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Role of Central Insulin-Like Growth Factor-1 Receptor Signalling in Ageing and Endocrine Regulation

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1. Introduction

Insulin-like growth factors (IGFs) are, besides other mechanisms, controlled by growth hormone (GH) secretion and there are at least two different IGFs: IGF-1 and IGF-2. IGFs regulate various cellular processes e.g. survival, differentiation and proliferation (McMorris et al. 1986; McMorris & Dubois-Dalcq 1988; Mozell & McMorris 1991).

Growth hormone, which induces IGF-1 secretion from the liver, is generated in the anterior pituitary and regulated by the hypothalamus via growth hormone releasing hormone (GHRH) and growth hormone inhibiting hormone (GHIH) (Jansson et al., 1985; Carlsson & Jansson 1990). IGFs in the brain are synthesised de novo or transported across the blood brain barrier (BBB) and seem to induce a variety of effects on the central nervous system (CNS). So far, the exact transport mechanisms of IGFs into the brain are not fully understood (Duffy, Pardridge, and Rosenfeld 1988).

In the rodent brain, IGF-1 is mainly expressed in neuron-dense regions like the hippocampus, striatum, thalamus, hypothalamus and olfactory bulb (Rotwein et al. 1988; Bondy et al. 1990; Garcia-Segura et al. 1991). Accordingly, the insulin-like growth factor-1 receptors (IGF-1Rs) are mainly found in the olfactory bulb, cerebellar cortex and granule cell layer of the dentate gyrus (Rotwein et al. 1988; Bondy et al. 1990; Bondy and Lee 1993; Werther et al. 1990). However, the function of IGF-1R mediated signals in the central nervous system (CNS) is still under investigation.

After binding of IGF-1 to the IGF-1R, a signalling cascade is activated which leads to recruitment and subsequently phosphorylation of intracellular adaptor proteins, the so called insulin receptor substrates (IRS) (Jacobs et al. 1983; Rubin et al., 1983; Sun et al. 1991; Lavan et al. 1997; Lavan et al., 1997). Via these adaptor proteins, the MAP kinase (MAPK, mitogen activated protein kinase) cascade, as well as the phosphatidylinositide(PI)3-kinase signalling pathway, is turned on leading to protein kinase B (PKB/AKT) activation, which phosphorylates forkhead box O transcription factors (FoxO) causing their nuclear export (Stokoe et al. 1997; Alessi et al. 1996; Partridge & Bruning 2008). FoxO mediated transcription is involved in cell proliferation, differentiation and oxidative stress defence (Clark et al. 1993; Brunet et al. 1999; Dijkers et al. 2000; Dijkers, Medema, Pals et al. 2000; Medema et al. 2000) suggesting a function of FoxO during development and cellular stress response.

Recently, the function of the IGF-1R signalling pathway in neurons has been investigated using different model organisms like worms and flies as well as conventional and conditional mutagenesis in mice. These experiments revealed possible functions of IGF-1 mediated signals in endocrine regulation, longevity, protein turnover and in the pathogenesis for ageing-associated diseases e.g. Alzheimer's Disease (AD). The current article discusses the mechanisms of regulation and the physiological as well as a possible pathophysiological role of IGF-1 mediated signals in the CNS.

2. The GH/insulin-like growth factor system

2.1 The somatotropic system

Growth hormone (GH, somatotropin) is produced in the anterior pituitary by certain specified cells and regulated via the hypothalamus by the growth hormone releasing hormone (GHRH, somatoliberin), the growth hormone inhibiting hormone (GHIH, somatostatin), but also by suppression of the short loop negative feedback of GH itself (Jansson, Eden, and Isaksson 1985; Carlsson and Jansson 1990).

The GH-producing cells of the anterior pituitary, also called somatotropes or somatotroph, form 30-40 % of the anterior pituitary (Gage et al. 1996). These cells require transcription factors of the POU-family (Mullis 2010) including the homeoproteins Pit-1 and Prop-1 (prophet of Pit-1) for normal embryonic development and differentiation (Mullis 2005) as well as for GH expression. The expression of these transcription factors and therefore the differentiation of the somatotroph are controlled by GHRH producing neurons of the hypothalamus. Additionally, GH-release in the pituitary is inhibited by serum IGF-1 and enhanced by serum ghrelin (Wortley et al. 2005; Zigman et al. 2005) (Figure 1).

In the periphery, GH mainly influences growth and development via IGF-1. IGF-1 and IGF-2 can act endocrine, paracrine and autocrine (Cohick and Clemmons 1993; Stewart and Rotwein 1996; Mohan, Baylink, and Pettis 1996; Butler and LeRoith 2001). Additionally, there is a truncated form of IGF-1, Des(1-3)IGF-1, which lacks the tripeptide Gly-Pro-Glu at the N-terminus probably resulting from post-translational cleavage of IGF-1. Des(1-3)IGF-1 is mainly expressed in brain and active in lower concentrations than un-truncated IGF-1 (Ballard et al. 1996; Francis et al. 1988; Carlsson-Skwirut et al. 1989; Ogasawara et al. 1989). Studies on hypoxic-ischemic brain injuries in rats suggest that the tripeptide fragment has neuroprotective properties and influences neuronal activity (Guan et al. 1999).

Circulating IGF-1 is mainly produced in the liver, but both IGF-1 and IGF-2 are expressed in many non-hepatic tissues (Cohick and Clemmons 1993; Stewart and Rotwein 1996; Butler and LeRoith 2001). The most important effects of IGFs are cell proliferation and differentiation, skeletal growth and mineralisation as well as the development and function of the reproductive organs and the central nervous system (CNS) (Duan and Xu 2005).

GH is secreted pulsatile in rodents as well as in humans (Jansson, Eden, and Isaksson 1985; Frohman and Jansson 1986; Giustina and Veldhuis 1998) and follows a circadian pattern with one major peak after falling asleep. There is a sexual dimorphism in GH secretion, which is more dominant in rodents than in humans (Jansson, Eden, and Isaksson 1985; Tannenbaum and Martin 1976). In females, the GH secretory pattern seems to be less regular compared to males (Giustina and Veldhuis 1998), with higher basal interpulse GH levels, more frequent but lower amplitude pulses and a lower major nocturnal GH pulse (Jaffe et al. 1998; Jessup et al. 2003). Spontaneous and GHRH-stimulated GH secretion is suppressed more efficiently by IGF-1 in men than in women (Ohlsson et al. 2009) suggesting that also

sex steroids interfere with GH secretion (Veldhuis et al. 2008, 2009; Leung et al. 2004). Body growth is influenced more efficiently by GH if it is applied in a pulsatile fashion than applied continuously (Jansson, Eden, and Isaksson 1985; Clark et al. 1985). This might be due to a higher induction of IGF-1 expression in growth plates and skeletal muscles by pulsatile GH, whereas continuous GH secretion stimulates liver IGF-1 expression and serum IGF-1 levels at least as well as a pulsatile GH release (Isgaard et al. 1988; Bick et al. 1992). Therefore, liver-derived IGF-1 is not essential for body growth itself. This effect might be achieved by locally produced IGF-1 and/or other factors (Ohlsson et al. 2009).
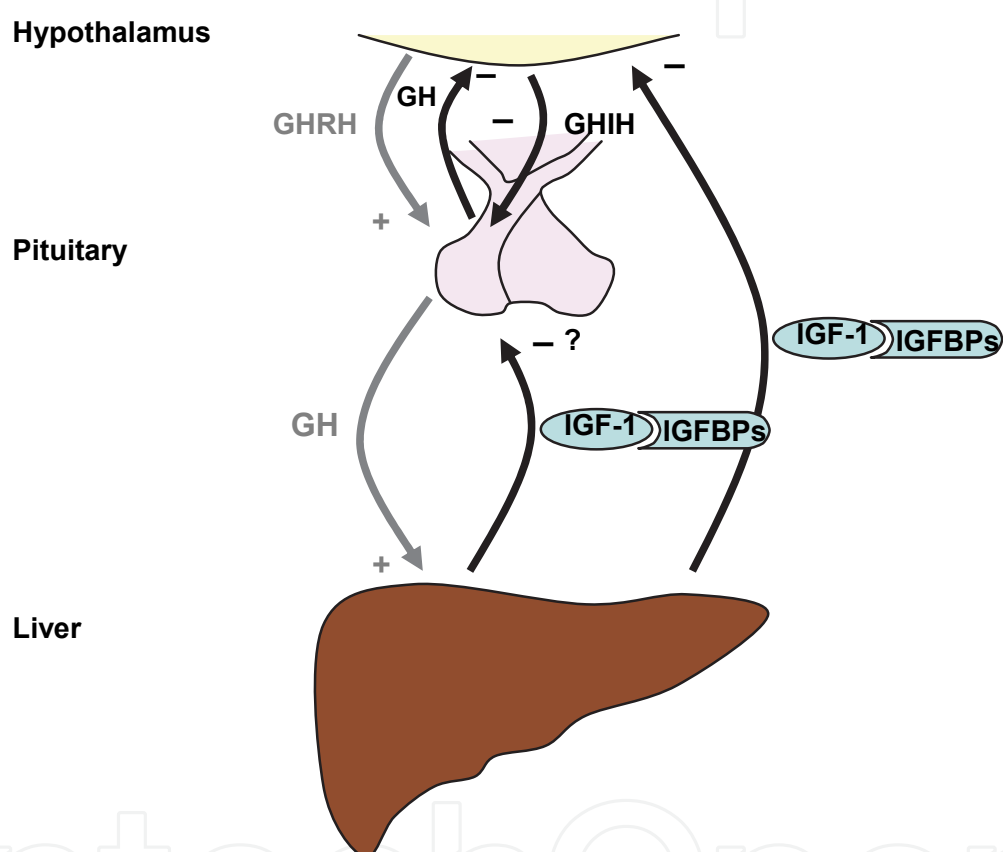

Fig. 1. GH/ IGF-1 system
Growth hormone releasing hormone (GHRH) and growth hormone inhibiting hormone (GHIH) are produced in neurons of the hypothalamus and transported via the hypothalmo-pituitary portal vein system to the anterior pituitary where they regulate growth hormone (GH) secretion and expression. GH stimulates insulin-like growth factor-1 (IGF-1) production in the liver. In addition, free IGF-1 serum levels are regulated by binding to the insulin-like growth factor binding proteins (IGFBPs). A short negative feedback loop of GH, as well as a negative feedback mechanism of IGF-1 on the hypothalamus and possibly on the anterior pituitary, determines serum IGF-1 levels.

Mouse models with tissue specific IGF-1 inactivation indicate that normal longitudinal bone growth is maintained by local bone-derived IGF-1 (Sjogren et al. 1999; Yakar et al. 1999). However, several other phenotypes, for example the one observed in the liver IGF-1

deficient (LID) mouse, suggest that locally derived IGF-1 cannot fully replace liver-derived IGF-1 function and vice versa.

A lacking negative feedback of liver-derived IGF-1 on GH secretion leads to a compensatory increase in serum GH levels in mice (Yakar et al. 1999; Sjogren et al. 1999) and also in humans (Veldhuis et al. 2001). Hence, the phenotype of the LID mice might either arise directly or is mediated by the elevated GH-levels. LID mice show an increased expression of pituitary GHRH- and ghrelin-receptors indicating that at least some action of up-regulating GH secretion influences the pituitary (Ohlsson et al. 2009). However, the target sites of IGF-1 for regulating GH-release remain unclear and might either be located in the hypothalamus and/ or the pituitary. Recently, a cell-specific knockout mouse in which the IGF-1 receptor (IGF-1R) was ablated from the somatotroph, the so called somatotroph IGF-1 receptor knockout (SIGFRKO) mouse, has been generated (Romero et al. 2010). The phenotype of the SIGFRKO mouse includes increased GH expression and secretion as well as increased serum IGF-1 levels (Romero et al. 2010). Feedback mechanisms in the hypothalamus resulted in decreased GHRH and increased GHIH mRNA levels (Romero et al. 2010). Furthermore, decreased growth hormone releasing hormone receptor (GHRH-R) expression was observed in the anterior pituitary (Romero et al. 2010). However, these changes were not able to reduce GH secretion in the SIGFRKO mouse indicating a role of IGF-1R signalling in the pituitary in addition to the hypothalamus in regulating GH secretion (Romero et al. 2010).

