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Aging of the brain, neurotrophin signaling, and Alzheimer's disease: is IGF1-R the common culprit?

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Abstract

The last decade has revealed that the lifespan of an organism can be modulated by the signaling pathway that acts downstream of the insulin/insulin-like growth factor 1 receptors (IR/IGF1-R), indicating that there is a “program” that drives the process of aging. New results have now linked the same pathway to the neurogenic capacities of the aging brain, to neurotrophin signaling, and to the molecular pathogenesis of Alzheimer's disease. Therefore, a common signaling cascade now seems to link aging to age-associated pathologies of the brain, suggesting that pharmacologic approaches aimed at the modulation of this pathway can serve to delay the onset of age-associated disorders and improve the quality of life. Work from a wide range of fields performed with different approaches has already identified some of the signaling molecules that act downstream of IGF1-R, and has revealed that a delicate checkpoint exists to balance excessive growth/“immortality” and reduced growth/“senescence” of a cell. Future research will determine how far the connection goes and how much of it we can influence.

Keywords

Aging; Alzheimer's disease; IGF1-R; neurotrophin receptors; amyloid β -peptide

1. Introduction

In 1906 the German physician Alois Alzheimer described the case of a severe cognitive decline in a 51-year-old woman that resembled previously described forms of senile “dementia”. He also attempted (and this was very unusual for his time, the beginning of the 20th century) to link the clinical/mental manifestations of the patient to a very detailed pathological analysis of the brain performed by his close collaborator, the Italian Gaetano Perusini (an exciting report on the early story of Alzheimer's disease is offered in ref [8]). The description of the disease included extracellular dense deposits (amyloid plaques) and twisted bands of fibers inside the neurons (neurofibrillary tangles). Today, this degenerative brain disorder bears his name, Alzheimer's disease (AD), and the observation of amyloid (or senile) plaques and neurofibrillary tangles at autopsy is still required to obtain a definitive diagnosis of AD.

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During the last century we have experienced a sharp increase in average lifespan, which has led to a marked increase in the number of individuals reaching the seventh and eighth decade of their life, resulting in a parallel increase in the prevalence and incidence of age-related disorders. In 2000, the number of individuals affected by AD in the world was estimated to be approx. 11.5 million, with approximately 4.5 million in the United States and the rest almost equally split between Europe and Southeast Asia. Because of the increased lifespan of the population, this number is expected to rise to approx. 14 million in the United States and 50 million worldwide by 2050. The distribution of AD patients among the different age-groups shows a sharp increase with aging. In fact, in 2000, 5% of the patients were between the ages of 65 and 74 years, 18% were between the ages of 75 and 84 years, and 45% were 85 years of age and older [64,149]. Therefore, the peculiar and unusual form of neurodegeneration described by Alzheimer has become the leading cause of dementia in the world and one of the most common age-related diseases [25,64,108].

This review will try to tie together the findings implicating the insulin-like growth factor 1 receptor (IGF1-R) in the regulation of lifespan to those that connect the same receptor to some of the events associated with normal aging of the brain and the Alzheimer form of neurodegeneration. Its main objective is to summarize these exciting new developments, and to bridge events thought to be totally unrelated. Hopefully, this approach will stimulate further interest of the scientific community in the molecular and biochemical events that influence the normal process of aging of the brain.

2. AD pathology

The pathological and histological hallmarks of AD include amyloid plaques, neurofibrillary tangles, and amyloid angiopathy accompanied by diffuse loss of neurons and synapses in the neocortex, hippocampus and other subcortical regions of the brain. The dominant component of the plaque core is the amyloid β -peptide ($A\beta$) organized in fibrils of approximately 7–10 nm intermixed with non-fibrillar forms of this peptide. The most characteristic form of the amyloid plaque, the “neuritic plaque”, is characterized by a dense core of aggregated fibrillar $A\beta$, surrounded by dystrophic dendrites and axons, activated microglia, and reactive astrocytes (reviewed in [136,137]). In addition, diffuse deposits of $A\beta$ (probably a pre-fibrillar form of the aggregated peptide) are also found without any surrounding dystrophic neurites, astrocytes, or microglia; these plaques appear diffuse (therefore, called “diffuse plaques”) and can be found in limbic and association cortices, as well as in the cerebellum (where the classical neuritic plaques are always absent) (reviewed in [136,137]).

