its Potential as a Therapeutic Target in Central Nervous System (CNS) Disorders

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Abstract: The insulin-like growth factor-1 (IGF-1) is a pleiotropic factor. Many studies have revealed its importance in the development and maintenance of the central nervous system (CNS). This review will discuss the IGF-1 axis, from the factor itself to the signalling pathways it activates, and its tight regulation. Particular focus will be brought on potential therapeutic targets of the IGF-1 axis in CNS disorders, including brain tumours and neurodegenerative diseases affecting neurons and oligodendrocytes.

1. INTRODUCTION

Numerous studies have focused on insulin-like growth factor-1 (IGF-1) and its pleiotropic effects. Indeed, it is now known to be involved in very diverse cellular events and, by interacting with its receptor the Type I IGF receptor (IGF-IR), can go from sending a mitogenic signal to protecting cells from a variety of apoptotic injuries, promoting cell size growth, regulating cell cycle progression, playing a crucial role in the establishment and maintenance of a transformed phenotype, regulating cell adhesion and cell motility, inducing terminal differentiation, affecting glucose transport and metabolism, or ageing [1-3]. Moreover, all cell types are known to possess the IGF-IR except for hepatocytes and mature B cells [1, 2]. Hence, this 70 amino acid polypeptide hormone has a broad spectrum of actions, making it a highly regulated factor. Deficient or excess amounts of IGF-1 lead to a number of disorders and have also been observed in different pathologies.

This review will center its attention on the IGF-1 axis components as possible therapeutic agents or targets in diseases of the central nervous system (CNS). More specifically, the focus will be on oligodendrocytes – which together with astrocytes and microglia form the neuroglia – and neurons. Microglia are the immune cells and the tissue macrophages of the CNS [4]. Astrocytes are essential for signalling, energy metabolism, extracellular ion homeostasis, volume regulation, neuroprotection [5] and are an integral part of the neurovascular system [6]. Finally, oligodendrocytes are the myelin-producing cells of the CNS [4]. The myelin sheaths are specialized insulating membranes that wrap around neuronal axons to form myelinated internodes (white matter) separated by the nodes of Ranvier. This arrangement allows the clustering of sodium channels at the nodes of Ranvier during axogenesis for fast conduction of electric impulses (saltatory conduction). Myelin also participates in the development and regulation of axonal caliber, the modulation of the maturation and survival of axons, and the inhibition of axonal growth and regeneration in the mature brain [7, 8]. Thus, it is clear that oligodendrocytes and neurons are intimately associated, and damage to the white matter as a result of trauma, hypoxia-ischemic injury, autoimmunity or neurodegeneration results in debilitating neurological diseases, including brain injury, stroke, Multiple Sclerosis (MS) and Alzheimer's disease (AD). IGF-1 plays important roles during brain development, regulating proliferation of neurons and oligodendrocyte progenitors as well as their differentiation. In addition, this growth factor can affect brain metabolism and protect neurons or oligodendrocytes from serum and glucose deprivation, hypoxia/ischemia and glutamate toxicity.

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2. INSULIN-LIKE GROWTH FACTOR-1 AXIS

The IGF-1 axis comprises IGF-1, the IGF binding proteins (IGFBPs), the IGF-IR and the signalling pathways that are activated following the interaction between IGF-1 and the IGF-IR.

2.1. IGF-1 and its Role in Brain Function and Development

IGF-1 is a 70 amino acid single-chain polypeptide structurally similar to insulin [9]. This factor is generated by various cell types and can therefore affect the CNS from different distances. It can be a short-range cue and act within the immediate vicinity of its source (autocrine and paracrine stimulation), or a long-range cue and act many cells away from where it was secreted (endocrine activation). IGF-1 is expressed in many regions of the CNS, including the spinal cord, the cerebellum, the brain stem, the diencephalon, the cerebral cortex and the hippocampus [10-12]. Its mRNA is detected in rat brain throughout development, reaching maximal levels between postnatal days 8 and 15, followed by a decrease to the final adult levels [13]. Neurons and astrocytes synthesize most of the IGF-1 found in the CNS, and this could account for the main source of regulation of IGF-1 in brain development and maturation. Nonetheless, microglia and oligodendrocytes also secrete IGF-1 that can function in an autocrine or paracrine manner [14-19]. In addition, IGF-1 is largely produced by the liver and can reach the brain sys-

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temically, since IGF-1 can cross the blood-brain barrier [20]. Indeed, peripherally injected IGF-1 was found to increase the proliferation of neural progenitor cells in the dentate gyrus of the adult rat brain [21]. However, this does not appear to be the most important source of IGF-1 in the brain, according to knockout studies of liver-specific IGF-1 and acid-labile subunit of the IGFBP-3 complex (see below for section on IGFBPs) [22]. Still, it is now well accepted that IGF-1 acts on an autocrine, paracrine and endocrine fashion in the brain [22].

Over the past ten years, it has become clear that IGF-1 promotes neurotrophic actions in the brain, increasing neural cell number, process outgrowth, synaptogenesis and myelination during development. IGF-1 has been shown to promote neuroprotection and regeneration following trauma or hypoxic-ischemic injury in the adult brain [22-25]. IGF-1 was also found to protect white matter after ischemic injury in near-term fetal sheep by decreasing apoptosis and promoting regeneration of oligodendrocytes [26]. In experimental autoimmune encephalomyelitis (EAE), an animal model of MS, IGF-1 promoted myelin regeneration [27]. In contrast, there was a decrease in CNS myelination and in the number of oligodendrocyte progenitors in IGF-1 null mutant mice [28]. The levels of IGF-1 are controlled at the stage of transcription, splicing, translation, secretion and by binding proteins [29-31].

2.2. The Binding Proteins

IGF-1 levels are tightly regulated by the IGFBPs; therefore, the IGF axis is incomplete without mentioning them and their respective proteases. There exists six different IGFBPs in mammals, termed IGFBP-1 to -6; these are highly conserved through evolution. Like their name suggests, these proteins bind IGF-1 to form a binary complex. This interaction is stronger than the binding of the IGF-1 to its receptor; therefore, there is competition for the IGF-1 favoring the IGFBPs. The latter are believed to act as titters by storing IGF-1, as it is not stored in secretory granules inside of cells, but in the circulation and in tissues. This also allows for IGF-1 to have a longer half-life. To add to the complexity of this system, a larger glycoprotein called the acid-labile subunit also attaches to IGFBP-3 and -5 in circulation. Due to the sequestration of IGF-1 from its receptor, the concentration at which IGF-1 is found in circulation or in tissues is much greater than the concentration required to achieve full activation of the IGF-IR (100 nM in circulation and 30 nM in tissues versus 1-2 nM needed to activate the IGF-IR at the cellular level) [32, 33]. The pool of IGF-1 is therefore quite important.