IGF-1 influences glucose metabolism directly, e.g. by inducing insulin-like effects on glucose-uptake in tissues expressing IGF-1-receptors, but also by suppressing the GH-release from the pituitary. GH is known to have diabetogenic effects (Yakar et al. 2004) by decreasing insulin-sensitivity in skeletal muscle, liver and fat. Consequently, LID mice show an impaired insulin-sensitivity. At the same time, those mice are protected against the increase in body fat mass that occurs in older age (Sjogren et al. 2001; Tang et al. 2005). This might be explained by elevated GH-levels in these mice (Ohlsson et al. 2009) as decreased GH secretion in both rodents and humans has been proposed to contribute to age-related obesity (Sonntag et al. 1980; Rudman et al. 1990).

The inactivation of IGF-1 or its receptor during early development reduces brain size including a reduction of the granule cell layer in the dentate gyrus and the number of oligodendrocytes and myelinated axons (Beck et al. 1995; Holzenberger et al. 2001; Vicario-Abejon et al. 2003) demonstrating the importance of IGF-1 signalling during brain development. LID mice show a milder phenotype with reduced exploratory activity (Svensson et al. 2005; Bohlooly et al. 2001), as well as impaired spatial learning and memory, suggesting that liver-derived IGF-1 enhances brain functions (Svensson et al. 2006). Circulating IGF-1 is essential for mediating exercise induced effects on the adult brain by promoting the numbers of newly generated neurons in the adult hippocampus, brain vessel growth, spatial learning and reducing anxiety (Trejo, Carro, and Torres-Aleman 2001; Trejo, Llorens-Martin, and Torres-Aleman 2008; Lopez-Lopez, LeRoith, and Torres-Aleman 2004). Additionally, liver-derived IGF-1 might enhance the clearance of brain amyloid-β (Aβ), whose aggregation is one of the hallmarks of AD (see 5.1).

2.2 IGF-binding proteins

Only a small amount of IGF-1 (~1 %) circulates "free" within the blood. The remaining 99 % are bound to IGF-binding proteins (IGFBPs). IGFBPs are a family of at least six proteins (IGFBP-1 to IGFBP-6), which bind IGF-1 with high affinities that are equal to or greater than

those of the IGF-1 receptor (Duan and Xu 2005). Additionally, there are several proteins with lower IGF-1 binding affinity, called IGFBP-related peptides (IGFBP-rPs), which have significant structural homologies with the amino(N)-terminal region of high-affinity IGFBPs (Rechler 1993; Kelley et al. 1996; Rajaram, Baylink, and Mohan 1997; Kim et al. 1997; Poretsky et al. 1999; Baxter 2000). So far, the functions of the IGFBP-rPs, also referred to as IGFBP- 7 to - 10, are not known (Mohan and Baylink 2002). Approximately 75-80 % of IGF is present as a 150 kDa complex, which consists of IGF-1/IGF-2 plus IGFBP-3 (70-75 %) or IGFPB-5 (5-10 %) and an acid-labile subunit (ALS) (Baxter, Meka, and Firth 2002). ALS is mainly produced in the liver (Baxter 1988; Baxter and Martin 1989; Baxter, Martin, and Beniac 1989) and its gene disruption leads to a reduction of circulating IGFs of 80 % (Boisclair et al. 2001). The ternary complex of IGF-1 or -2/ IGFBP-3 or -5/ ALS extends the half-life of IGFs to 15-20 h, compared to a half-life of 20-30 min for free IGF-1 in circulation (Guler, Zapf, and Froesch 1987) suggesting a reservoir function of this complex, which cannot cross the vascular endothelial barrier (Rajaram, Baylink, and Mohan 1997; Baxter 2000). 20-25 % of the IGFs bind to IGFBP-1,-2,-4 or -6 to form a complex, which is able to cross vascular endothelium (Baxter 2000; Rajaram, Baylink, and Mohan 1997). Thus, the endocrine actions of IGF-1 in serum are regulated by the IGFBPs determining how much IGF is bio-available to the local tissues.

Furthermore, IGFBPs are located in the extracellular matrix or on the cell surface where they either inhibit (mainly IGFBP-4 and -6) or potentiate (mainly IGFBP-3 and -5) IGF-1 binding to its receptors (Rajaram, Baylink, and Mohan 1997; Mohan et al. 1995; Qin et al. 1998; Jones and Clemmons 1995; Firth and Baxter 2002; Rechler and Clemmons 1998). Functions of the IGFBPs might vary indicated by the inhibiting or potentiating effect of IGFBP-1, -2, -3 and -5 on IGF-1 action depending on the experimental conditions (Yin, Xu, and Duan 2004).

The actions of IGFBPs are, in turn, modulated by IGFBP proteases that are further dependent on activators and inhibitors (Mohan et al. 2002). Those IGFBP proteases are able to cleave IGFBPs, thereby reducing their affinity for IGF-1. Some of them are relatively specific for a given IGFBP. For example, pregnancy-associated plasma protein-A (PAPP-A), which is produced by a variety of cell types, cleaves specifically IGFBP-4 (Lawrence et al. 1999; Byun et al. 2001; Conover et al. 2001), whereas complement C1s (Busby et al. 2000) and a disintigrin and metalloprotease-like (ADAM)-9 (Mohan et al. 2002) were identified to be relatively specific for IGFBP-5. Additionally, a number of other serum proteases were shown to be capable of cleaving IGFBPs, e.g. plasmin, cathepsin D and prostate specific antigen (Conover 1995; Fowlkes et al. 1995; Rajah et al. 1995; Rajaram, Baylink, and Mohan 1997; Maile and Holly 1999). Therefore, the binding affinity and hence the bio-availability of IGF-1 is regulated via the degradation of IGFBPs through the IGFBP protease system.

IGFBPs also have IGF independent functions, for example IGFBP-2 and -3 can induce direct cellular effects (Firth and Baxter 2002; Oh et al. 1993; Yamanaka et al. 1999; Schutt et al. 2004) and it has been shown that IGFBP-3 at least partially mediates these effects by binding to the cell surface, possibly to specific receptors (Mohseni-Zadeh and Binoux 1997; Rechler and Clemmons 1998). IGFBP-2, -3 and -5 contain sequences for nuclear localisation (Schutt et al. 2004; Radulescu 1994; Schedlich et al. 1998; Hoeflich et al. 2004) and might as well influence gene expression.

2.3 The insulin- and insulin-like growth factor-1 signalling pathway

Insulin and IGF-1 receptors are receptor tyrosine kinases. Receptor tyrosine kinases contain a membrane-bound domain with tyrosine kinase activity which phosphorylates tyrosine-residues of downstream signalling proteins. Typical members of the receptor tyrosine kinase

family are the epidermal growth factor receptor (EGFR), the nerve growth factor receptor (NGFR) and the insulin receptor (IR). The IR was discovered in 1974 and its tyrosine kinase was found in 1982 (Kasuga, Karlsson, and Kahn 1982; Kasuga et al. 1982). Later, in addition to the IR, the insulin-like growth factor-1 receptor (IGF-1R) was discovered as a tyrosine kinase activity containing receptor (Jacobs et al. 1983; Rubin, Shia, and Pilch 1983).

The IR and IGF-1R are heterotetrameric structures. The different subunits are linked by disulfide bonds. The α-subunits are exclusively localised extracellular (Van Obberghen et al. 1981; Ullrich et al. 1986). The β-subunits consist of a short extracellular part, a transmembrane domain and an intracellular part with ATP-binding motifs, autophosphorylation sites and tyrosine-specific protein kinase activity, which is activated after binding of insulin or IGF-1 to their receptors (Chou et al. 1987).

The insulin receptor gene consists of 22 exons and 21 introns (Seino et al. 1989). Alternative splicing of exon 11, which codes for 12 amino acids, causes two different isoforms: A, which lacks the 12 amino acids, and B. This alternative splicing does not exist for the IGF-1 receptor, because this receptor contains no equivalent to exon 11 of the IR. The A- and B-isoforms both bind to insulin with similar affinity (McClain 1991). The A-isoform has a higher affinity to IGF-1 (Yamaguchi et al. 1991) and IGF-2 (Frasca et al. 1999) compared to the B-isoform. The A-isoform is expressed in hematopoietic cells, fetal tissue and the adult nervous system. The B-isoform of the IR is mainly present in liver, adipose tissue and muscle (Seino and Bell 1989; Moller et al. 1989; Goldstein and Kahn 1989; Mosthaf et al. 1990). The selective binding of insulin or IGF-1 is also dependent on the assembly of the receptors (Pandini et al. 2002). The hybrid of IGF-1 receptor and the A-isoform of the IR binds IGF-1, IGF-2 and insulin with similar affinity. The hybrid of the IGF-1R and the B-isoform of the IR only binds IGF-1 (Louvi, Accili, and Efstratiadis 1997).

2.3.1 Insulin receptor substrates

The binding of IGF-1 or IGF-2 to the IGF-1R causes a conformational change of the receptor, which induces autophosphorylation. This leads to the recruitment of insulin receptor substrates (IRS) to the autophosphorylated receptor tyrosine kinase, which in turn phosphorylates the tyrosine residues of the IRS proteins (Figure 2). The IRS protein family consists at least of four proteins, IRS-1 to IRS-4 (Sun et al. 1991; Lavan et al. 1997; Lavan, Lane, and Lienhard 1997).

The IRS proteins show different expression patterns. IRS-1 and -2 are ubiquitously expressed, but IRS-3 is only present in rodent adipose tissue. IRS-4 mainly occurs in thymus, hypothalamus, kidney and heart. All IRS proteins share the same structural characteristics and have similar functions (Giovannone et al. 2000; Schubert et al. 2003).

The four IRS family members contain an N-terminal pleckstrin homology (PH) domain, a phosphotyrosine-binding (PTB) domain and a C-terminal tail containing multiple tyrosine phosphorylation sites. The phosphotyrosine motifes of the IRS proteins are binding sites for Src homology(SH)2 domain-containing proteins (Yenush and White 1997). The PH domain binds to lipids and with high affinity to phosphoinositides (Fruman, Rameh, and Cantley 1999). The PTB domain of IRS binds to phosphotyrosine residues of other proteins including the IR and IGF-1R. In more detail, the PTB domain binds to the phosphorylated NPXP motif at the juxtamembrane domain of the receptor after binding of insulin or IGF-1. Following binding to this motif, the IRS proteins are tyrosinephosphorylated (Cheatham and Kahn 1995; White 2002).

Only IRS-2 contains a domain which binds to the phosphorylated kinase regulatory loop of the β-subunit of the IR. This domain is called the KLRB domain (Sawka-Verhelle et al. 1997; Sawka-Verhelle et al. 1996). However, the physiological function of the KLRB domain of IRS-2 remains unclear.