$A\beta$ is a 39 to 43 amino acid hydrophobic peptide proteolytically released from a much larger precursor, the amyloid precursor protein (APP) (Figure 1). The generation of $A\beta$ from APP requires the sequential recruitment of two enzymatic activities: β -secretase, also called BACE1 (for beta-site APP cleaving enzyme) [73,139,156,170], and γ -secretase, a multimeric protein complex containing presenilin, nicastrin, Aph-1, Pen-2, and CD147 [45,54,172,176]. The β cleavage is the rate-limiting step and occurs before γ cleavage. It liberates a large N-terminal fragment of the protein ($s\beta$ APP) that is released in the extracellular *milieu*, and a small (~12 kDa) membrane-anchored fragment called β -APP-CTF (or C99). The release of the large N-terminal domain allows subsequent γ cleavage, and liberation of $A\beta$ and the signaling active intracellular domain of APP (AICD) (Figure 1). γ cleavage does not seem to be sequence specific and normally occurs either at position 40 or 42 of the $A\beta$ region generating $A\beta_{40}$ and $A\beta_{42}$, respectively. Release of $A\beta$ in the extracellular *milieu* is followed by oligomerization and aggregation in the form of amyloid plaques. The molecular mechanisms involved in the secretion, aggregation, and toxicity of $A\beta$ are still in part unknown (reviewed in [136,160]).

Neurofibrillary tangles are observed almost exclusively in the cytoplasm of neurons. They appear as paired, helically twisted protein filaments and are made of highly stable polymers of cytoplasmic proteins called tau. Tau proteins constitute a group of alternatively spliced proteins found in the cytoplasm that possess either three or four microtubule-binding domains and that can assemble with tubulin, thus helping the formation of cross bridges between adjacent microtubules. Tau proteins can be phosphorylated in multiple sites and the degree of phosphorylation inversely correlates with binding to microtubules. Therefore, highly phosphorylated tau proteins dissociate from microtubules and polymerize into the above described filaments (reviewed in [92]). In addition to AD, the abnormal accumulation of filamentous tau is observed in frontotemporal forms of dementia, which include progressive supranuclear palsy, corticobasal degeneration, and Pick's disease. Finally, multiple mutations in the *tau* gene have been found associated with frontotemporal dementia with parkinsonism, therefore indicating that tau themselves can produce neurodegenerative disorders (reviewed in [92]). The possible role of tau proteins in the pathogenesis of AD, and their potential interaction with A β is still a matter of discussion. Studies in transgenic animals indicate that human A β – but not tau – is sufficient to cause a mouse neuropathology that resembles human AD (reviewed in [53]). However, studies in both AD patients [37] and mouse models (reviewed in [53]) seem also to suggest that A β and tau can synergistically interact, fostering their respective aggregation and the neuronal loss. These arguments seem to find further validation in the fact that suppression of tau can improve memory function in an AD mouse model [131].

3. Insulin/IGF1 receptors: a signaling pathway for the general program of aging

Insulin and insulin-like growth factor 1 (IGF1) have similar tertiary structures and substantial amino acid identity. IGF1 is mostly secreted into the blood by the liver where its synthesis is regulated by the pituitary growth hormone (GH). However, many other tissues, including the brain, are also able to synthesize IGF1 locally where it is not under the control of GH [26, 100,144]. The proof that brain IGF1 is not under the control of circulating GH comes essentially from *Ghr*^{-/-} and Ames dwarf (*Prop 1*^{df}) mice. The former animals have a selective disruption of the GH receptor and cannot secrete IGF1 in response to GH [100], whereas the latter have a defect in the production and secretion of GH by the anterior pituitary [144]. Both animals have undetectable levels of IGF1 in the serum, but completely normal levels of IGF1 in the brain [100,144]. In addition, Ames dwarf mice [144] also show normal activation of IGF1-R signaling in different areas of the brain. This is further supported by the fact that primary neurons secrete IGF1 in the conditioned media in the absence of any hormonal stimulation [26]. In contrast to IGF1, insulin is almost exclusively synthesized and secreted into the plasma by pancreatic beta cells.