In order for IGF-1 to reach its receptor, there are proteases that specifically cleave the IGFBPs to induce a conformational change that will decrease their affinity for IGF-1. The different IGFBPs have similar C- and N-terminal sequences, but differ in their mid-regions thus conferring them distinct roles. Many *in vitro* and *in vivo* studies are being focused on those specific roles; however, it seems that there is some level of redundancy between the different IGFBPs, which makes it difficult to extensively dissociate the function of one IGFBP from another. Moreover, it has been found that the IGFBPs have IGF-independent functions in development, as they are believed to act upon cell receptors on their own. Hence, dissociation from IGF-1 also permits the IGFBPs to fulfill their IGF-independent functions, see for review [32-34]. In addition, Chesik and colleagues (2004) recently found evidence of IGFBP-4 localization on microtubules and centrioles of astrocytes exclusively [35]. However, the exact role of IGFBP-4 at this site requires further research.

The mRNA expression profiles of the IGFBPs in the brain have been characterized by regional and developmental specificity, which concurs with peaks of IGF expression [36, 37] and reviewed in [38]. In the CNS, the mRNAs of IGFBP-2, -4 and -5 are the most abundant, and those of IGFBP-3 and -6 are expressed in lower levels, see for review [22]. The IGFBP-1 mRNA is not expressed in the CNS; however, there is some evidence that overexpression of liver-specific IGFBP-1 affects brain development [39]. Moreover, IGFBP-1 expression can be induced in the CNS under certain experimental conditions, reviewed in [22]. More specifically to oligodendrocytes, it was found that progenitors express IGFBP-4, while IGFBP-3, -5 and -6 are expressed by oligodendrocyte progenitors, pro-oligodendrocytes and oligodendrocytes [40]. Kuhl and colleagues recently showed that IGFBP-1, -2 and -6 are negative effectors of oligodendrocyte survival and differentiation *in vitro* [41, 42]. On the other hand, astrocytes mainly express IGFBP-2, and together with its protease, allows proper recruitment of IGF-1 to promote proliferation of this cell type *in vitro* [43, 44]. Similar results were obtained in activated microglia from post mortem human brains [45]. Yet, conflicting data have been reported on the roles of IGFBPs in different *in vivo* models.

2.3.The Receptor

IGF-1 interacts with the IGF-IR to initiate downstream responses such as proliferation and differentiation. In contrast to all receptor tyrosine kinases, excluding the insulin receptor (IR), the IGF-IR exists as a $\alpha_2\beta_2$ heterotetramer, where the α_2 extracellular subunits contain the ligand-binding sites, while the β_2, one time transmembrane subunits transmit the ligand-induced signal. These different subunits are linked by disulfide bridges [19, 46]. The IGF-IR does not require ligand binding to dimerize. However, upon binding of its ligand, the IGF-IR goes through a conformational change that results in adenosine 5'-triphosphate (ATP) binding and autophosphorylation of conserved tyrosine residues [19].

The extracellular domain of the IGF-IR contains a cysteine-rich region that determines the specificity for its ligand, IGF-1. On the cytosolic side, the IGF-IR has three main domains characterized by three clusters of tyrosine residues within different motifs: the juxtamembrane domain, the tyrosine kinase domain and the carboxyl-terminal domain [19]. The former domain allows for the recruitment of signalling adaptor proteins. The tyrosine kinase domain is the catalytic domain of the receptor. Finally, the carboxyl-terminal domain is also important for proper signalling from the receptor (it interacts with different proteins than the juxtamembrane domain) [46].

The IGF-IR shows two different patterns of gene expression during development of the rat brain. Initially, all cells

derived from neuroepithelial lineages express the receptor in similar levels. It is believed that the first function of the IGF-IR in these cells is to respond to circulating IGF-1 secreted by the liver to fulfill essential metabolic or trophic roles. Then, after birth, different subsets of neurons and glial cells express varying amounts of the IGF-IR, which seem to respond to the locally produced IGF-1 [47]. The expression of IGF-IR by oligodendrocytes is temporally correlated with the processes involved in CNS myelination [13, 23, 48-50]. Moreover, the specific disruption of the gene encoding IGF-IR in the mouse brain by Cre-mediated recombination causes failure to myelinate. In these mutants, oligodendrocyte progenitors do not accumulate, proliferate or survive compared to the wild type, indicating that signalling through the IGF-IR is critical for remyelination [51].

2.4. The Signalling Pathways

From the information collected in various cell types, the IGF-IR has intrinsic tyrosine kinase activity that can phosphorylate the insulin receptor substrates 1 and 2 (IRS-1 and 2). Together with IRS-1/2, the IGF-IR activates several main downstream signalling pathways, more specifically the PI3K/Akt/mTOR and ERK cascades Fig. (**1**). Focus on these kinases will be brought in this section.

2.4.1. Phosphoinositide 3-Kinases (PI3Ks)

The membrane-associated PI3Ks lie downstream of the IGF-IR where they can be directly phosphorylated by the receptor or through the IRSs upon IGF-1 stimulation. A great amount of work has focused on the characterization of the PI3Ks and their tissue distribution because of their importance in pathophysiology. The PI3Ks are heterodimeric, with a catalytic and regulatory subunit. In the inactive form of the enzyme, both subunits are bound to each other. Upon cell stimulation, the catalytic subunit is dissociated from the regulatory subunit. This is accomplished through the interaction of the regulatory subunit SH2 (Src homology 2) domain with the phosphorylated receptor or IRS on critical tyrosine residues [52, 53]. The catalytic subunit is then capable of catalyzing the phosphorylation of the inositol ring of phosphatidylinositol (PtdIns) producing different phosphoinositides (PIs), either phosphatidylinositol (3) phosphate (PI3P), phosphatidylinositol (3,4) phosphate 2 [PI(3,4)P_2] or phosphatidylinositol (3,4,5) phosphate 3 [PI(3,4,5)P_3] *in vitro* [54]. The different PIs have unique functions in cells, activating different downstream effectors [53]. Furthermore, PI3Ks' action is regulated through two families of phosphoinositide phosphatases, namely PTEN (phosphatase and tensin homologue deleted on chromosome 10) and SHIPs (SH2-containing inositol phosphatases) [53]. Deregulation of PI3Ks has been linked to cancer, type II diabetes and CNS disorders [52]. More specifically, PTEN is a tumour suppressor gene and its mutations are associated with gliomas, macrocephaly and mental deficiencies [55]. The tumour-suppressive properties of PTEN are dependent on its lipid phosphatase activities to regulate the PI3K pathway [56]. This in turn will affect cell-cycle control escaping from apoptosis, therefore allowing brain invasion and aberrant neoangiogenesis [57, 58]. In addition, Fraser and colleagues (2008) showed that PTEN deficiency during brain development causes defects in synaptic structure, transmission and plasticity, as well as myelination abnormalities [59].