Insulin induces tyrosine and serine phosphorylation of IRS-1 (Gual, Le Marchand-Brustel, and Tanti 2005). These phosphorylations lead to specific regulation of downstream signalling. The phosphorylation of serine residues of IRS-1 contribute to positive or negative regulation of IRS-1 action (Weigert et al. 2005; Weigert et al. 2008). Important for this regulation are the particular phosphorylation sites (Herschkovitz et al. 2007) as well as the timing of phosphorylation (Weigert et al. 2005; Weigert et al. 2008). Currently, the serine phosphorylation sites with positive effect on IRS-1 action are regarded to be phosphorylated at first to support IRS-1 activity protecting from phosphorylation at residues with inhibitory effect (Weigert et al. 2005; Weigert et al. 2008; Gual, Le Marchand-Brustel, and Tanti 2005; Luo et al. 2007). In addition, serine phosphorylation with activating effect might prevent the association of IRS-1 with tyrosine phosphatases (Luo et al. 2005). The serine residues with inhibitory effect are located near the PTB domain. These residues are phosphorylated later than the residues with positive effect upon insulin stimulation or other signals. The phosphorylation of serine sites near the PTB domain causes disruption of the binding between IRS-1 and the IR followed by degradation of IRS-1. The phosphorylation of inhibitory serine residues in the C-terminus of IRS-1 disturb their interaction with the phosphatidylinositide (PI)3-kinase (Figure 2) (Gual, Le Marchand-Brustel, and Tanti 2005; Boura-Halfon and Zick 2009). Serine sites with inhibitory effect are phosphorylated by serine kinases like the mammalian target of rapamycin (mTor), PKCzeta and p70S6 (S6K) kinase (Boura-Halfon and Zick 2009; Herschkovitz et al. 2007; Gual et al. 2003). Insulin and IGF-1 resistance might be induced via kinases like c-Jun N-terminal kinase (JNK), mTor/S6K, inhibotory-κB kinase β (IKKβ), SIK-2 and extracellular signal regulated kinases (ERK) promoting the phosphorylation of the inhibitory sites of the IRS proteins (Boura-Halfon and Zick 2009; Herschkovitz et al. 2007). The IRS-2 serine phosphorylation sites are still under investigation. It is known that JNK phosphorylates Thr348 of IRS-2 which is located near the PTB domain (Solinas et al. 2006) and might cause disruption of the binding between IRS-2 and the receptor. Furthermore, JNK phosphorylates Ser488 of IRS-2 promoting the phosphorylation at Ser484 by glycogen synthase kinase (GSK)-3β and thereby inhibiting the signalling pathway (Sharfi and Eldar-Finkelman 2008).

2.3.2 PI3K signalling

The mammalian phosphatidylinositide(PI)3-kinases are subdivided into three classes, class I-III. Class I is further divided into Ia and Ib (Vanhaesebroeck et al. 2005). These classes catalyse the phosphorylation of the 3´hydroxyl position of phosphatidyl-myo-inositol lipids. The PI3K of the insulin and IGF-1 signalling pathway belongs to the class Ia kinases (Fruman, Meyers, and Cantley 1998). These kinases display a heterodimeric structure containing a catalytic subunit of 110 kDa. This subunit is non-covalently associated with a 50-, 55- or 85 kDa regulatory subunit. Following activation of the insulin receptor and IRS binding, the PI3K is recruited to the membrane via the p85 regulatory subunit. Other recruited factors are the growth factor receptor binding protein (GRB)-2 and the SH2-Phosphatase(SHP)2 (Figure 2).

The activated PI3K, in turn, phosphorylates phosphatidylinositide-diphosphate ($PI_{4,5}P$) to produce phosphatidylinositide-triphosphate ($PI_{3,4,5}P$). This event is reversible by PTEN (the

phosphatase and tensin homolog deleted on chromosome ten). The generation of $PI_{3,4,5}P$ causes activation of the downstream signalling proteins like phosphoinositide-dependent protein kinase (PDK) and protein kinase B (PKB, AKT). PDK is present in two isoforms, PDK-1 and PDK-2. PDK-1 phosphorylates AKT at Thr308, which partially activates AKT. To completely activate AKT, phosphorylation of Ser473 is necessary (Alessi et al. 1996; Lawlor and Alessi 2001; Stokoe et al. 1997). AKT is a serine/threonine kinase with a size of 57 kDa. It contains a PH domain and there are three isoformes, AKT-1, AKT-2 and AKT-3. These isoforms display a conserved domain structure: a kinase domain, a PH-domain at the N- as well as a regulatory subunit at the C-terminus (Hresko, Murata, and Mueckler 2003). AKT phosphorylates tuberin 2 (TSC-2). TSC-1 and -2 form a heterodimer with GTPase activity that inhibits the GTPase RHEB (RAS homolog enriched in brain). The phosphorylation via AKT causes the accumulation of the RHEB-GTP complex which activates mTOR (Astrinidis and Henske 2005; Hay and Sonenberg 2004). Furthermore, S6K is activated by phosphorylation of PDK-1 and mTOR (Figure 2). The regulation of protein synthesis via IGF-1 occurs through controlling the intrinsic activity and/or binding properties of specific translation initiation and elongation factors called eIFs and eEFs. mTOR phosphorylates 4E-BP (4E binding protein). This causes the release of eIF4E (eukaryotic initiation factor 4E) to form an active complex, which promotes translation initiation and also activation of S6K. S6K phosphorylates the eEF2 (eukaryotic elongation factor 2) kinase which releases eEF2 and initiates elongation (Figure 2) (Nojima et al. 2003; Oshiro et al. 2004).

Other proteins, which are regulated via IR and IGF-1R signalling, are the glycogen synthase kinase(GSK)-3β, a major tau kinase, and BAD (Bcl-2/Bcl-X-associated death promoter), a proapoptotic factor. These proteins are inactivated via the IR/IGF-1R signalling cascade (Song, Ouyang, and Bao 2005). BAD interacts with the apoptosis suppressors Bcl-2 and more intense with Bcl-X_L (Yang et al. 1995). BAD directly binds to Bcl-X_L with its BH3 homology domain (Zha et al. 1997). This interaction is regulated by the phosphorylation state of BAD. Therefore, the IGF-1R signalling is a potent inhibitor of neuronal apoptosis (Schubert et al. 2003).

2.3.3 Forkhead box O transcription factor

AKT phosphorylates the Forkhead box O transcription factors (FoxOs). This induces the binding to 14-3-3 and nuclear exclusion of FoxOs and thereby inactivation of FoxO-mediated transcription. FoxOs regulate transcription of genes, which are involved in apoptosis, metabolism, growth, ageing and development (Partridge and Bruning 2008).

The mammalian FoxO protein family consists of 4 members: FoxO1, FoxO3a, FoxO4 and FoxO6. These transcription factors contain a conserved DNA binding domain, the forkhead domain (FKHR) (Clark et al. 1993). FoxO1 and FoxO3a are ubiquitously expressed, whereas FoxO6 is exclusively found in the brain, and FoxO4 has yet not been detected in the brain (Furuyama et al. 2000; Jacobs et al. 2003). The expression pattern of the different FoxOs in the adult mouse brain is distinct. FoxO1 is predominantly expressed in the striatum, dentate gyrus and ventral hippocampus and FoxO3a in the cortex, cerebellum and hippocampus. FoxO6 is expressed in amygdala, hippocampus and cingulite cortex (Hoekman et al. 2006).

The FoxO transription factors are regulated by post-translational modifications. One major modification is the phosphorylation of the FoxOs. FoxO1 is phosphorylated by AKT at Thr24, Ser256 and Ser319 (Biggs et al. 1999; Brunet et al. 1999; Kops et al. 1999; Rena et al. 1999; Tang et al. 1999). Phosphorylation triggers binding to 14-3-3 and subsequently

translocation out of the nucleus terminating FoxO mediated transcription (Figure 2) (Brunet et al. 1999). Additionally, FoxOs are phosphorylated by other kinases depending on the stimulus (Huang and Tindall 2007). Furthermore, FoxOs are regulated by ubiquitylation. Ubiquitylation is dependent on phosphorylation of Ser256 of FoxO1 via AKT (Huang et al. 2005). FoxO1 and FoxO3a need to be polyubiquitylated for degradation. In contrast, FoxO4 requires monoubiquitylation to be degraded (van der Horst et al. 2006). Another regulatory mechanism for FoxO transcription is acetylation. CBP and p300 with their associated proteins, for example CBP- and p300-associated factor (PCAF), display intrinsic histone acetyl-transferase activity. These proteins promote transcription via histone acetylation and they directly regulate transcription via acetylation of particular transcription factors (Li et al. 2002). It has been shown that CBP acetylates FoxO transcription factors and inhibits their action (Daitoku et al. 2004). Silent information regulator 1 (SIRT1) is a nicotinamide adenine dinucleotide(NAD)-dependent histone deacetylase, which forms a complex with acetylated FoxOs upon stress stimuli and deacetylates the transcription factors (Brunet et al. 2004; Kitamura et al. 2005) to regulate FoxO mediated transcription.
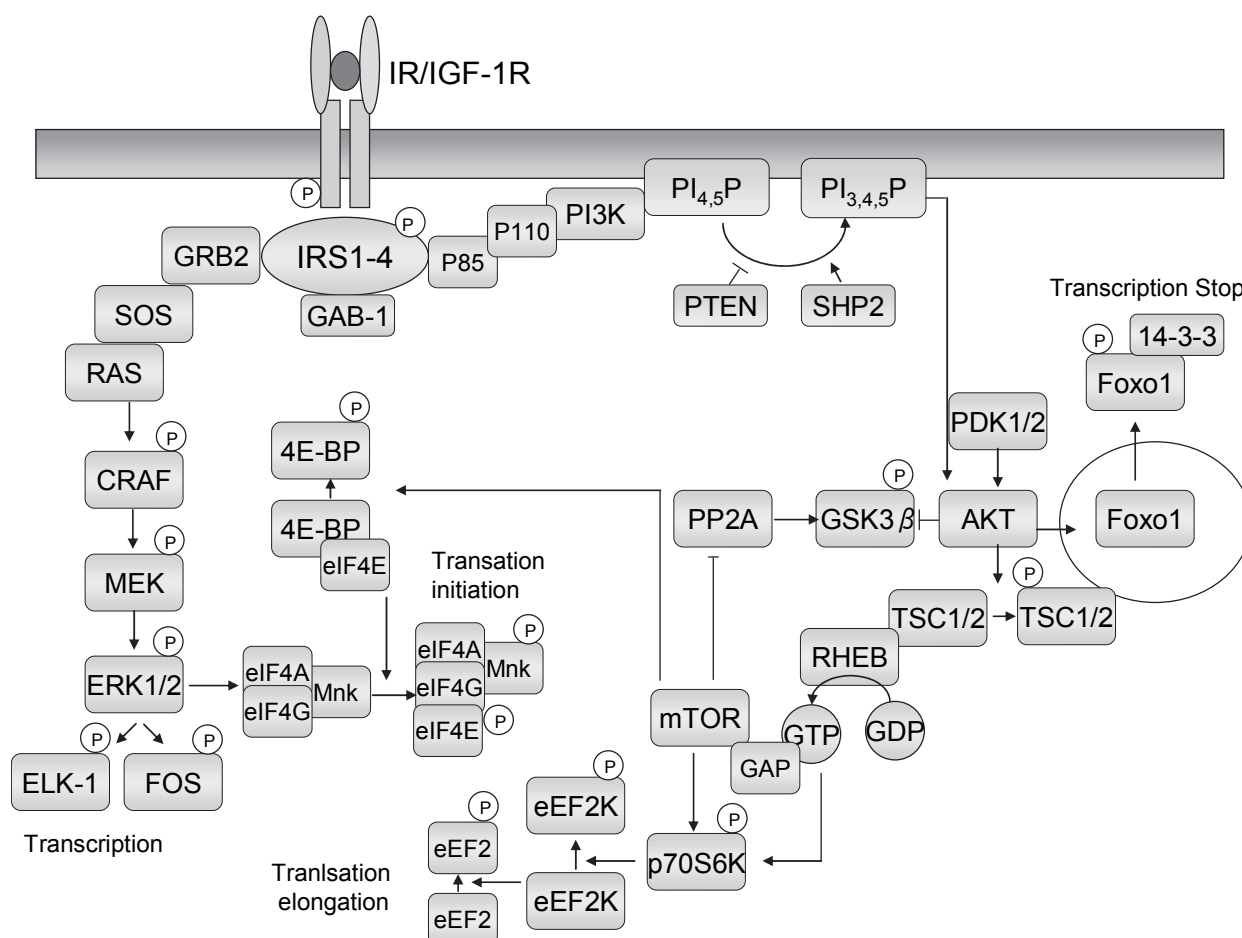

Fig. 2. IR/IGF-R signalling
The binding of Insulin or IGF-1 to the IR/IGF-1R causes autophosphorylation and activation of the receptor. Insulin receptor substrates (1-4) are recruited to the activated receptor and IRS phosphorylation results in activation of the MAP kinase (MAPK, mitogen activated protein kinase) and phosphatidylinositide(PI)3-kinase (PI3K) pathway.