Although plasmatic IGF1 decreases during aging, brain IGF1 shows either no change or a slight increase during aging [18]. In addition, the plasmatic levels of its cognate ligand, insulin, increase during aging, most likely because of progressive peripheral resistance. Insulin resistance is also a risk-factor for AD [18,49] and has been implicated with several aspects of AD neuropathology [18], including production/secretion of A β [18,31,49,161].

Insulin and IGF1 bind to high-affinity tyrosine kinase receptors, the insulin receptor (IR) and the IGF1 receptor (IGF1-R), which are widely expressed throughout the body, including the brain [12]. Co-expression has been reported in many brain areas, including cortex and hippocampus [12,163,164]. IR and IGF1-R are also expressed on brain capillaries and mediate the high-efficiency translocation of insulin and IGF1 into the brain across the blood-brain-barrier (BBB) [127]. Cross binding of insulin to IGF1-R at the level of the BBB has been reported, but IGF1 translocation occurs with higher efficiency [127]. IGF1 can mimic insulin-like signaling in the brain [12], suggesting a partial overlapping of IR and IGF1-R signaling

abilities. Even though cross-reaction can occur, each receptor binds to its own ligand with a 100- to 1000-fold higher affinity than that of the heterologous peptide. In agreement with these biochemical observations, IR and IGF1-R have certain shared functions, but also very distinct biological roles, and activate completely different sets of genes [40,79].

IR and IGF1-R share a high degree of identity in their primary and tertiary structure. The functional active receptor contains two α and two β subunits. The two disulfide linked α subunits constitute the extracellular ligand-binding domain of the functional IR and IGF1-R. The signal transducing and largely intracellular β subunits share a high degree of amino acid identity in the tyrosine kinase domain (~85%). IGF1-R has a slightly longer carboxyl-terminal domain with an additional tyrosine phosphorylation site, which represents the only apparent structural difference between IR and IGF1-R. This domain shows only a ~45% identity between the two receptors [153]. As a consequence of this high level of homology/identity, hybrid receptors, comprised of an insulin $\alpha\beta$ -hemireceptor and an IGF1 $\alpha\beta$ -hemireceptor, can form in tissues and cells expressing both IR and IGF1-R [42,43]. Whether hybrid receptors play specific roles in mediating insulin and/or IGF1 signaling is still unknown.

Upon binding to their own ligand, IR and IGF1-R undergo auto-phosphorylation, associate with intracellular adaptor proteins called insulin/IGF1 receptor substrates (IRS) proteins, and activate either the PKB/Akt or the Ras/MEK/ERK signaling pathways in order to transduce IGF1 actions [12] (Figure 2; *left panel*). Akt activation requires phosphorylation of phosphatidylinositol (3,4)biphosphate (also called PIP2) by a phosphatidylinositol 3-kinase (PI3K) in order to generate the second messenger phosphatidylinositol (3,4,5)triphosphate (also called PIP3). This pathway is under the inhibitory control of the phosphate and tensin homologue deleted on chromosome ten (PTEN) anti-oncogene, which converts PIP3 back to PIP2 and down-regulates the expression levels of IGF1-R [101,102]. An additional point of regulation is provided by the p44:p53 ratio. p44 is a naturally occurring short isoform of the transcription factor p53 [135], and seems to act by stabilizing p53 tetramers [15]. Conditions that favor p44 *versus* p53 will down-regulate PTEN -thus releasing its inhibitory block- and activate the signaling cascade downstream of PIP3, and the “fail-safe” pathway downstream of Ras/Raf [102] (some of the above events are schematically described in the left panel of Figure 2).

Compelling evidence indicates that the IR/IGF1-R signaling pathway plays a major role in controlling maximum lifespan and, at some extent, the incidence/prevalence of age-associated diseases [13,84,98]. IGF1-R's role during aging has been demonstrated in all species analyzed so far, including yeast, *C. elegans*, *D. melanogaster*, and mammals [13,84,98]. A partial block of the IGF1-R signaling pathway is also achieved by caloric restriction, which extends the maximum lifespan and delays many biological changes that are associated with aging [141, 162].