The PI3Ks are divided in three classes or types, according to their structure and function (classes I, II and III). All PI3Ks contain a homologous region that comprises a catalytic core domain linked to the PI kinase homology (PIK) domain. The function of the latter domain is still unclear. In some cases, an additional class of PI3Ks is added, class IV, which includes PI3K and PI4K-related kinases in terms of significant homology with the kinase core domain. These kinases have similar serine/threonine protein kinase activity, but no known lipid phosphorylation activity. Among this class is mTOR [54].

The type or class I PI3Ks are distinguished by their regulatory subunits. The PI3Ks activated by cell surface tyrosine kinase receptors, such as the IGF-IR, belong to the class IA of PI3Ks. Members of this class are p110α, p110β and p110δ for the catalytic subunits, and p85α, p55α, p50α, p85β and p55γ for the regulatory subunits. The class IB members are activated via cell surface receptors coupled to the heterotrimeric G-proteins. The catalytic subunits in this class are p101 and p84, and the regulatory subunit is p110γ. The class II is composed of PI3KC2α, PI3KC2β and PI3KC2γ. These kinases are activated through cell surface receptors and/or endocytosis. They are thought to be an alternative route of phosphorylation from the class I kinases. Finally, the class III PI3Ks are believed to be constitutively active and are involved in vesicular trafficking. The members of this type of PI3Ks are hVPS34 (human vesicular protein-sorting protein) for the catalytic subunit, and p150 for the regulatory subunit [53, 54]. Classes I, II and III of PI3Ks can potently and selectively be blocked by Wortmannin, a fungal metabolite, and LY294002, a synthetic morpholino derivative of quercetin. These inhibitors are structurally unrelated and affect PI3Ks differently. Wortmannin makes a covalent bond with the catalytic subunits of PI3Ks; on the other hand, LY294002 is a competitive inhibitor at the level of the ATP site [54]. Both inhibitors possess antitumor activity as assessed in different *in vivo* models, but are very unstable (short half-lives), insoluble in water and toxic (target all p110 subunits). Therefore, they are not viable drug candidates [60]. A number of small isoform-specific inhibitors have been recently developed and have provided important information on the specific functions of class I isoforms [61-67]. Some of these compounds are actively being studied for their potential in the treatment of cancer as well as in inflammatory diseases, and will be mentioned in the last section of this review.

In the rat brain, the catalytic p110α subunit of PI3K is expressed in high levels throughout the entire neuraxis from E15-E18 and then decreases gradually to low adult levels during postnatal development [68], whereas all five regulatory isoforms (p85α and β, p55α, p50α and p55γ) are expressed throughout development [69-71]. Using the specific kinase inhibitors, Wortmannin and LY294002, it has been shown that PI3K is necessary for the survival of progenitors or mature oligodendrocytes [72], for the full mitogenic response by PDGF [73, 74], and for IGF-1-mediated cell survival, proliferation and protein synthesis [75, 76] (Bibollet-Bahena and Almazan 2008, under revision). Based on the differential inhibition of thymidine incorporation to low nM concentrations of Wortmannin in early progenitors as compared to pro-oligodendroblasts, it was postulated that a dif-

ferent PI3K is involved at each developmental stage [74]. However, it remains to be determined which PI3K isoform(s) is expressed and crucial for IGF-1-mediated effects in oligodendrocytes.

Interestingly, while the p85 subunit enhances myelin basic protein promoter activity in oligodendrocytes, this effect appears to be independent of PI3K catalytic activity but dependent on the adaptor functions of its SH2 domains [77]. Mice lacking the p85α regulatory subunit and its splice variants (p55α and p50α) developed hypoglycemia, liver necrosis, perinatal death, growth retardation and increased frequency of apoptosis [78]. These mutant mice also presented altered IGF-1-mediated cell cycle regulation with a G0/G1 cell cycle arrest and upregulation of p27 (KIP), whereas signalling through CREB and MAPK was enhanced [79]. In addition, mice deficient in p110α [80] and p110β [81] displayed an early embryonic lethality and proliferative defect. Other gene-targeting studies in mice have revealed important roles for specific PI3K specific isoforms in immunity, metabolism and cardiac function [54, 82-84]. For downstream interactions, the PIs produced by the PI3Ks are selectively recognized by two different lipid-binding domains, namely FYVE (acronym of the first four proteins known to contain the domain: Fab1p, YOTB, Vac1p and Early Endosome Antigen 1) and PH (Pleckstrin homology) domains. PI3P binds proteins containing the FYVE domains, and $PI(3,4)P_2$ and $PI(3,4,5)P_3$ bind proteins containing the PH domains. Proteins known to possess the FYVE domains are mainly involved in membrane trafficking. As for the proteins that have the PH domains, they are part of signalling pathways promoting a wide array of cellular events [54].

2.4.2. Akt/Protein Kinase B

This kinase was initially identified by homology to the viral oncogene akt (v-Akt) [85] of transforming retrovirus AKT8, which was isolated from a spontaneous thymoma of an AKR mouse [86]. It was subsequently found to encode a serine/threonine protein kinase [87] with homology to PKA [88] and PKC [89, 90]. Upon production of $PI(3,4,5)P_3$ by PI3K, Akt is recruited to the plasma membrane where it can be phosphorylated by two different kinases on two critical residues. The first residue is threonine 308 (thr308) located in the activation loop of the catalytic region of Akt, and the second residue is serine 473 (ser473) found in the hydrophobic motif of the carboxy-terminal of the non-catalytic domain. In order to be fully activated, Akt must transition from a disordered to an ordered conformation, a state that can only be reached by the phosphorylation of ser473, see for review [91]. The kinase responsible for the phosphorylation of thr308 is called the phosphoinositide-dependent kinase 1 (PDK1), a direct substrate of PI3K [53], which is essential for mammalian development, as mice lacking PDK1 die at day E9.5 due to multiple abnormalities [92]. For a long time, it remained unclear which protein phosphorylated ser473 of Akt. For that reason, the unknown kinase was termed PDK2 [91]. However, recent studies in different human cancer cell lines suggest that PDK2 is in fact the rictor-mTOR complex (mTORC2) [93]. Nevertheless, this kinase does not seem to be exclusive for the above-mentioned Akt residue as another study showed residual phosphorylation at ser473 after deletion of rictor [94].