3. IGF-1 signalling in the brain

3.1 IGF-1's transport across the blood brain barrier

In the brain, present IGFs arise either by de novo synthesis or by transport from the blood into the brain. So far, the exact mechanisms of how IGFs cross the blood-brain barrier (BBB) are not fully understood. Early *in vitro* studies by Duffy and colleagues on isolated human brain capillaries showed that the affinity of IGF-2 to isolated human brain capillaries was approximately twofold higher than the affinity of IGF-1 binding and binding of both IGFs was nonsaturable over the range of 1 to 200 ng/ml IGF suggesting that there is a very efficient endocytosis mechanism (Duffy, Pardridge, and Rosenfeld 1988). Insulin displaced binding of IGF-1 (50% inhibited by 2 µg/ml Insulin) and IGF-2 (50% inhibited by 0,5 µg/ml Insulin). Furthermore, binding was largely inhibited by adding human serum, which was assumed to be due to the presence of IGFBPs (Duffy, Pardridge, and Rosenfeld 1988). Subsequent studies suggested that there might be a high capacity transport system across the BBB, which is influenced by the IGFBPs (Pan and Kastin 2000). Tores-Aleman and co-workers found that via the choroid plexus epithelium, circulating IGF-1 is transported into the CSF through a mechanism involving the multicargo protein tranporter low-density lipoprotein receptor related protein 2 (LRP2), and concluded that increasing levels of IGF-1 in the CSF, as a result of increasing IGF-1 levels in the serum, might be explained via this transport mechanism (Carro et al. 2000; Carro et al. 2005). LRP1, another membrane cargo-transporter, was suggested as targeting platform for the circulating IGF-1/IGFBP-3/ALS-complex (Nishijima et al. 2010). LRP1 is abundantly expressed in brain endothelium and seems to be a cellular receptor for IGFBP-3 (Huang et al. 2003). Recently, it has been demonstrated that neuronal activity increases the permeability of the BBB for IGF-1 through neurovascular coupling (Nishijima et al. 2010). Therefore, serum IGF-1 might influence brain processes like synaptic plasticity and cognition. Furthermore, neurovascular coupling was proposed to locally change cerebral blood flow leading to activation of matrix metalloprotease 9 (MMP9) through diverse mediators (arachdonic acid derivates, ATP, etc.). MMP9 is an IGFBP-3 cleaving protease, which is released in response to neuronal activity (Michaluk and Kaczmarek 2007) and might link neuronal activation to the transport of serum IGF-1 via a LRP1 depending mechanism across the BBB (Nishijima et al. 2010). Hence, neurovascular coupling might result in neurotrophic coupling explaining the neuroprotective effects of physical as well as mental exercise and active social life on brain function (Carro et al. 2000; Fratiglioni, Paillard-Borg, and Winblad 2004).

3.2 Brain IGF receptors

IGF-1 and to less extend IGF-2 bind and therefore activate the type 1 IGF-receptor (IGF-1R) (Rubin and Baserga 1995; White and Kahn 1994; LeRoith 2000). Several IGF-1R subtypes have been reported, for example the hybrid IGF-1Rs, which are hybrid dimers of the insulin-receptor (IR) and the IGF-1R (see 2.3) binding insulin as well as IGFs with similar affinity (Soos and Siddle 1989; Soos et al. 1990; Siddle et al. 1994; Moxham, Duronio, and Jacobs 1989; Pandini et al. 2002). The physiological significance of these receptor subtypes is still unclear (Russo et al. 2005).

Additionally, there is a type 2 IGF-receptor (IGF-2R) with a short cytoplasmic domain lacking a tyrosine kinase harbouring a higher affinity for IGF-2 than the IGF-1R (Sakano et al. 1991; Oh et al. 1991; Dore, Kar, and Quirion 1997; Braulke 1999; Kiess et al. 1994). This IGF-2R is a cation-independent mannose-6 phosphate (M6P) receptor binding not only IGF-

2 but M6P-containing ligands. This receptor functions in the mediation of endocytosis and lysosomal enzyme trafficking and regulation of apoptotic/ mitogenic effects (Morgan et al. 1987; von Figura and Hasilik 1986; Ghahary et al. 2000). Recent studies have demonstrated that IGF-2 influences memory enhancement via the IGF-2R suggesting that the IGF-2R might transmit some intracellular signalling (Chen et al. 2011).

3.3 IGF receptor expression in the brain

IGF-1R mRNA is widely expressed in the developing CNS and persists at high levels in the mature brain especially in neuron-rich regions such as the olfactory bulb, the granule cell layer of the dentate gyrus and cerebellar cortex (Rotwein et al. 1988; Bondy et al. 1990; Bondy and Lee 1993; Werther et al. 1990). Glia cells have a lower IGF-1R expression than neurons and therefore regions mainly containing those cells, like white matter zones, show low IGF-1R mRNA levels (Bondy and Lee 1993). Some neurons, which are still in the process of developing, express increasing IGF-1R mRNA levels postnatal until they have reached maturity, for example Purkinje cells (Bondy et al. 1992). In the adult brain, high expression levels of IGF-1R mRNA are also found in the choroid plexus, meninges and vascular sheaths (Bondy et al. 1992; Bohannon et al. 1988; Werther et al. 1989; Matsuo et al. 1989; Marks, Porte, and Baskin 1991).

The IGF-2R is abundantly expressed in the CNS, especially in the pyramidal cell layers of the hippocampus, the granule cell layer of the dentate gyrus, olfactory bulbus, choroid plexus as well as in the microvasculature, retina, pituitary, brainstem and spinal cord (Hawkes and Kar 2004; Couce, Weatherington, and McGinty 1992; Wilczak et al. 2000; Valentino, Ocrant, and Rosenfeld 1990).

In addition to the IGF-1R and the IGF-2R, IR and IGF-1R hybrids are expressed in the brain, through which IGFs and insulin induce intracellular signalling. IRs are mainly expressed in regions that are linked to olfaction, appetite and autonomic functions, such as the olfactory bulb, limbic system and hypothalamus (Werther et al. 1987; Unger, Livingston, and Moss 1991) and seem to play a key-role in controlling feeding, body weight and reproduction (Bruning et al. 2000). Furthermore, IR expression is also present in remarkable concentration in the choroid plexus, circumventricular organs and brain microvessels (van Houten and Posner 1979, 1981; Werther et al. 1987) suggesting the IRs might contribute to the transport of insulin and possibly IGF-1 across the BBB.

4. IGF-1 action in the developing brain

4.1 Brain growth and myelination

Different mouse models indicated the essential actions of IGF-1 signalling for normal brain development. Homozygous IGF-1 knockout mice (IGF-1$^{-/-}$), homozygous IGF-2 knockout mice (IGF-2$^{-/-}$) as well as doubly deficient mutants are viable but have small brains (Beck et al. 1995; Liu et al. 1993). The majority of homozygous IGF-1$^{-/-}$ mice die perinatally and those which survive (< 5 %) demonstrate severe growth retardation with reduction in brain weight of 38 % distributed evenly over all major brain areas (Beck et al. 1995). However, certain cell-types and brain-regions were especially affected by the IGF-1 gene disruption such as white matter, striatum and hippocampus (Beck et al. 1995). The reduction of white matter was due to a net loss of axons and an additional shift from myelinated to unmyelintated fibres indicating the role of IGF-1 in axonal growth and/or maturation and its effect on the amount of oligodendrocytes and axon-myelination (Beck et al. 1995). These findings are in line with many *in vitro* studies, which demonstrated a stimulating effect of

IGF-1 on oligodendrocyte survival, development and proliferation (McMorris et al. 1986; McMorris and Dubois-Dalcq 1988; Mozell and McMorris 1991). In addition, formation of hippocampal granule cells and striatal parvalbumin-containing neurons was reduced in IGF-1$^{-/-}$ mice and therefore seems to require IGF-1 (Beck et al. 1995). Most dentate granule neurons as well as the myelination of axons are generated during postnatal development (Altman and Bayer 1990, 1990; Morell et al. 1972; Matthieu, Widmer, and Herschkowitz 1973) suggesting that IGF-1 plays a more important role during late embryonic and postnatal development. Intrauterine development was analysed in detail in single and combined homozygous knockout mice for IGF-1 and IGF-2 suggesting that before E13.5 the IGF-1R exclusively mediates IGF-2 actions and later, with increasing IGF-1 expression, the IGF-1R interacts with both IGFs (Baker et al. 1993). IGF-2 was found to be upregultaed in IGF-1$^{-/-}$ mice suggesting that IGF-2 may partially compensate for the loss of IGF-1 expression and function (Ye et al. 2002).

Homozygous IGF-1R knockout mice (IGF-1R$^{-/-}$) die at birth and have smaller brains (Liu et al. 1993). A similar growth retardation of the CNS was observed in transgenic mice overexpressing human IGFBP-1 (hIGFBP-1) suggesting reduced IGF-1 action via IGF-1Rs (D'Ercole et al. 1994). Conversely, transgenic mice overexpressing human IGF-1 (hIGF-1) show increased brain growth and myelination (Carson et al. 1993; Ye, Carson, and D'Ercole 1995). In both mouse models, the transgenic hIGFBP-1 and hIGF-1 mouse, the cerebral cortex, hippocampus and diencephalon were the most affected brain regions (Ye, Carson, and D'Ercole 1995). Myelination was increased in hIGF-1 and reduced in hIGFBP-1 transgenic mice as well as the number of oligodendrocytes and the expression of myelin-specific proteins, respectively (Ye, Carson, and D'Ercole 1995). During development, the increase of myelin protein expression in the cerebral cortex of hIGF-1 transgenic mice correlates with the hIGF-1 transgene mRNA levels (Ye, Carson, and D'Ercole 1995). In conclusion, IGF-1 plays a crucial role in regulating neuronal growth and differentiation (Werther et al. 1998), but also enhances oligodendrocyte survival and myelination (Beck et al. 1995).

Several studies suggested that transcriptional programs control the development of axons or dendrites including their growth and branching (Jan and Jan 2003; Goldberg 2004; Polleux, Ince-Dunn, and Ghosh 2007). Recently, the role of FoxO-transcription factors, major downstream-targets of IIS (Insulin/IGF-1 signalling pathway), within the developing brain and their action of conducting IGF-1 signalling started to become clearer. FoxO proteins were found to be key-regulators of neuronal polarity in the mammalian brain and to trigger differentiation from immature neurons to post-mitotic neurons with specified axon- and dendrite-formations (de la Torre-Ubieta et al. 2010). In addition, protein kinase Pak1 was identified as direct target of FoxO-transcription factors linking FoxO-dependent transcription in the nucleus to an enzyme that promotes axonal polarity by controlling actin and microtubule dynamics (Edwards et al. 1999; Wittmann, Bokoch, and Waterman-Storer 2004) as well as dendritic spine morphogenesis and synapse differentiation (Hayashi et al. 2004; Hayashi et al. 2007; Nikolic 2008). Apart from Pak1, FoxO knockdown neurons demonstrated a number of downregulated polarity genes, such as Par6, R-Ras, APC and CRMP2 (de la Torre-Ubieta et al. 2010). Additionally, FoxO3a was shown to regulate homeostasis of neuronal stem cells (NSCs) both *in vitro* and *in vivo* by controlling a set of genes that determines cell cycle re-entry and optimal oxygen and glucose metabolism (Renault et al. 2009). However, the effect of FoxO3a deficiency in NSCs only became apparent in adult animals, as NSCs were shown to influence learning, memory and mood

(Zhang et al. 2008). Therefore, NSC homeostasis regulated by FoxO3a might influence the decline of cognitive function and possibly the onset of neurodegenerative diseases (de la Torre-Ubieta et al. 2010).