The initial evidence linking the IGF1-R signaling pathway to the general process of aging came from *C. elegans*, where mutations in *age-1*, coding for PI3K, (Figure 2; *right panel*) resulted in extension of adult life span [46,87]. This initial observation was later on linked directly to IGF1-R when mutations in *daf-2*, coding for the common insulin/IGF1 receptor, were found to double the maximum lifespan of the animal [85,86]. These effects were also observed with mutations of the *D. melanogaster* ortholog of the common insulin/IGF1 receptor [148]. Similar approaches led also to the identification of *daf-16*, coding for a FOXO family transcription factor, *daf-18*, coding for PTEN, and *chico*, coding for an insulin/IGF1 receptor substrate (IRS)-like signaling protein (reviewed in [84,150]).

Later on, *C. elegans* served to show that DAF-2 acts upstream of AGE-1, which in turn regulates DAF-16, therefore providing a clear molecular cascade that controls aging in the worm [84,

98]. DAF-16 is the apparent final downstream output of this pathway, as indicated by the fact that null mutations of *daf-16* suppress the phenotype produced by the double-mutant combination of *daf-2* and *age-1* [97,119]. In addition, the regulation of *daf-16* seems to involve lipophilic-hormone signaling between the reproductive system and the intestine of *C. elegans*, can be modulated by different outputs (including *kri-1* and *daf-9*), but can also be bypassed by a parallel and partially independent pathway mediated by *daf-12* [6,50,71,109,129]. Finally, the *daf-2/daf-16* pathway seems also to be—at least in part—under the control of the *lin-4/lin-14* system, which provides a regulatory function of IGF1-R signaling in the adult tissue of *C. elegans* [2,11]. Therefore, a complex cross-talk between different genes (and tissues) is required to achieve fine tuning of a program that determines the lifespan and aging process of an organism. A more detailed overview of the many genes found to modulate life span in different model organisms can be found in [4,84,98,150]. It is worth stressing the fact that the longevity induced by *daf-2* mutations requires the functional activity of AAK-2, the catalytic subunit of the AMP-activated protein kinase (AMPK), which regulates many metabolic and transcriptional events [3]. In *D. melanogaster*, AMPK exerts an inhibitory control on the biosynthesis of fatty acids and isoprenoids, and on the hydrolysis of diet-derived cholesterol esters. Disruption of AMPK in *D. melanogaster* produces the *loe* phenotype, which is characterized by a vacuolar form of neurodegeneration and by a marked increase in the α/β -like shedding of APPL, the fly homolog of human APP [151]. Therefore, an increased activity of AMPK extends lifespan in the worm [3], whereas a functional inactivation induces a dramatic form of neurodegeneration and activates the processing of APPL in the fly [151].

In contrast to worms and flies, mammals have separate receptors for insulin and IGF1. Homozygous disruption of IGF1-R in mice is not viable; however, heterozygous animals lacking only one allele of the receptor have a lifespan that is longer than wild-type (~30% in females and ~18% in males; the difference in males did not reach statistical significance) with no apparent manifestation of disease [70]. Similar results (~18% increase in lifespan) were obtained with the selective disruption of IR in the adipose tissue [10]. This effect is not limited to the receptor itself, but can also be extended to the ligand. In fact, Ames dwarf mice, which have a defect in the pituitary gland and do not secrete IGF-1 in the plasma, live longer than normal animals and exhibit normal cognitive functions (even in old age) [13,14,44].

In contrast to the above, hyper-activation of the IGF1-R signaling pathway in $p44^{+/+}$ transgenic mice accelerates the progression of aging and shortens the maximum lifespan [102]. The $p44^{+/+}$ phenotype is reminiscent of the $p53^{+/m}$ mice, where truncation of the N-terminal domain of p53 generates a hypermorphic p53 and leads to short lifespan and early onset of aging phenotypes [152]. The $p44^{+/+}$ mouse system offers a very attractive model by delineating a previously unknown level of regulation of IGF1 signaling [102]. The involvement of the p53:p44 system in the regulation of lifespan and age-related events has received further demonstration by the observation that the genetic disruption of p53 reverts the accelerated aging phenotype observed in *Zmpste24*^{-/-} mice [155].