Akt phosphorylation is regulated by three proteins: the carboxy-terminal modulator protein (CTMP), TRB3 and the PH domain leucine-rich repeat protein phosphatase (PHLPP). The first two proteins bind to the carboxy-terminal tail or the catalytic domain of Akt, respectively. The mechanisms by which they inhibit Akt activity remain unclear. However, PHLPP is a known phosphatase that acts at the level of ser473 to inactivate Akt [91].

There are three isoforms of Akt, Akt1, 2 and 3 (PKBα, β and γ), derived from three different genes. Akt1 is the most abundant, present in most tissues. Akt2 is mainly in insulin responsive tissues [95]. Finally, Akt3 is primarily found in the brain and testes. It was recently found that oligodendrocyte progenitors predominantly express Akt2:Akt1:Akt3 in a 10:5:1 ratio [75]. All Akt isoforms contain a PH domain, a catalytic domain and a hydrophobic domain. They also have the same affinities for the same substrates. What distinguishes their actions is their different cellular localization [91]. Transgenic studies demonstrate that Akt1 and Akt2 are required for normal growth and metabolism, respectively. Akt3 is not required for the maintenance of normal carbohydrate metabolism but is essential for the attainment of normal organ size [96-98]. In contrast to $Akt1^{-/-}$ mice, which display a proportional decrease in the sizes of all organs, $Akt3^{-/-}$ mice present a selective 20% decrease in brain size. Moreover, although Akt1- and Akt3-deficient brains are reduced in size to approximately the same degree, the absence of Akt1 leads to a reduction in cell number, whereas the lack of Akt3 results in smaller and fewer cells [99, 100] and reduced myelin staining in the corpus callosum [100]. The crucial role of Akt played in oligodendrocyte protection by NGF was demonstrated by the overexpression of the dominant-negative Akt that negated the protective effects of NGF on TNFα-mediated oligodendrocyte cytotoxicity [101]. Conversely, the overexpression of constitutively active Akt protected oligodendrocytes from TNFα-induced injury [101]. Similarly, the overexpression of dominant negative Akt but not of wild-type Akt by adenoviral gene transfer induced significant apoptosis in primary cultures of both oligodendrocytes and their progenitors [102]. Akt is also involved in IGF-I-induced oligodendrocyte progenitors survival following growth factor deprivation as demonstrated with the inhibitor 1L-6-Hydroxymethyl-chiro-inositol2-(R)-2-O-methy-3-O-octadecylcarbonate and a dominant-negative mutant [76].

Akt phosphorylates its target proteins within a consensus peptide motif (RXRXXpS/T) [103]. A few examples of the Akt targets are glycogen synthase kinase 3β (GSK3β), Forkhead box O (FoxO) transcription factors, tuberous sclerosis complex 2 (TSC2), Bad, caspase-9 and 4E-BP1 [54, 91, 104]. The phosphorylation of these proteins can be blocked with LY294002 and Wortmannin. Nonetheless, these are indirect effects as these drugs inhibit PI3K. New compounds have been developed to block Akt activity, of interest, Akt inhibitor III and Akt inhibitor IV. The former is a PI analog that prevents $PI(3,4,5)P_3$ formation, and the latter blocks an unknown kinase upstream of Akt, but downstream of PI3K [105, 106]. The Akt inhibitor III has been shown not to interfere with the Ras-Raf-MEK/ERK cascade [106]. Other tools have been developed in order to study Akt's actions more closely. Among them, viral constructs of genetically altered Akt proteins can be used, expressing dominant-negative or

constitutively-active (myristoylated) forms of Akt. In a recent study, we have shown that both Akt inhibitors III and IV and dominant-negative Akt expression can block IGF-1-stimulated protein synthesis in oligodendroctyte progenitors, underlying the importance of this kinase in the PI3K and mTOR pathway in oligodendrocyte growth (Bibollet-Bahena and Almazan 2008, under revision).

2.4.3. Mammalian Target of Rapamycin/FKBP and Rapamycin-Associated Protein

As mentioned above, Akt can phosphorylate TSC2, which in turn is inactivated to relieve the inhibition it exerts on mTOR (also known as FRAP) [91]. mTOR was initially discovered as the substrate of rapamycin (hence its name). The latter is a macrolide that was first intended for antifungal usage. However, it was found to have interesting immunosuppressant activity and is now used after organ transplants to avoid rejection. Rapamycin is also being considered a drug of choice against cancer due to the role that mTOR signalling plays in the PI3K/Akt pathway (see below) [91, 107]. Three drug candidates have made it to different phases of clinical trials with encouraging preliminary results, although more data need to be collected to fully determine their effectiveness [60, 108, 109]. These three agents are temsirolimus (also known as cell cycle inhibitor-779, CCI-779, Wyeth), which is an ester derivative of rapamycin; everolimus (RAD001, Novartis Pharma AG), which is an orally bioavailable hydroxyethyl ether derivative of rapamycin; and, deforolimus (also known as AP23573, Ariad Pharmaceuticals Inc), which is a non-pro-drug analog of rapamycin.

mTOR is a large (~400 amino acids) unique protein with serine/threonine kinase activity that has significant homology with lipid kinases, as discussed in the section dedicated to PI3K. mTOR contains a few conserved structural regions: HEAT, FAT, FRB, catalytic domain and the FATC. At the amino-terminal end, there is the HEAT [acronym for the first four proteins found to have that motif: Huntingtin, Elongation factor 3, A subunit of protein phosphatase 2A (PP2A), Tor1] domain. This region possesses repeats of hydrophobic, proline, aspartic acid and arginine residues to allow protein-protein interactions. Directly downstream of the HEAT domain lies the FAT (another acronym for FRAP, ATM and TRAP) region. Slightly apart from FAT, at the complete carboxyl terminus is FATC (FRAP, ATM and TRAP, carboxy-terminal homology domain). FAT and FATC are always in proximity of each other. It has been speculated that intramolecular interactions between these two regions could modulate mTOR activity by exposing its catalytic domain. Another interesting region of mTOR is the FRB [FKBP12 (FK506-binding protein 12)-rapamycin binding] domain, located between the FAT and catalytic regions. When bound to a hydrophobic pocket in FKBP12, rapamycin can interact with another hydrophobic pocket in mTOR allowing for the FKBP12-mTOR interaction to take place. However, this is not how rapamycin is believed to inhibit mTOR's kinase activity [91, 110, 111].