4.2 Neuroendocrine regulation

Embryonic brain IGF-1R and therefore the action of the IGF-1 pathway in the developing brain was found to play a crucial role in determining somatotrophic plasticity and hence postnatal GH and IGF-1 signalling. These observations were made in a brain specific IGF-1R knockout mouse model (bIGF-1RKO$^{-/-}$; bIGF-1RKO$^{+/-}$) by the group of Holzenberger (Kappeler et al. 2008). Whereas homozygous mutants (bIGF-1RKO$^{-/-}$) showed severe growth retardation and were infertile, heterozygous mutants (bIGF-1RKO$^{+/-}$) were healthy and had an increased mean lifespan compared to controls (Kappeler et al. 2008). In bIGF-1RKO$^{+/-}$ mutants, serum IGF-1 and GH were lowered and pituitaries, like most other organs, were smaller compared to controls (Kappeler et al. 2008). As IGF-1Rs are only diminished in the brain but not in the anterior pituitary in this mouse model, the observed phenotype was proposed to result from alterations in GH-regulatory neurons of the hypothalamus. Hypothalamic GHRH expression was found to be significantly lower, as well as the Pit-1 mRNA levels. bIGF-1RKO$^{+/-}$ mice had preserved gonado- and thyrotropic functions but were growth retarded with a body length 5 % shorter than controls and a body weight of about 90% of controls at the age of 90 days (Kappeler et al. 2008). Interestingly, weight gain with age was slightly higher in adult bIGF-1RKO$^{+/-}$ mice than in controls, and female mutants finally reached the same body weight than controls (Kappeler et al. 2008). The gain of weight was most probably due to an enlargement of subcutaneous adipose tissue (AT), as there was less or no increase in visceral AT (Kappeler et al. 2008). In line with GH-deficient mouse models (Berryman et al. 2004; Berryman et al. 2006), the bIGF-1RKO$^{+/-}$ mice showed impaired glucose homeostasis and fat metabolism. Heterozygous inactivation of IGF-1R had no detectable effects on behaviour or other brain functions apart from the somatotrophic deficit. Compared to control littermates, bIGF-1RKO$^{+/-}$ mice had a significantly longer mean lifespan. However maximum lifespan was unchanged probably due to increased late-life mortality caused by hyperglycemia and dyslipidemia (Kappeler et al. 2008). Early dietary restriction showed a similar neuroendocrine response as the brain specific IGF-1R knockout (Kappeler et al. 2008), indicating a connection between nutrition, somatotrophic hormones, growth and their determination of lifespan.

Similar observations, in which morbidity in later life was determined during prenatal development, were made in humans. Long-term studies have been conducted on the Dutch famine birth cohort as well as on the Chinese famine cohort. Babies exposed in utero to calory restriction in late or mid gestation were growth retarded and showed impaired glucose tolerance in later life (Ravelli et al. 1998; Painter, Roseboom, and Bleker 2005). However, babies exposed in early gestation were not smaller than controls but demonstrated the most striking consequences of in utero undernutrition, namely a three-fold increase in coronary heart disease, hyper-/dyslipidemia and more frequent obesity (Painter, Roseboom, and Bleker 2005; Ravelli et al. 1999; Roseboom, van der Meulen, Osmond, Barker, Ravelli, Schroeder-Tanka et al. 2000; Roseboom, van der Meulen, Osmond, Barker, Ravelli, and Bleker 2000). Interestingly, mortality rates at older (50+) ages are significantly higher in the exposed group, and residual life expectancy at age of 50 was reduced by approximately 3 years (Lindeboom, Portrait, and van den Berg 2010), which is in line with the increased late-life mortality observed in the bIGF-1R$^{+/-}$ mice. In the cohort of

the Chinese famine, fetal and infant exposure to undernutrition also resulted in increased risk for metabolic syndrome (Li et al. 2010; Li et al. 2011; Yang et al. 2008; Luo et al. 2006).
In summary, IGF-1 signalling during early development is defined by the number of brain IGF-1Rs or their sensitivity and determines endocrine as well as metabolic function in later life possibly playing a key-role in pathogenesis of age-associated diseases.

IGF-1 function in the developing brain	IGF-1 function in the adult brain
• growth and differentiation of neurons • neuronal polarity and synapse formation • growth of oligodendrocytes • enhancement of myelination • neuroendocrine regulation of metabolism	• preservation of neuronal plasticity, for example in the olfactory bulb • brain vessel growth • spatial learning and other cognitive functions • neuroprotecetive in ischemic or traumatic injuries and several neurological disorders • reduced signalling extends lifespan

Table 1. Function of IGF-1 in the brain

5. IGF-1 in Alzheimer's disease

Alzheimer's disease (AD) is a chronic and progressiv neurodegenerative disease and the most common form of dementia leading to the loss of cognitive abilities and finally to death (Citron 2002; Cole et al. 2007).
AD was first described by Alois Alzheimer, a German physician, in 1906 (Alzheimer et al. 1995). The disease is characterised by β-amyloid accumulation, formation of extracellular amyloid plaques as well as neurofibrillary tangles. The β-amyloid plaques mainly contain aggregated amyloid-β (Aβ) peptides (Masters et al. 1985). In contrast, the main components of neurofibrillary tangles are hyperphosphorylated and aggregated tau proteins (Ross et al., 2005). The aggregation of Aβ is thought to be the molecular basis of neurodegenration in AD (Masters et al. 1985).

5.1 Tau

The tau proteins consist of a N-terminal projection domain, a short tail sequence and a C-terminal domain with microtubule-binding (MTB) repeats. Six isoforms of tau are known in the human brain. These isoforms emerge from alternative splicing of exons 2, 3 and 10. Exon 2 and 3 encode N-terminal parts of tau and exon 10 codes for an additional MTB repeat. Thus, tau can present three or four MTB repeats (Ballatore, Lee, and Trojanowski 2007; Goedert and Spillantini 2006). Tau is predominantly located in the axons of neurons (Hirokawa et al. 1996) and is to less extend found in dendrites (Ittner et al. 2010). The function of tau is yet not completely understood, but it might influence the stabilisation of microtubules and regulation of axonal transport (Gotz, Ittner, and Kins 2006). Tau is phosporylated at several sites via kinases like glycogen synthase kinase 3 (GSK-3β), cyclin-dependent kinase 5 (Cdk5), c-Jun N-

terminal kinase (JNK) and ERK1/2 (Robertson et al. 1993; Hanger et al. 1992; Flaherty et al. 2000; Cho and Johnson 2004; Stoothoff and Johnson 2005). Abnormal high phosphorylation is called "hyperphosphorylation". Hyperphosphorylated tau proteins form so called paired helical filaments, which are characteristic for AD. The degradation of tau is inhibited by phosphorylation at the caspase cleavage sites. It has been shown that the mutation of Ser422, which causes a stable phosphorylation at this site, prevents caspase cleavage (Guillozet-Bongaarts et al. 2006). GSK-3β is one of the major tau kinases and is inactivated upon phosphorylation of Akt at Ser9 connecting insulin and IGF-1 signalling to tau phosphorylation. The major tau phosphatase in human brain is PP2A (Sontag et al. 1996), which is as well regulated via the IR/IGF-1R pathway suggesting that IR/IGF-1R signalling maintains an equilibrium of phosphorylation and dephosphorylation of tau (Liu et al. 2008; Millward, Zolnierowicz, and Hemmings 1999).

5.2 Amyloid-β

Aβ is generated by proteolytic cleavage of the amyloid precursor protein (APP), a type-1 integral membrane protein. APP was first described and cloned in 1987 (Kang et al. 1987; Tanzi et al. 1987; Goldgaber et al. 1987; Robakis et al. 1987). The APP gene is located on chromosome 21. Hence, patients with trisomy 21 show a higher risk to develop Alzheimer´s disease, because of the additional APP allele. Accordingly, the duplication of the isolated APP gene causes cerebral amyloid angiopathy and amyloidosis suggesting that increased APP expression itself is sufficient to cause Alzheimer-like pathology (Rovelet-Lecrux et al. 2006; Sleegers et al. 2006). Another risk factor for AD are mutations of the APP gene (Vassar 2004; Bertram and Tanzi 2005). APP contains a N-terminal extracellular domain and a shorter C-terminal cytoplasmic domain. Alternative splicing of the APP gene results in different isoforms of APP which are distinguishable by length. APP with 751 and 770 (APP751 and APP770) amino acids mainly occur in non-neuronal tissue. APP695 is mainly localised in neurons (Kang and Muller-Hill 1990). The function of APP and the APP-like proteins (APLP) is not clear yet. These proteins are possibly involved in cell adhesion, apoptosis and axonal transport.

The β-secretase BACE1 (β-site APP-cleaving enzyme) plays an essential role in the production of Aβ. It cleaves APP at Asp^{+1} at the N-terminus. The resulting fragments are called APPsβ and the C-terminal fragment C99. Upon cleavage of C99 by the γ-secretase, a complex formed by presenilin, nicastrin, Aph-1 and Pen-2, Aβ peptides (4 kDa) and the APP intracellular domain (AICD) with a size of 6 kDa are generated. Aβ-peptides mainly occur in two variants: Aβ40 which ends at residue 40 and Aβ42 ending at residue 42 after cleavage. Predominantly, the Aβ42 is prone to aggregate and forms toxic oligomers. Furthermore, APP is cleaved by the α-secretases ADAM10 (a disintegrin and metalloproteinase-like 10) or TACE (tumour necrosis factor-alpha convertase). This results in the C-terminal fragment C83 and APPsα. The cleavage of APP by α- or β-secretase is dependent on the competition between both enzymes. In case the β-secretase cleavage of APP increases, α-secretase processing decreases and vice versa (Vassar et al. 1999; Skovronsky et al. 2000) (Figure 3).

In a healthy brain, there is more production of Aβ40 (~90 %) than there is of Aβ42 (~5-10 %) (Walsh and Selkoe 2007). The accumulation of Aβ42 is an important step in the formation of amyloid plaques (Iwatsubo et al. 1994). The Aβ42:Aβ40 ratio is a diagnostic tool for APP processing and development of AD (Haass and Selkoe 2007).

In addition to age-associated Aβ42 accumulation, mutations in presenilin 1, presenilin 2 and the APP gene lead to familiar early-onset AD (Tabaton and Tamagno 2007; Sherrington et al.

1996; Tanzi et al. 1992; Schellenberg et al. 1992; Van Broeckhoven et al. 1992; St George-Hyslop et al. 1992; Rogaev et al. 1995).