It is also important to point out that p53 is found mutated in many forms of cancers, suggesting that the p53:p44 ratio regulates the balance between excessive growth/tumor generation and reduced growth/early senescence [15]. Interestingly enough, $p44^{+/+}$ mice, which have increased p53 activity, show a premature loss of neurogenic capacity in the brain that is linked to accelerated brain aging [105]. Notably, the altered p53:p44 activity observed in $p44^{+/+}$ mice affects the balance between cell proliferation and cell death by affecting only the rate of cell proliferation—but not the rate of cell death. Therefore, loss of p53 activity leads to accelerated cell growth (and cancers), whereas increased p53 activity leads to early arrest of cell growth, premature aging, and increased production of A β (see later).

Although IGF1 levels in the cerebrospinal fluid (CSF) exhibit no change or a slight increase during aging [18], the expression levels of the receptor (IGF1-R) show a dramatic and progressive increase in both cortex and hippocampus that correlates with learning deficits in aged rats [23,24,143]. A recent study in the brain of normally aged individuals has also found an age-associated increase in the expression of IR [99]. Finally, correlation studies in normally aged volunteers confirm that disturbances in the IGF1/IGF1-R pathway are associated with poor performance on neuropsychological tests evaluating different cognitive functions normally affected by age [145]. These events are not reverted by administration of GH or normalization of serum IGF1 levels, suggesting -but not proving- a direct involvement of the receptor-mediated signaling pathway in the brain rather than plasmatic IGF1 [145].

4. IGF1-R, neurotrophin signaling, and AD: a tale of receptors and second messengers

4.1 p75^{NTR} and ceramide: an unexpected link

While trying to analyze the role that the cell-surface sphingolipids GM1 and sphingomyelin (SM) played in the clustering of APP into cholesterol-rich-domains (lipid rafts) and in the metabolism of A β , we surprisingly found that ceramide, the product of SM hydrolysis, could regulate the rate of A β generation by affecting the molecular stability of BACE1 [125]. Ceramide is a lipid second messenger that can regulate many of the biochemical and genetic events that occur during senescence/aging, and is, therefore, an attractive candidate as molecular bridge between normal aging and AD.

The existence of a relationship between ceramide and “aging signaling” is mostly indicated by cellular studies showing that both exogenous and endogenous ceramide can reduce the replicative capacities of primary cells and induce a senescent phenotype [157,158]. It is worth remembering that somatic cells have a limited lifespan in culture beyond which they can no longer proliferate (also known as the “Hayflick limit”) [138]. The endpoint of this mitotic life in culture has been termed “cellular senescence”. Senescence *in vitro* does not imply death in cells any more than *in vivo* senescence; indeed, cells may live for years after they stop dividing. The length of the proliferative lifespan inversely correlates with both the age of the donor organism and the life expectancy of the species from which the cells were obtained [140]. Finally, spontaneous senescence is a dominant and irreversible process that can only be overridden by DNA tumor viruses, and delayed (at least in certain instances) by overexpression of telomerases [32,158]. As a result, cellular senescence is acknowledged as a model for aging research. Indeed, many of the factors that influence cellular senescence have also been involved with longevity; conversely, molecular/genetic events that are affected by organismal aging are also affected by cellular senescence [138,140,158].

An interesting connection between replicative capacity of a cell and ceramide comes from the yeast *Saccharomyces cerevisiae*, which shows a marked increase in lifespan when a gene called longevity-assurance gene 1 (*LAG1*) is deleted [38]. Lag1 resides in the endoplasmic reticulum and shows C26-ceramide synthase activity both *in vivo* and *in vitro* [58,133]. The extension of lifespan by *LAG1* deletion in the yeast is rescued by the human homolog *LAG1Hs*, which is highly expressed in the brain, along with testis and skeletal muscle [77]. Even though it is difficult to draw a direct connection between the yeast phenotype and mammalian aging, the fact that ceramide levels increase during cellular senescence and organismal aging [33,96, 107,110] adds support to the concept that this lipid plays a important role in longevity and age-associated events. Of particular interest is also the fact that ceramide levels are higher (~3-fold) in the brains of AD patients, when compared to age-matched controls [33,60].