Endogenous mTOR autophosphorylates on ser2481. This event absolutely requires the presence of the corresponding region of the lipid kinase activity of PI3K on mTOR. Upon growth factor stimulation, the PI3K/Akt pathway is responsible for the phosphorylation of mTOR on ser2448. The importance of this phosphorylated site is still unclear and currently being investigated by various groups. This is due to the fact that, after growth factor stimulation, a mutation in the serine at that position still allows proper phosphorylation of downstream effector. Nevertheless, it is agreed that insulin and growth factors stimulate mTOR activity [110, 111]. In addition, another phosphorylation site has been identified on thr2446. When phosphorylated, thr2446 acts as a negative regulator, since it is activated by nutrient deprivation [112].

mTOR can form two different complexes in the cell, namely mTOR complex 1 (mTORC1) and mTOR complex 2 (mTORC2). mTORC1 comprises mTOR and the rapamycin-sensitive adaptor protein of mTOR (raptor). The latter interacts with mTOR at various contact points and is important in the recruitment of mTOR substrates 4E-BP and p70S6K, both essential for cap-dependent protein translation. As opposed to mTORC1 which only has two proteins identified so far necessary to function, mTORC2 requires the presence of four proteins. These are mTOR, rapamycin-insensitive companion of mTOR (rictor), SIN1 and mLST8. mTORC2 requires the presence of all its 4 subunits in order to phosphorylate its downstream effector Akt, and possibly PKCα. SIN1 binds to mTOR at the level of the HEAT domain and is necessary for rictor to be recruited to the complex. Rictor and SIN1 are the docking proteins for mTORC2 substrates. Moreover, mLST8 binds to the catalytic domain of mTOR in order for mTOR to function, see for review [91, 110, 111].

From studies in *S. cerevisiae*, the functioning of mTOR was elucidated. Orthologs of the important proteins involved were found in mammalian cells. Two of these important proteins are α4, a phosphoprotein, and PP2A, a phosphatase. Although still controversial, a recent finding indicated that rapamycin interrupted the interaction between α4 and PP2A. This, in turn, relieves the repression exerted on PP2A by α4. This could explain how rapamycin inhibits mTOR activity. In addition, nutrient status also affects the α4-PP2A binding. Phosphorylation of α4 is modulated by mTOR signalling and renders α4 more competent to interact with PP2A. However, in a state of nutrient deprivation, α4 is dephosphorylated and mTOR signalling is negatively affected [107].

2.4.4. Extracellular-Signal-Regulated Kinase

The Ras-Raf-MEK (MAP/ERK kinase)/ERK cascade is highly conserved through species as a signalling pathway that integrates mitogenic stimuli (in the text, ERK refers to both ERK1/2 and MEK to MEK1/2). In quiescent cells, ERK is maintained in the cytoplasm by direct interaction with MEK. Upon growth factor stimulation, ERK is rapidly activated by MEK and translocated to the nucleus of cells where it is believed to interact with most of its substrates. ERK is activated through phosphorylation on thr and tyr (tyrosine) residues, which occurs at the level of the thr-glu-tyr (TEY) sequence in its activation loop. MEK activity is sensitive to, and can be inhibited by, the PD98059 compound, 2'-amino-3'-methoxyflavone [113, 114].

In order to interact with its substrates, ERK contains a C-terminal common docking (CD) domain and its substrates contain the docking site for ERK and FXFP (DEF) domain (FXFP stands for the recognized amino acids in this docking

site, where X is any amino acid) [113]. ERK is a proline (pro) directed protein kinase in that it phosphorylates ser or thr residues neighbouring pro residues [115]. The main substrates of ERK are the p90 ribosomal S6 kinases (RSKs), the mitogen- and stress-activated kinases (MSKs) and the MAPK-interacting kinases (MNKs). Of particular interest are the RSKs. These kinases do not significantly affect S6 phosphorylation as was first believed. S6 was found to be the major physiological target of the p70S6Ks. The latter contain a characteristic amino-terminal kinase domain highly homologous to RSKs', but lack the carboxy-terminal kinase domain of the RSKs. Nevertheless, they can be phosphorylated by ERK [113]. On the other hand, the MNKs have been shown to directly phosphorylate eIF4E, although the relevance of the phosphorylation on eIF4E is not well understood [116].

ERK activity is controlled by dual specificity phosphatases (DUSPs), more specifically DUSP1/2/4/5/6/7/9, as ERK is phosphorylated in two sites [117]. In addition, other phosphatases such as PP2A, protein ser/thr phosphatases (PPs) and certain protein tyr phosphatases (PTPs) are also known to dephosphorylate ERK [115]. Moreover, another level of regulation exists with MEK, since it can translocate into the nucleus to bring back ERK to the cytoplasm [114]. Using the MEK1 inhibitor PD98059 in combination with biological and biochemical assays, we have recently demonstrated that ERK is required for both IGF-1-stimulated proliferation and protein synthesis but not survival of oligodendrocyte progenitors [75, 76] (Bibollet-Bahena and Almazan 2008, under revision).

3. CNS DISORDERS

The IGF-1 Axis is quite complex, and IGF-1 has a broad spectrum of actions. Therefore, it is a highly regulated factor; deficient or excess amounts of IGF-1 lead to a variety of disorders of the CNS. In addition, abnormal levels of IGF-1 have been observed in different pathologies of the CNS. From brain tumours to neurodegenerative diseases, all have now been linked to the IGF-1 Axis.

3.1.Brain Tumours

By definition, a tumour is a cluster of cells going through uncontrolled proliferation. The latter has been associated to the overexpression of growth factors and/or their receptors. More specifically, *in vitro* and *in vivo* animal studies have shown a causal link between the IGF-IR and/or IGF-1 overexpression, and malignancy [118]. In addition, a study carried out by Hadsell and colleagues (2000) suggested the IGF-1 Axis to be the "second hit" required for malignant transformation after the expression of a tumour suppressor is lost [119]. As mentioned above, IGF-1 is a mitogen, promotes cell size growth, regulates the cell cycle progression, plays an important role in the establishment and maintenance of a transformed phenotype, and regulates cell adhesion and motility, among others. All these events are known to be crucial in tumour and cancer progression. Nonetheless, it is important to keep in mind that the IGF-1 Axis is more than the receptor and the factor, as some human studies have shown that often enough there are no correlations between the level of one or the other, and malignancy (which complicates the conclusions obtained from *in vitro* and *in vivo* animal studies) [118]. However, tumours are quite heterogeneous and their profiling should be extensive to allow monitoring the whole axis, as the signalling pathways are also known to be affected.