The toxic effect of Aβ is not fully understood yet, but might be induced via generation of ion channels, membrane disruption, oxidative stress, induction of apoptosis and inflammation (Hardy and Selkoe 2002; Nakagawa et al. 2000; Soto 2003; Roberson and Mucke 2006). The Aβ aggregation process produces different intermediates. Aβ monomers are soluble and amphipathic with an α-helical conformation and kink regions in water-alcohol mixture (Coles et al. 1998; Crescenzi et al. 2002). Aβ40 displays a random coil structure in aqueous solution (Zhang et al. 2000) and Aβ42 shows β-sheet structure at physiological conditions (Barrow and Zagorski 1991). Aβ dimers are located intracellular *in vivo* and show a hydrophobic core (Roher et al. 1996). Small Aβ oligomers are highly cytotoxic compared to mature Aβ fibrils (Dahlgren et al. 2002; McLean et al. 1999; Cleary et al. 2005; Lesne et al. 2006). The so called Aβ-derived diffusible ligands (ADDLs) show no fibrillar structure and are neurotoxic in a size of about 17 to 42 kDa (Chromy et al. 2003; Klein, Stine, and Teplow 2004; Lambert et al. 1998). The levels of ADDLs are linked to cognitive impairments in AD (Georganopoulou et al. 2005). Aβ protofibrils are the precursors of Aβ fibrils. These protofibrils are present as rod-like and flexible structures. The dyes Congo red and thioflavin T bind to the core of the protofibrils, which indicates a high level of β-sheets (Harper et al. 1999; Arimon et al. 2005; Harper et al. 1997; Kheterpal et al. 2003; Walsh et al. 1997; Williams et al. 2005). Aβ fibrils are insoluble, thermodynamically stable aggregates containing repeats of β-sheets (Ross and Poirier 2005). They also bind Congo red and thioflavin T (Klunk, Jacob, and Mason 1999; LeVine 1999). The amyloid plaques are extracellular aggregates of insoluble Aβ fibrils (Muller-Hill and Beyreuther 1989). These plaques are surrounded by activated microglia, astrocytes and dystrophic dendrites (Selkoe 2004).

Different clinical studies revealed an association of AD and type 2 diabetes (Janson et al. 2004; Ott et al. 1999; Stewart and Liolitsa 1999). A connection of glucose intolerance, impairment of insulin secretion and the risk to develop AD was recently discovered (Ott et al. 1996; Luchsinger et al. 2004; Ronnemaa et al. 2008). Furthermore, AD patients develop more frequently impaired glucose tolerance and type 2 diabetes (Janson et al. 2004) indicating that IR/IGF-1R signalling might influence AD pathogenesis.
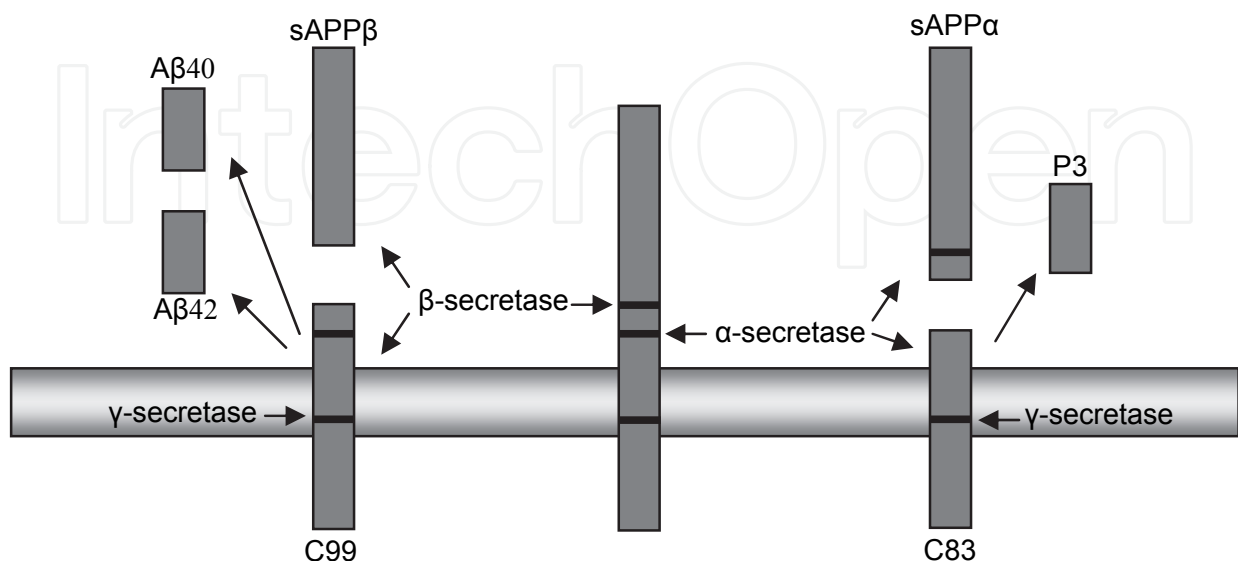

Fig. 3. Processing of amyloid precursor protein (APP).

APP might be cleaved via the α-, β- or γ-secretase. α-secretase cleavage generates a membrane bound C83 fragment and sAPPα. In case C83 is proteolytically cleaved by the γ-secretase the P3 fragment occurs. β-secreatse processing produces the fragments sAPPβ and C99. In case of a simultaneous or subsequent cleavage via β- and γ- secretase the Aβ40 or Aβ42 peptides are released.

5.3 IR, IGF-1R signalling and Alzheimer's disease

The IR and IGF-1R signalling pathway is disturbed in the central nervous system (CNS) of AD patients (Frolich et al. 1998; Frolich et al. 1999; Moloney et al. 2010). Analysis of the mRNA level of insulin and the IR showed a decrease of about 80% in AD patients. Additionally, the expression of the IGF-1R was reduced in AD brains compared to controls (Moloney et al. 2010; Rivera et al. 2005). In contrast, the IGF-1 serum levels of AD patients are increased indicating IGF-1 resistance in AD (Rivera et al. 2005; Vardy et al. 2007). Furthermore, IRS-1 and -2 expression is reduced in AD brains and phosphorylation of IRS-1 at Ser312 and Ser616 is increased, which decreases IRS-1 action characterising AD as "brain type" diabetes (Pilcher 2006). Thus, brains of AD patients are insulin and IGF-1 resistant. Whether these changes are cause or consequence of neurodegeneration is a matter of debate. IGF-1 knockout mice display increase of tau phosphorylation at Ser396 and Ser202 while the tau protein level was not influenced (Cheng et al. 2005). In NIRKO mice, the brain-specific IR knockout mice, tau was hyperphosphorylated at Thr231 (Schubert et al. 2004), whereas IRS-2 knockout mice showed hyperphosphorylation at Ser202 (Schubert et al. 2003). The different phosphorylation patterns of tau in different insulin and IGF-1 resistant mouse models indicate that additional factors may play a role for tau phosphorylation in these models (Freude et al. 2009).

Tg2576 mice express the Swedish mutation of APP (APPsw) and are an established mouse model for analysing amyloid pathology (Vassar et al. 1999; De Strooper 2003; Harada et al. 2006). IRS-2 (IRS-2$^{-/-}$) or neuron specific IGF-1R knockout (nIGF-1R$^{-/-}$) in Tg2576 mice protects these mice from premature death and decreases Aβ-accumulation (Freude et al. 2009).

BACE-1 and Presenilin-1/-2, which cleave APP and generate neurotoxic Aβ42, are possible targets for AD treatment since β-secretase cleavage is the rate limiting step of Aβ generation. During ageing, the expression of the neurotrophin receptor tyrosine kinase receptor A (TrkA) and the p75 neurotrophin receptor (p75^{NTR}) changes considerably. Whereas TrkA receptor expression decreases, the p75 neurotrophin receptor increases with age. Human neuroblastoma cells SHSY5Y and primary cultured neurons showed a switch from TrkA to p75^{NTR} expression after treatment with IGF-1 (Costantini, Scrable, and Puglielli 2006). This increases BACE-1 activity via hydrolysis of sphingomyelin and release of ceramide stabilising BACE-1 (Puglielli 2008; Puglielli et al. 2003). It has been shown that embryonic hippocampal neurons treated with Aβ42 as ligand of p75^{NTR} cause cell death. Neurons, which are deficient in p75^{NTR} and also treated with Aβ42, show less cell death. This may represent the molecular mechanism linking IR and IGF-1R signalling pathway to ageing and neurodegeneration (Sotthibundhu et al. 2008).

In *Caenorhabditis elegans* the knockdown of DAF-2, the orthologue of mammalian IR and IGF-1R, reduces Aβ42 toxicity (Cohen et al. 2006). This reduced Aβ42 toxicity results from the activity of the downstream transcription factors DAF-16, the orthologue of mammalian FoxO1 and 3a as well as heat shock transcription factor-1 (HSF-1) (Hsu, Murphy, and Kenyon 2003; Birkenkamp and Coffer 2003; Cohen et al. 2006). The

detoxification of Aβ42 by decreased DAF-2 signalling involves two possible mechanisms. First, HSF-1 regulates disaggregation of toxic oligomers followed by degradation of the resulting fragments. Second, DAF-16 regulates the formation of aggregates with high molecular weight and low toxicity, which are built from aggregates with low molecular weight but high toxicity (Aβ hyperaggregation) (Cohen et al. 2006). Recently, Aβ hyperaggregation has been identified as a mechanism of Aβ detoxification in an IGF-1 resistant mouse model of AD (Cohen et al. 2009).

Several ways of Aβ clearance from the brain have been discovered contributing to Aβ detoxification. Aβ clearance is achieved via transport over the blood brain barrier, enzymatic degradation and phagocytosis by microglia. Recently, several enzymes have been discovered which degrade Aβ, e.g. insulin degrading enzyme (IDE), endothelin converting enzyme (ECE), neprilysin, and angiotensin converting enzyme (ACE). The expression of IDE is activated by IR and IGF-1R signalling (Zhao et al. 2004). Transport across the blood brain barrier (BBB) is mediated by distinct receptors. This transport is achieved via binding to the low-density lipoprotein receptor related protein (LRP). The binding of Aβ to LRP occurs directly or in complex with APOE (apolipoprotein E) and/or α2-macroglobulin (α2M). After crossing the BBB, Aβ is transported to peripheral tissues for degradation, for example the liver (Tanzi, Moir, and Wagner 2004). It has been proposed that high IGF-1 levels cause degradation or clearance of Aβ. Tg2576 mice present decreased IGF-1 levels compared to wild type mice. The treatment with IGF-1 yield to increased transport of Aβ from the brain, possibly via the choroid plexus (Carro et al. 2002). Accordingly, the inactivation of the IGF-1R signalling in the choroid plexus caused AD-like pathology (Carro et al. 2006). In contrast, studies in rats and Tg2576 mice using acute, subchronic and chronic IGF-1 treatment found no changes in tau phosphorylation and Aβ concentrations (Lanz et al. 2008). Possibly, chronic peripheral treatment with IGF-1 causes downregulation of the IGF-1R signalling pathway as it has been shown for a cohort of individuals with high serum IGF-1 level but low IGF-1R signalling (Suh et al. 2008). This might explain the conflicting results of the different studies. AD mouse models with induced insulin resistance via high fat diet displayed an exacerbation of amyloid pathology (Ho et al. 2004).

The different studies dealing with IR/IGF-1R signalling and AD prove a connection between this signalling pathways and AD pathology. However, the exact molecular mechanisms need to be elucidated.

6. IGF-1 in the brain and ageing

IR/IGF-1R signalling is a conserved pathway functioning in development, fertility (Liang et al. 2003; Tatar, Bartke, and Antebi 2003; Broughton et al. 2005), growth (Butler and Le Roith 2001; Ikeya et al. 2002) and metabolic regulation (Saltiel and Kahn 2001). Decreased IR/IGF-1R signalling causes lifespan extension in model organisms like *Drosophila melanogaster*, *Caenorhabditis elegans* and *Mus musculus* (Clancy et al. 2001; Holzenberger et al. 2003; Tatar et al. 2001).