Following our initial observation, we have recently found that ceramide production in the mouse brain is activated in an age-dependent fashion [27], and is closely followed by a parallel increase in BACE1 steady-state levels, β cleavage of APP, and A β generation. The age-associated activation of ceramide was specifically linked to the expression levels of the tyrosine-kinase A (TrkA) and p75 (p75^{NTR}) neurotrophin receptors. Indeed, an expression pattern in which TrkA predominates in younger animals switches to one in which p75^{NTR} predominates in older animals. The TrkA to p75^{NTR} molecular switch is responsible for an age-dependent activation of nSMase, the enzyme that is responsible for the hydrolysis of SM and consequent liberation of the second messenger ceramide (Figure 3; *right panel*). The strict requirement for p75^{NTR} was proved by using animals expressing a truncated version of the receptor that lacks the ligand binding domain (p75^{NTR}*ExonIII*^{-/-}), whereas the requirement for ceramide was confirmed by treating wild-type animals with an irreversible and competitive inhibitor of nSMase [27]. In addition, nSMase inhibitors were not effective when used with either primary neurons or animals that express a signaling inactive form of p75^{NTR}, therefore positioning ceramide down-stream of p75^{NTR} (Figure 3; *right panel*) [27]. Finally, when NGF was administered to neuroblastoma cell lines expressing either TrkA or p75^{NTR}, only p75^{NTR} expressing cells responded by increasing ceramide production and the β cleavage of APP [27]. In contrast, TrkA expressing cells showed an apparent decrease in β cleavage of APP, suggesting a dual and differential role in the regulation of the initial enzymatic step for A β generation. However, this effect might not be limited to β cleavage since TrkA activation seems also able to reduce the generation of AICD [147].

The use of a cellular system where only one receptor was expressed proved to be very important. In fact, when analyzing TrkA and p75^{NTR} binding to NGF, we must be aware of the fact that TrkA acts as homo- (TrkA-TrkA) or hetero- (TrkA-p75^{NTR}) dimer (Figure 4) forming high-affinity binding complexes with NGF (the normal stoichiometry of the NGF:TrkA binding is 2:2), whereas p75^{NTR} can bind to NGF as a monomer, with a stoichiometric ratio of 2:1 (NGF:p75^{NTR}) [63,173]. One “bizarre” consequence of this is that the TrkA-p75^{NTR} complex forms a high-affinity binding site ($K_d \sim 10^{-10}$ – 10^{-11} M instead of 10^{-8} – 10^{-9}) for the mature NGF that transduces TrkA –but not p75^{NTR}– signals [82]. This issue, which was initially interpreted as a simple controversy caused by the different experimental approaches used, is now being reinterpreted as a fundamental and important property of neurotrophin signaling [22,82,118]. Therefore, over-expression of p75^{NTR} on a TrkA background may very well potentiate TrkA-, rather than p75^{NTR}-, mediated events (Figure 4). Indeed, TrkA can “silence” p75^{NTR} signaling in cellular systems [82,124], in addition to promoting p75^{NTR} proteolytic clearance [39,81,83,165] through a mechanism that seems to involve both trans-activation [83] and ligand-binding [39]. These events may all be part of a rather complex form of regulation of neurotrophin signaling, potentially influenced by aging itself [5,26,27,78].

p75^{NTR} is a member of the tumor necrosis factor receptor superfamily (TNFRSF) and interacts with all the different members of the neurotrophic factor family: the nerve growth factor (NGF), the brain-derived neurotrophic factor (BDNF), neurotrophin-3, and neurotrophin-4 (reviewed in [74]). In addition to p75^{NTR}, the above neurotrophins also bind to tyrosine kinase receptors (TrkA, TrkB, and TrkC). Signaling specificity is determined by ligand binding affinities to the different receptors. Several studies have shown the existence of cross talk between the different neurotrophins and the Trk receptors: more than one neurotrophin may bind to the same Trk receptor, and more than one Trk receptor may bind to the same neurotrophin (reviewed in [74]). Even in the case of p75^{NTR}, there seem to be subtle differences in the ligand-binding affinities, which allow p75^{NTR} to discriminate between the different neurotrophins.