More specifically to the CNS, IGF-1 has been found in increased levels in neuroglial-derived tissues of brain tumours compared to controls [120-123]. Of these tumours, the most common malignant intracranial neoplasms are the gliomas, which account for 40 % - 45 % brain tumours, and are the most lethal. Current treatments include surgery, radiation therapy, hormone therapy and chemotherapy, but have been limited in their effects. This is due to poor specificity of the treatments and low bioavailability of the drugs in the CNS after crossing the blood brain barrier. Still, a few groups are working in the development of multi-targeted therapies with conventional inhibitors of growth factor receptors (epidermal growth factor receptor – gefitinib – and vascular-endothelial growth factor) and of mTOR (rapamycin) with some level of success so far [124, 125] and see for review [126, 127]. However, research has now turned to molecular and genetic tools – such as antisense molecules, triple helix forming oligomers and sense oligodeoxynucleotides – to produce better therapies [127]. Blocking IGF-1 with antisense molecules and triple helix forming oligomers has been giving encouraging results in rat and human glioma cells as it generates immunogenic anti-tumour phenomena and induces apoptosis [128-131]. Moreover, the expression of the IGFBP-2 is increased in gliomas and other cancers, and could be used as a marker of disease or a therapeutic target (as mentioned above, IGFBP-2 is involved in proper recruitment of IGF-1 to the IGF-IR) [132]. In addition to targeting IGF-1 and the IGF-IR, the main downstream signalling pathways activated by their interaction are also being considered because they can be induced by other growth factors and their receptors in the context of tumours. For instance, a lot of attention has been given to PTEN as it is often deregulated allowing longer activation of the PI3K/Akt pathway [52]. Indeed, it was found that biallelic inactivation of PTEN occurrence increases with glial tumour progression and has been detected in 30 % to 40 % of glioblastoma multiforme, reviewed in [133]. Furthermore, gain-of-function mutations in the p110α gene (PI3KCA) are found in various cancers, including brain anaplastic oligodendrogliomas, high grade astrocytomas and medulloblastomas [134, 135]. The transformation process by PI3Kα appears to depend on mTOR and its downstream targets [136]. The last study identified a PI3Kα inhibitor, PI-103, that induced proliferation arrest *in vitro* and inhibited growth of malignant human gliomas xenografts *in vivo*. This compound displayed combinatorial inhibition of mTOR and p110α and appeared to have great potential for the treatment of human tumours.

3.2. Alzheimer's Disease

With a high incidence of dementia in the population over 85 years old, Alzheimer's disease (AD) accounts for 40 % of the recorded cases. This condition is characterized by extracellular plaques of amyloid β (Aβ) peptide and intracellular neurofibrillary tangles of neuritic deposits rich in the hyperphosphorylated microtubule-associated protein tau [137]. Linking aging, obesity and diabetes to AD led research to

focus on the possible involvements of IGF-1 in this disorder [138]. As previously discussed, the levels of IGF-1 decrease with age, and hence, are inversely correlated with the occurrence of AD. Interestingly, in primary rat embryonic hippocampal cultures, an area of the brain sensitive to AD lesions, it was found that IGF-1 can protect and rescue neurons against Aβ toxicity [139]. Moreover, this is not common to all growth factors as the nerve growth factor had the opposite effect [140]. Mechanistic studies have followed up on these observations and showed that the IGF-1 protective actions are implicated at different levels of AD progression in addition to the previously mentioned effects on neuronal survival [141, 142]. On the one hand, IGF-1 is now known to promote neuronal secretion of Aβ, and to increase the transport of albumin and transthyretin, two Aβ-carrier proteins, into the brain to allow clearance of Aβ into the circulation [143, 144]. On the other hand, the signalling pathways leading to tau hyperphosphorylation have been characterized. GSK3β is directly responsible for the phosphorylation of tau and is activated through the inactivation of Akt. Indeed, if the IGF-1 signalling pathway is disrupted, Akt is no longer phosphorylated and cannot inhibit the actions of GSK3β [145, 146]. The latter was further evidenced by IRS-2 knockout mice as they had increased levels of tau phosphorylation in the CNS [147].

Following up on the work of Langstrom and coworkers (1989) demonstrating that mRNA translation is altered in the brain of AD patients [148], it was found that mTOR plays an important role in inducing protective effects of IGF-1 [149]. In addition, Carro and colleagues (2006) showed that IGF-1 treatment in one-year-old transgenic mice expressing mutant forms of Aβ precursor protein and presenilin-2, both proteins implicated in AD, helped recover cognitive performance in spatial learning and memory [150].

The levels of IGF-1, IGFBPs and IGF-IR were examined in AD patients compared to age-matched controls. The former were significantly induced in serum but not in the CFS. Only IGFBP-2 and -6 levels were significantly increased in the CSF of AD patients [151]. Finally, the IGF-IR densities were unchanged in the frontal cortex or in white matter [152]. Neither were the IGF-IR binding sites in the cortex or the hippocampus [153].

To date, there is no treatment of AD. Many different approaches have been proposed to fight the disease, such as vaccines against Aβ, but controversial results have been obtained. Hence, the importance to consider other options.

3.3. Amyotrophic Lateral Sclerosis

Although less prevalent than MS, with approximately 3,000 Canadians or 30,000 Americans having the disease at any given time, Amyotrophic Lateral Sclerosis (ALS) is much more aggressive. At diagnosis, the life expectancy of people affected with this disease is between two to five years. ALS selectively targets and causes the progressive loss of motor neurons in the spinal cord, brainstem and cerebral cortex, and atrophy of the innervated muscles. Mutations on the human Cu/Zn superoxide dismutase (SOD1) locus on chromosome 21 have been linked to 10 % of all ALS cases [154]. However, ALS has been poorly characterized, and no cure exists. Currently, there is only one drug approved by the Drug and Food Administration (FDA) for the treatment of ALS. It is riluzole (Sanofi-Aventis), a benzothiazole known to inhibit glutamate release, postsynaptic glutamate receptor activation and voltage-sensitive sodium channel activation. Unfortunately, the effects on survival are modest. Only two clinical trials were conducted to test this product, and very little has been done to build on the knowledge gathered from the beneficial effects of riluzole [155-157]. Other attempts to treating this disease have come from the rationale that neurotrophic factors prevent axonal degeneration, neuronal atrophy and cell death [158]. Positive results were obtained from different animal models of ALS. Of direct relevance, it had been shown that subcutaneous injections of IGF-1 increase muscle endplate size in rats and accelerate functional recovery following sciatic nerve crush in mice [159]. In addition, it was found that administration of rhIGF-1 in wobbler mice, a model of lower motor neuron disorders, significantly increased the mice behavioural scores as measured by grip strength, and the mean muscle fiber diameter as assessed histochemically [160].