The life expancancy of humans has been increased upon environmental amelioration (Wilmoth 2000). However, this is accompanied by an increase of age associated disorders. Therefore, the study of the molecular mechanism of ageing might lead to identification of disease modifying pathways. One of these pathways is the IR/IGF-1R signalling cascade. Studies investigating temporal or spatial restricted changes of the IR/IGF-1R signalling pathway in different model organisms, using the RU486-induced GAL4/UAS (upstream

activation sequence) in *Drosophila*, as well as RNAi (RNA interference) incorparation via feeding of bacteria to *C. elegans* and Cre/loxP system in mice (Roman et al. 2001; Sauer 1998), have been performed.

The CNS is responsible for endocrine release of insulin-like peptides which activate the IR/IGF-1R signalling cascade and subsequently shorten lifespan (Ikeya et al. 2002; Broughton et al. 2005). Confusingly, acute increase of IR/IGF1-R signalling is neuroprotective but reduction of the signalling causes lifespan extension (Bateman and McNeill 2006; Chrysis et al. 2001).

6.1 IGF-1 signalling in *C. elegans*

The impact of IR/IGF-1R-like signalling (IIS) pathway on lifespan was first discovered in *C. elegans*. IIS in *C. elegans* is similar to the pathway in mammals (Taguchi and White 2008). It is activated through binding of insulin-like peptides (INS) to DAF-2 (abnormal Dauer formation-2), the IR/IGF-1R in worms (Kenyon et al. 1993). Upon stimulation of DAF-2 an insulin receptor substrate 1 orthologue (IST-1) is recruited to DAF-2 and AGE-1 (AGEing alteration-1), orthologue to human p110. P110, the catalytic subunit of PI3K, promotes the generation of phosphatidylinositide-triphosphate ($PI_{3,4,5}P$) which then activates AKT kinase family members (Morris, Tissenbaum, and Ruvkun 1996; Kops et al. 1999; Paradis and Ruvkun 1998).

The mutations of DAF-2 and AGE-1 cause lifespan extension in a DAF-16 dependent manner which is a forkhead transcription factor in worms (Kenyon et al. 1993; Lin et al. 1997; Ogg et al. 1997; Morris, Tissenbaum, and Ruvkun 1996) and homologue to the mammalian FoxO1 and FoxO3a.

AGE-1 and DAF-2 mutant worms show enhanced thermotaxis learning behaviour during ageing. This might be due to resistance to neuronal diseases and oxidative stress (Murakami 2007).

The insulin-like peptides (INS) are found throughout the whole body of *C. elegans* (Pierce et al. 2001; Li, Kennedy, and Ruvkun 2003). Specific sensory neurons regulate lifespan through DAF-16 (Alcedo and Kenyon 2004). The ablation of olfactory neurons causes lifespan extension being only partially dependent on DAF-16 indicating an involvement of other factors. The regulation of INS is not well analysed, but the sensory neurons seem to be the major source of INS for peripheral tissues (Alcedo and Kenyon 2004).

A study using tissue-specific expression of AGE-1 and DAF-16 revealed that wild-type AGE-1 recovers the extended lifespan of AGE-1 mutants. This was shown for wild-type AGE-1 expressed in neurons and the intestine. In addition, wild-type DAF-16 rescues reduced lifespan of DAF-16/AGE-1 double mutants when expressed in neurons or intestine. Moreover, wild-type DAF-16 exerts its full effect when expressed in neurons and the intestine exclusively. However, DAF-16 expression showed only minor effects when expressed in other tissues (Broughton and Partridge 2009; Iser, Gami, and Wolkow 2007).

6.2 IGF-1 signalling in *Drosophila melanogaster*

D. melanogaster posseses endocrine tissues, which are similar to mammals (Toivonen and Partridge 2009). The median neurosecretory cells (mNSCs) of *Drosophila* are localised in the pars intercerebralis. mNSCs generate three of the seven *Drosophila* insulin-like peptides (DILPs). These mNSCs are functionally similar to β-cells of the pancreas which produce

insulin. These neurosecretory cells show an analogue development to the mammalian anterior pituitary (Wang et al. 2007). The ablation of mNSCs causes lifespan extension, because of the depletion of DILP-2, -3 and -5 (Broughton et al. 2005). In a further study using a dominant-negative form of p53 expressed in the CNS of flies, lifespan extension was induced (Bauer et al. 2005; Slee, O'Connor, and Lu 2004). This correlates with decreased DILP-2 expression and reduced PI3K activity in the periphery (Bauer et al. 2007).

In addition to ablation of mNSCs, mutation of the insulin-like receptor (InR) or of its substrate Chico extends lifespan (Clancy et al. 2001; Tu, Epstein, and Tatar 2002; Tatar et al. 2001). The activation of the InR causes phosphorylation of dFOXO, which is equivalent to nematode DAF-16 and mammalian FoxO1 and FoxO3a (Puig et al. 2003; Junger et al. 2003). dFOXO activation in the pericerebral fat body has been shown to regulate ageing. This activation of dFOXO reduces the expression of DLP-2 in mNSCs followed by downregulation of the InR signalling pathway in peripheral fat tissue (Hwangbo et al. 2004) The JNK signalling pathway in neurons enhances stress resistance and lifespan extension partially via dFOXO (Essers et al. 2004; Wang, Bohmann, and Jasper 2005). Oxidative stress induces JNK signalling and subsequently promotes the nuclear localisation of dFOXO and induces expression of antioxidant proteins (Huang and Tindall 2007; Kops et al. 2002). Neurons are prone to oxidative stress based on the high production of ROS and low amount of antioxidant proteins (Lin and Beal 2006). Peroxiredoxin abolishes hydroperoxide using thioredoxin as hydrogen donor, which decreases ROS (reactive oxygen species) (Lim et al. 1993). Mammalians express six peroxiredoxins (I-VI). Peroxiredoxin II is solely expressed in the brain (Jin et al. 2005). Jafrac1, the homologue of the human Peroxiredoxin II (hPrxII), is a downstream protein of JNK signalling and target gene of dFOXO in neurons. Jafrac1 reduces reactive oxygen species (ROS) and extends lifespan (Lee et al. 2009) linking decreased IIS to increased clearance of ROS as possible mechanism for lifespan extension.

6.3 IGF-1 signalling regulates mammalian lifespan

In mice, it is well known that adult body size is an indicator of GH/IGF-1 actions and negatively correlated to longevity (Rollo 2002; Miller et al. 2002). Furthermore, IGF-1 plasma levels are negatively correlated with median lifespan (Yuan et al. 2009). Up to date, several mouse models of healthy ageing and longevity have been identified and analysed. Most of those long-lived mice have alterations within the IIS, GH or mTOR signalling pathway, indicating their key-role in influencing the process of ageing itself (Broughton and Partridge 2009; Kenyon 2010; Kenyon 2005; Piper et al. 2008; Bluher, Kahn, and Kahn 2003; Kappeler et al. 2008; Selman et al. 2008).

Highest impact on lifespan extension seems to have the ablation of GH signalling, as mutants with impaired GH action demonstrate higher increase of median and maximal lifespan than those with mutations that directly impact IGF-1 signalling (Coschigano et al. 2000; Coschigano et al. 2003; Brown-Borg et al. 1996; Flurkey et al. 2001). Examples for altered GH signalling are the Ames dwarf mice (Prop1[def/def]), Snell dwarf mice (Pit-1[def/def]) and Laron dwarf mice (GHR^{-/-}). As the transcription factors Prop1 and Pit-1 are also essential for induction of thyroidea stimulating hormone (TSH) and prolactin, Ames dwarf mice and Snell dwarf mice are not only GH deficient but in addition produce less thyroidea stimulating hormone (TSH) and prolactin. Therefore, it can not be excluded that some of the effects seen in Ames and Snell dwarf mice might arise through deletion of TSH and prolactin. Laron dwarf mice (GHRKO ,GHR^{-/-}) are only resistant to GH signalling, and their longevity phenotype has been reproducible in different laboratories on different genetic

backgrounds and diets (Coschigano et al. 2003; Bartke and Brown-Borg 2004; Bonkowski et al. 2006).

As described above, GH action is mainly, but not completely, mediated by IGF-1 and circulating levels of IGF-1 are drastically reduced in GH-deficient Ames and Snell dwarf mice as well as in GH-resistant Laron dwarf mice (Brown-Borg et al. 1996; Coschigano et al. 2000; Flurkey et al. 2001). This reduction is primarily due to decreased expression of IGF-1 in the liver, whereas locally derived IGF-1 is, if at all, less affected (Bartke 2011). Normal expression of IGF-1 in the brain, especially in the hippocampus, might explain the maintenance of cognitive function in the long-lived mutants of the GH/IGF-1 system (Kinney et al. 2001). Besides reduced circulating IGF-1, lower insulin levels and enhanced insulin sensitivity are among the most prominent endocrine features shared by Ames dwarf, Snell dwarf and GHRKO mice (Bartke 2006) and have been found to be beneficial for ageing and survival (Bartke 2011). Additionally, increased adiponectin levels, which are associated with improved insulin sensitivity, anti-inflammatory and anti-atherogenic effects, were observed in all three mouse lines (Berryman et al. 2004; Wang et al. 2006). GH-deficient and -resistant mice were also found to have other phenotypic characteristics through which lifespan is thought to be increased, such as resistance to oxidative and other cytotoxic stresses (Bartke et al. 2001; Murakami, Salmon, and Miller 2003), increased activity of antioxidant enzymes (Hauck et al. 2002; Bartke et al. 2001; Romanick, Rakoczy, and Brown-Borg 2004), reduced body temperature (Hunter et al. 1999; Hauck et al. 2001) and reduced susceptibility to cancer (Yang et al. 1996; Deitel et al. 2002; Ikeno et al. 2003).

Another model for extended healthy lifespan in mammals is the fat-specific insulin receptor knockout (FIRKO) mouse (Bluher, Kahn, and Kahn 2003). These mutant mice maintain low body fat despite normal food intake, have normal lipid metabolism and demonstrate improved glucose tolerance and insulin sensitivity throughout life (Bluher, Kahn, and Kahn 2003). The underlying mechanisms of this model are not well understood and apart from impaired IR signalling, altered inflammatory state and mitochondrial activity in these animals are discussed.

A remarkable increase of mean and maximal lifespan has been found in female and male mice lacking PAPP-A. PAPP-A is a metalloproteinase that cleaves inhibitory IGFBPs (as described above), thereby increasing local bioavailability of IGF-1 without altering IGF-1 expression (Lawrence et al. 1999). Conversely, deletion of PAPP-A in PAPP-A$^{-/-}$ mice results in reduced local IGF-1 levels, and thus PAPP-A$^{-/-}$ mice are born as dwarfs (Conover et al. 2004). In these mutants, extension of lifespan was not associated with impaired glucose or fat metabolism and serum IGF-1, insulin and GH levels were unaltered (Conover and Bale 2007). However, these mice have markedly reduced incidence of spontaneous tumors (Conover and Bale 2007) and were found to be resistant to develop experimentally induced neointimal hyperplasia and atherosclerosis (Harrington, Simari, and Conover 2007; Resch, Simari, and Conover 2006).

As described above, homozygous deletion of the IGF-1R or IGF-1 is lethal or produces severe developmental defects, however extended lifespan was reported in mice with heterozygous deletion of the IGF-1R (IGF-1R$^{+/-}$) (Holzenberger et al. 2003). IGF-1R$^{+/-}$ mice have upregulated serum IGF-1 levels, which might indicate an endocrine compensatory response to the reduced numbers of IGF-1R, and these mice do not develop dwarfism (Holzenberger et al. 2003). Those mutants have no alterations in energy metabolism, physical activity, fertility and reproduction but display greater resistance to oxidative stress (Holzenberger et al. 2003) probably causing the observed lifespan extension, which is

predominantly seen in females. As described earlier, the selective reduction of IGF-1 signalling in the brain of bIGF1R$^{+/-}$ mice leads to an increase in median but not maximal lifespan (Kappeler et al. 2008).