This lead, in the nineties, to two randomized double-blind placebo-controlled clinical trials with subcutaneous administration of rhIGF-1 (Cephalon). They lasted nine months. One was performed in eight North American centers and the other in eight European centers. The former study gave encouraging results as it showed a significant decrease in disease progression according to the Appel ALS rating scale, which measures patients' functions including swallowing, speech, respiratory and limb motor function. However, the European trial gathered data that was inconclusive. Nonetheless, in both studies, rhIGF-1 was well tolerated with less than 4 % of patients withdrawing from the trial due to adverse side effects [161, 162] reviewed in [154, 163-165]. A third study was completed last December (NTC00035 815), and the results are pending. This double-blind placebo-controlled trial was conducted on 300 ALS patients of 16 different medical centers over a period of two years, with examinations every six months (clinicaltrials.gov).

So, with the data collected to date, why so little success in humans? The abovementioned trials have been extensively reviewed by different groups, and all concur in that more clinical trials need to be conducted with better assessment of the disease stage in which the patients initially are, and inclusion of survival as an outcome measure (hopefully, the third trial will respond to these criteria). An important factor that must be taken into consideration is the delivery system. IGF-1 is a large molecule that goes through extensive regulation, as discussed above. ALS patients have been found to have increased levels of IGFBPs, namely IGFBP-2, -5 and -6, in serum and spinal cord sections, making it hard for IGF-1 to successfully reach the IGF-IR [166-168]. However, ALS patients also have increased levels of the IGF-IR on spinal cord neurons [169, 170]. Hence, research has now focused on alternative ways of benefiting from the IGF-1 axis for the treatment of ALS.

A study by Nagano and colleagues (2005a) revealed that intrathecal administration of IGF-1 has improved motor performance, delayed disease onset and extended survival in the mouse model of familial ALS (SOD1 mutant-mediated ALS), with increased phosphorylation levels of Akt and

ERK in spinal motor neurons [171]. Moreover, the same research group conducted a small double-blind clinical trial on nine patients. The latter received intrathecal administration of either a high (effective concentration) or a low (negative control) dose of IGF-1 every two weeks for 40 weeks. The rate of decline of bulbar and limb functions (Norris scales) and forced vital capacity were determined. Disease progression was slowed as shown by total Norris and limb Norris scores. No serious adverse side effects were encountered during the trial [172]. Further studies remain to be performed to confirm these results due to the small number of participants in this project. In parallel, Kaspar and colleagues (2003) found that adeno-associated virus (AAV) carrying a gene encoding IGF-1 can be efficiently transported retrogradely from muscle (hindlimb quadriceps and intercostal muscles) to motor neurons of the spinal cord in the SOD1 mutant mouse model of ALS [173]. Moreover, IGF-1 delivered in this manner increased animal survival and delayed disease progression. Since both IGF-1 and AAV have been shown to cause little adverse side effects in humans, the possibility of finding a treatment for ALS now seems closer than ever [173-175]. More recently, administration of an AAV encoding IGF-1 into lumbar parenchyma of SOD1 mutant mice has produced similar results [176]. It is now time to bring AAV-IGF-1 into humans. A small phase IIa clinical trial has been planned by Ceregene Inc, [157].

3.4. Multiple Sclerosis (MS)

Although the cause of MS remains elusive, it is well accepted that MS is an autoimmune disease affecting primarily the white matter. According to the Multiple Sclerosis Society of Canada and the National Multiple Sclerosis Society, the prevalence of MS in North America ranges from one in 500 to one in 1000 people depending on the region. Worldwide, there is an estimated 2.5 million cases of the disease. Therefore, there are a lot of efforts targeted towards finding treatments to fight MS. With research showing promising results using IGF-1 on myelination, oligodendrocytes and neurons *in vitro* and *in vivo* (as mentioned above and below), it is only a matter of time before the use of IGF-1 advances to clinical studies. The evidence gathered from IGF-1 treatments to rats or mice with various models of EAE indicates that IGF-1 reduces demyelination, increases myelin protein synthesis and improves clinical recovery of the animals [27, 177, 178].

In 2002, Frank and colleagues conducted a pilot study of recombinant IGF-1 (rhIGF-1; Cephalon) on seven patients [179]. However, this open-label crossover study did not show any particular beneficial effects on disease progression of the 6-month treatment with 50 mg of rhIGF-1 administered twice a day subcutaneously compared to the 6-month baseline. On the other hand, the rhIGF-1 was well tolerated. The authors suggest not discarding the possibility of future studies using rhIGF-1, alone or in combination, for the treatment of MS as their study was conducted on a small group of patients and many positive effects of IGF-1 in the CNS have been proposed. Moreover, a few studies have shown that the levels of IGF-1 and IGFBP-1 to -4 in serum or the cerebrospinal fluid (CSF) remain constant in MS patients [166, 180]. Still, when looking at the lesions in postmortem brains, there were increased amounts of IGF-1, IGFBP-2 and IGFBP-4, but not of the IGF-IR, see for review [34, 181,182]. The first three proteins were all upregulated by reactive astrocytes; and microglia participated at the lesions by increasing the levels of IGFBP-2. As previously discussed, IGFBP-2 targets IGF-1 to astrocytes for proliferative purposes, possibly promoting glial scarring, but does not contribute to oligodendrocyte survival or differentiation. Altering the levels of IGFBP-2 might also be of interest in a search for MS treatments. To date, current therapies for MS patients modulate the inflammatory response but do not target the disease itself. New and more selective targets of anti-inflammatory drugs may be the P13Kγ and βisoforms: the first is activated by a variety of chemokine receptors; and knockout of the second makes mice remarkably resistant to the development of inflammatory diseases [53, 183].

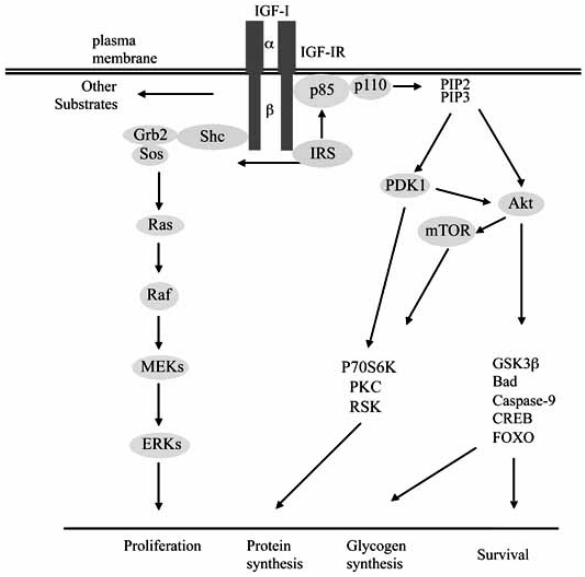

Fig. (1). Simplified schema of the molecular pathways implicated in IGF-1 signalling.
Binding of IGF-1 to the IGF-IR causes receptor tyrosine phosphorylation and association with IRS docking proteins. IGF-IR and IRS can phosphorylate Shc, which forms a complex with Grb2 and Sos and activate the Ras-Raf-MEK-ERK pathway. PI3K generates phospholipids required for PDK1 and Akt/PKB activation. PDK1 can phosphorylate Akt, P70S6K, PKC and RSK; Akt/PKB can phosphorylate GSK3β, Bad, Caspase-9, CREB and FOXO. The multiple signalling pathways regulate protein and glycogen synthesis and promote proliferation and survival.

3.5. Periventricular Leukomalacia (PVL)

Axonal maturation and myelination development need long periods of growth (as discussed above); therefore, insults during this time can cause severe neurological disorders, such as diseases associated with myelin dysfunction including PVL. The latter is the most common brain injury to occur in preterm infants born between 23 and 32 weeks postconceptional age, corresponding to the period that precedes the onset of myelination in human white matter development. PVL is characterized by focal cystic necrotic lesions in the subventricular zone and the periventricular white matter, affecting blood vessels, axons, astrocytes and oligoden-

drocytes [184]. These brain injuries are due to the relatively immature cerebral vasculature and, hence, a failure in perfusion and/or ischemia and hypoxia [185]. The intrinsic vulnerability of oligodendrocyte precursors is considered central to the pathogenesis of PVL [186], leading to the death of premyelinating oligodendrocytes [187] and the impairment of myelination in the periventricular white matter [188]. These result in global cognitive and developmental delay, as well as motor disturbances. A number of studies have demonstrated that oligodendrocyte progenitors and immature oligodendrocytes are more vulnerable than mature oligodendrocytes to ischemia [189, 190] and other insults [191]. Both free radical generation and glutamate toxicity play a major role in the initiation of oligodendrocyte progenitor death [192-195]. A recent study has shown that IGF-1 protects oligodendrocyte progenitors from tumour necrosis factor-α, a known inducer of injury in the context of PVL, by interrupting the mitochondrial apoptotic pathway via the activation of the PI3K/Akt pathway [196]. Moreover, Wood and colleagues (2007) demonstrated that IGF-1 administered after glutamate-induced cell death in primary cultures of oligodendrocytes or administered intraventricularly after hypoxic-ischemic brain injury in perinatal rats rescues oligodendrocyte progenitors in the immature white matter and promotes myelination [197].

Prematurely born infants are also susceptible to develop retinopathy of prematurity (ROP), which is not exclusive from PVL. ROP affects the retinal vasculature. Many factors have been shown to influence the proper course of retinal vasculature in the preterm infants, among others low serum levels of IGF-1 [198]. During normal pregnancy, the levels of IGF-1 rise significantly in the third trimester and are provided by the placenta and the amniotic fluid [199]. After birth, the infant is subjected to much lower amounts of IGF-1, since the premature liver cannot make up for the loss. Therefore, preterm infants lack significant exposure to IGF-1. Based on these observations, studies have suggested that IGF-1 is a permissive cue for the vascular endothelial growth factor (VEGF) to promote normal retinal angiogenesis [200-202]. In addition, the levels of serum IGF-1 and IGFBP-3 of preterm infants have been shown to be good predictive factors of ROP, together with postconceptional age at birth and birth weight [203-205]. Clinical trials restoring the IGF-1 and IGFBP-3 levels to *in uteri* levels are been planned in the hope to prevent or reduce the risk of ROP [206]. A pilot randomized controlled study indicated that insulin therapy in the first week of life of preterm infants increases IGF-1 bioactivity levels and could reduce morbidity associated with prematurity [207]. Both PVL and ROP are due to poor vascularisation in preterm infants and presumably low IGF-1 levels, therefore the usefulness to combine data obtained from both diseases.

4. CONCLUSION

All in all, IGF-1 is essential for proper development and homeostatic control. The levels of this growth factor are highly regulated and abnormal levels of IGF-1 lead to pathological states. For instance, brain tumours show cases of elevated IGF-1, while the neurodegenerative disorders described above exhibit decreased levels of IGF-1. Targeting the IGF-1 axis is therefore an interesting route to explore. Different studies have shown an acceptable level of safety when administering IGF-1 in clinical trials for MS and ALS. Studies in patients of all ages, from young children – with growth disorders [208] – to fully developed adults, support these data. The latest clinical trial results are pending from the study on ALS that was completed in December and will hopefully allow to better assess the use of IGF-1 in this disease. Moreover, genetic and molecular approaches are being exploited to inhibit the effects of IGF-1 in cancer. Delivery methods, such as retrograde viral delivery of IGF-1 from muscle cells to motor neurons in ALS, are being developed to maximize the chances of proper delivery to the IGF-IR in the CNS. The levels of IGF-1 are also good indicators of disease progression, as explicitly seen in gliomas and ROP. This is true as well for the IGFBPs. Therapeutic approaches can also target the individual classes of IGFBPs for better or worse bioavailability of IGF-1, depending on the context. Immunotherapy against the IGF-IR could also be exploited as it has been for other growth factors with some level of success. Finally, the signalling pathways activated by the IGF-1/IGF-IR interaction can also be targeted for therapeutic purposes. Several first generation kinase inhibitors have led the way to more specific, stable and water soluble compounds in the hope to overcome pharmacodynamic and pharmacokinetic problems encountered in the past. Viral constructs of genetically altered proteins can induce activation of the signalling pathways and are presently being looked into more closely in the context of therapeutics.

On another note, glatiramer acetate – the acetate salt of a standardized randomized mixture of synthetic polypeptides consisting of L-glutamic acid, L-lysine, L-alanine and L-tyrosine – is a widely prescribed drug for relapsing-remitting MS. It acts as an immunomodulator in the periphery with probable induction of TH2-like regulatory cells that can cross the blood brain barrier and cause a bystander suppression effect by blocking inflammation, [209-211]. A recent study in a mouse model showed that glatiramer acetate helps in the treatment for Alzheimer's disease by inducing dendritic-like microglia that express IGF-1 [212]. This could account for some of the reasons why this drug is beneficial to MS patients and also lead towards targeting IGF-1 in Alzheimer's disease patients. Glatiramer acetate does not need to cross the blood brain barrier to be efficacious, which facilitates delivery purposes, and has already been approved in North America and Europe as a therapeutic agent for MS. These data have research come full circle, since different methodological approaches (building on the rationale that IGF-1 has beneficial effects on different cell types of the CNS or trying to understand how different agents are beneficial to the CNS) have put the spotlight on IGF-1.

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