The knockout models for IRS-proteins provide evidence that interference with IGF-1/insulin signalling downstream of the IGF-1 and insulin receptor influences lifespan in mice. Female IRS-1 knockout (IRS-1$^{-/-}$) mice were reported to be long-lived and resistant to a number of conditions related to neurological and neuromuscular, immune, skin and bone disease (Selman et al. 2008). In these animals, body weight including fat mass was reduced, but endocrine function of the pituitary as well as circulating IGF-1 levels were preserved (Selman et al. 2008). Additionally, female IRS-1$^{-/-}$ mice were hyperinsulinemic and IGF-1/insulin resistant and rectal temperature was significantly elevated (Selman et al. 2008). All these characteristics are in contrast to the long-lived GH-deficient and GH-resistant mice, however female IRS-1$^{-/-}$ mutants have similar alterations in expression of genes involved in oxidative stress defence and DNA repair (Selman et al. 2008). In the same study, no significant increase of lifespan was found for male IRS-1$^{-/-}$ mice, as well as for IRS-1$^{+/-}$ and IRS-2$^{+/-}$ mice of both sexes, and IRS-2$^{-/-}$ mice were even short-lived (Selman et al. 2008).

IRS-2$^{+/-}$ mice were found to be long-lived, slightly larger and more insulin sensitive and glucose tolerant than wild-type mice (Taguchi, Wartschow, and White 2007). However, the animals studied by Selman et al. (2008) were fed a 'standard' rodent diet with a fat content of 5 %, while those studied by Taguchi et al. (2007) were on a 'high energy' diet with a fat content of 9 %, hence indicating that the IRS-2$^{+/-}$ mice might be protected from the harming effects of a high-fat diet (Bartke 2008). In addition, Taguchi et al. (2007) reported that brain specific alterations of IRS-2 in bIRS-2$^{+/-}$ and bIRS-2$^{-/-}$ mice result in increased lifespan despite glucose and insulin resistance (Taguchi, Wartschow, and White 2007). Further work will be needed to clarify and reconcile the observations made in those two laboratories (Bartke 2008).

Regardless the criticism on the reproducibility of the observations made by Holzenberger (Kappeler et al. 2008) and Taguchi (2007), they provide evidence that selective disruption of the IIS pathway in neurons might not only extend lifespan in *C.elegans* and *Drosophila* (Wolkow et al. 2000; Kenyon 2005) but also in mammals. These findings may indirectly be verified by other studies that demonstrate a protection from AD pathology in a transgenic AD mouse model via deletion of IGF-1R or IRS-2 (Cohen et al. 2009; Freude et al. 2009; Killick et al. 2009).

6.4 IGF-1 signalling and its relevance to human longevity

The IIS pathway is highly conserved throughout evolution from nematodes and flies to mammals. In the last years, an increasing body of data suggests that this pathway is important for human longevity as well.

GH secretion and IGF-1 levels decrease with age (Rudman et al. 1981), which contributes to ageing-associated changes in body composition such as increased adipose tissue and reduced lean body mass leading to impaired insulin sensitivity and cardiovascular disease. The same observations are made in patients with GH deficiency (Khan et al. 2001) and mutation in the GHR gene: Low serum IGF-1 levels, short stature, obesity, glucose intolerance and possible mental retardation but no decrease in life expectancy (Rincon, Rudin, and Barzilai 2005). Conversely, pathologic GH excess in acromegaly leads to reduced life expectancy due to cardiovascular disease, diabetes and malignancies (Orme et al. 1998). Additionally, body height has been identified as a cancer risk in a number of large

population studies (Bartke 2011) and serum IGF-1 levels correlate with cancer mortality in elderly men (Major et al. 2010). Therefore, the decline of GH secretion in the process of ageing might not simply reflect a progressive failure of the hypothalamus-somatotrope axis, but might be protective for the development of insulin resistance and cancer (Bartke 2003; Shechter et al. 2007). GH/IGF-1 therapy in elderly and GH deficient patients improves the ratio of lean and fat body mass, the lipid profile, protein synthesis, bone density, immune functions and memory (Khan et al. 2001), but certainly bears adverse side-effects, as GH is known to be diabetogenic and IGF-1 might increase the risk of cancer (Juul 1999; Khan et al. 2001; Pollak, Schernhammer, and Hankinson 2004; Major et al. 2010).
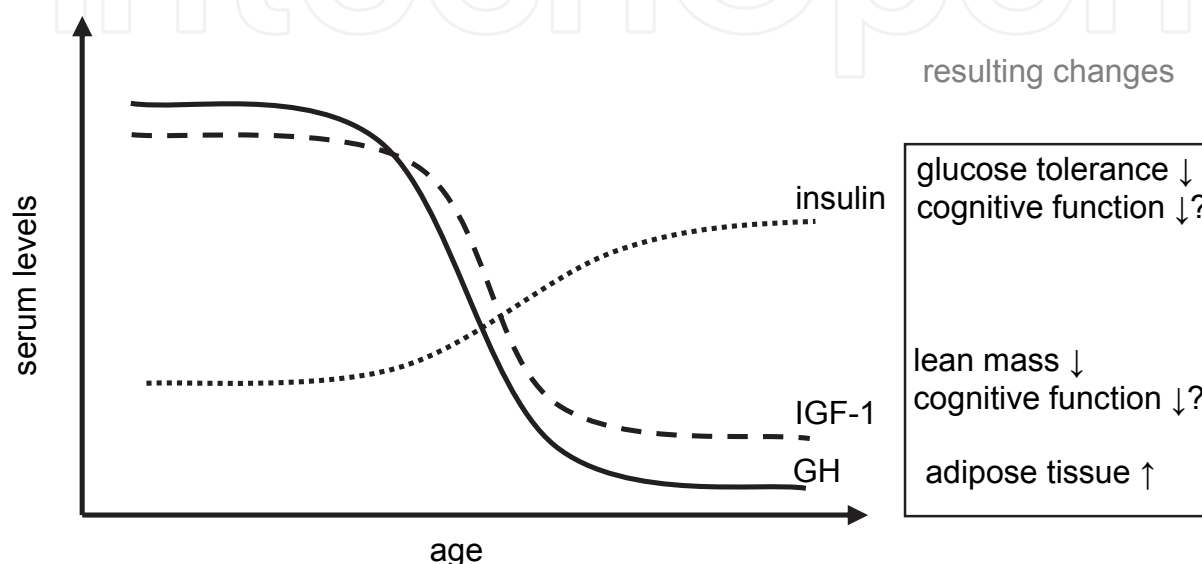

Fig. 4. GH/IGF-1 in ageing
Serum levels of growth hormone (GH) and insulin-like growth factor-1 (IGF-1) decrease during ageing contributing to increased fat mass and decreased lean mass and might influence cognitive function negatively. Serum insulin levels increase with age indicating age-associated insulin insensitivity possibly leading to impaired glucose tolerance and diabetes.

Recently, a study on a cohort of Ecuadorian patients carrying mutations in the GHR gene was published after 22 years of monitoring. Patients demonstrated severe GH resistance and reduced circulating IGF-1 and IGF-2 levels resulting in short stature (Guevara-Aguirre et al. 2011). No extension in lifespan was found in this cohort, which is in contrast to the GHR deficient mouse model (Guevara-Aguirre et al. 2011). However, causes of death were different in unaffected relatives compared to GHR deficient subjects, which died much more frequently from accidents, alcohol-related diseases and convulsive disorders, which might be the reason for unchanged lifespan (Guevara-Aguirre et al. 2011). Cancer accounted for 17 % and diabetes for 5 % of all diseases in non-affected relatives, whereas only one nonlethal malignancy and no cases of diabetes, probably due to improved insulin sensitivity, were reported for the individuals with GHR mutations (Guevara-Aguirre et al. 2011). Importantly, GHR deficient subjects appear to have no increased mortality from vascular diseases compared to their relatives (30 % of deaths verses 33 % of deaths in the non-affected relatives), however the proportion of strokes (3 % verses 12 %) and cardiac disease (27 % verses 21 %) was slightly different (Guevara-Aguirre et al. 2011).

In a cohort of Ashkenazi Jewish centenarians, a gender-specific increase in serum IGF-1 associated with smaller stature in female offspring was found to be due to heterozygous mutations in the IGF-1R gene (Suh et al. 2008). These rare mutations were significantly more common in female centenarians and overrepresented compared to controls (Suh et al. 2008). These observations are in line with the IGF-1R$^{+/-}$ mouse model, in which female mice show growth retardation and extended lifespan (Holzenberger et al. 2003) but IGF-1 resistance.

Further studies on human centenarians, mainly screening selectively genes of the IIS pathway, identified certain genes in the insulin/IGF-1 pathway to be important for human longevity. Several cohorts with different genetic background have reported an association of FOXO3A single nucleotide polymorphisms (SNPs) with longevity (Willcox et al. 2008; Flachsbart et al. 2009; Anselmi et al. 2009; Pawlikowska et al. 2009; Li et al. 2009). Interestingly, the study on long-lived Han Chinese revealed a SNP of FOXO1 associated with female longevity exclusively (Li et al. 2009).

Furthermore, in the Leiden 85-plus Study an association of a certain FOXO1 haplotype with higher HbA1c levels, higher prevalence of diabetes, myocardial infarction as well as increased mortality was observed (Kuningas et al. 2007). In addition, a certain haplotype of the FOXO3A gene revealed increased risks for stroke and mortality (Kuningas et al. 2007). These findings indicate that alterations within the FOXO genes might be causative involved in age-associated diseases and regulation of lifespan (Flachsbart et al. 2009).

7. Conclusion

Recent studies in different model organisms, including *C. elegans*, *Drosophila melanogaster* and *Mus musculus* have generated piling knowledge about the IIS pathway and its relevance for healthy ageing and longevity. The data obtained in these model organisms have been translated to humans and lead to the identification of the IIS pathway as regulator for human lifespan and ageing.

The GH and IGF-1 signalling pathway plays a key-role in regulating growth and metabolism, and alterations within this pathway have crucial effects on health and lifespan. Model-organisms with reduced GH or IGF-1 signalling are frequently long-lived or show an increased mean lifespan. Interestingly, serum GH and IGF-1 levels decrease with age, and this might be interpreted not solely as progressive failure of the hypothalamus-somatotrope axis but rather as protection for insulin resistance and malignancies.

IGF-1R signalling is required for normal brain development, and acute IGF-1 action might enhance cognitive functions and ameliorates ischemic or traumatic brain injuries. Additionally, recent studies demonstrate that IGF-1R signalling or the number of IGF-1Rs in the brain during early development determines metabolism and possibly age-associated diseases indicating a role of IGF-1 mediated signals as neuroendocrine regulator of health and lifespan.

Foxo-transcription factors have been identified as main downstream-target of IIS and seem to be essential for activating gene transcripton that mediates longevity. Furthermore, genomic screening of centenarians with different genetic background found matching SNPs or haplotypes in the FOXO3A gene suggesting a key-role of FOXO3A in influencing lifespan not only in model organisms but also in humans.

However, the role of IIS in AD still raises questions, as the impaired signalling might be cause or consequence of neurodegeneration.

Therapeutic approaches altering the IIS pathway might not only improve treatment of neurodegenerative disorders but provide a possibility to prevent ageing-associated diseases in the future.

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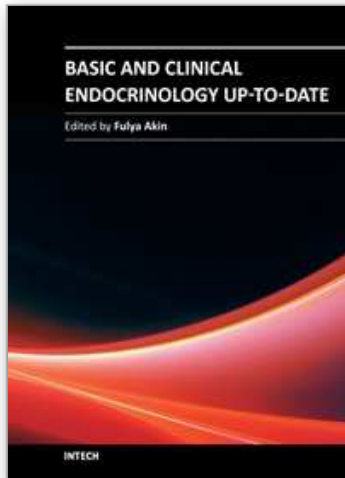
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