Like all other TNFRSF members, p75^{NTR} can transduce both death and survival signals [36]. This may involve either different affinities to the ligand(s) [74], in concert with co-receptors that would determine the exact message to be translated [106,117], or cytoplasmic interactors,

which modulate the interaction of the receptor with the “active” signaling molecule [36,173]. On this front, it is important to stress the fact that p75^{NTR} is devoid of intrinsic catalytic activity and, therefore, its signaling abilities rely on intracellular interactors. In the case of the second messenger ceramide, it is not known how p75^{NTR} activates nSMase. Whether such activation requires adaptor proteins, physical “connection”, or molecular interaction with nSMase remains to be determined.

Mature NGF normally interacts with both TrkA and p75^{NTR} with similar affinities (dissociation constant K_d in the 10^{-8} – 10^{-9} M range) [82]. However, pro-NGF, the uncleaved form of NGF, binds to p75^{NTR} with five times greater affinity than mature NGF, and shows very low affinity binding to TrkA [91]. This might be particularly relevant, since the levels of pro-NGF found in the brain of AD patients are higher than in age matched controls [41,121], therefore providing a further level of risk over that already provided by normal aging. This line of thoughts seems to find its own validation from the AD11 mouse model expressing transgenic antibodies that neutralize brain NGF (reviewed in [16]). In fact these mice develop several features of AD neuropathology, which include high A β levels, amyloid plaques, and neurofibrillary tangles. This phenotype was initially interpreted as solely caused by the lack on NGF signaling in the areas of the brain that are typically affected by AD pathology. However, it was soon realized that the transgenic NGF-neutralizing antibody produced by AD11 mice had very low or no affinity to pro-NGF, suggesting an alternative model in which the lack of NGF signaling (most likely through TrkA) would facilitate pro-NGF signaling through p75^{NTR}. This model found its own validation when it was observed that genetic disruption of p75^{NTR} completely abolished the high A β levels, the intracellular deposits of A β , and the plaque pathology observed in these mice. In conclusion, the different experimental approaches employed with the AD11 mice (reviewed in [16]) overall suggest that when NGF is neutralized by the recombinant anti-NGF antibodies, pro-NGF signals through p75^{NTR}, and activates the production of A β and its consequent aggregation/accumulation into intracellular and extracellular (amyloid plaques) deposits. Conversely, when p75^{NTR} is removed or NGF signal (through TrkA) is restored, the amyloid pathology is also abolished. Therefore, a complex set of interactions between ligands (NGF and pro-NGF) and receptors (TrkA and p75^{NTR}) might be acting upstream of the cascade of events that leads to AD (also discussed below).

The connection between the TrkA/p75^{NTR} receptor system and AD neuropathology seems to find additional validation from the association between gender and AD. In fact, it is long known that women experience a sharp increase in the risk of developing AD after menopause [65, 103]. This is further strengthened by the fact that ovariectomy promotes the amyloidogenic processing of APP [76,122,166,175], and that these effects are partially or totally reverted by estrogen treatment [122,175]. Animal studies have also shown that surgical ovariectomy increases the expression of p75^{NTR}, while decreasing TrkA, at both mRNA and protein levels. These effects are completely abrogated by exogenous estrogens [51,80,89,123]. Therefore, the loss of ovarian function after menopause would only aggravate the age-associated changes in neurotrophin receptors, further increasing the risk for AD in normally aging women.

It is also worth noting that different studies have found a selective and marked reduction in the expression of cortical TrkA in early and late stages of AD, when compared to age-matched controls [30,68,111]. This seems to occur in the face of stable [30,68,111] or increased [72, 113] p75^{NTR}, and increased pro-NGF [41,121]. Because pro-NGF preferentially binds to p75^{NTR} (reviewed in [91]), the above changes ultimately lead to increased activation of p75^{NTR} signaling. Interestingly, p75^{NTR} expressing cholinergic neurons seem to be more susceptible to cell death (reviewed in [28]) and are also characterized by increased accumulation of hyperphosphorylated tau [72]. Therefore, the above studies seem to support the notion that the balance between TrkA and p75^{NTR} signaling in the hippocampus and cortex might be directly linked to the three classical features of AD: A β , tau, and neuronal death.

4.2 IGF1-R and PIP3: the common culprit

The fact that caloric restriction was able to block/revert the TrkA to p75^{NTR} switch in mice [27] led us to explore the potential role of IGF1-R, the common regulator of lifespan. Studies *in vitro* with both human neuroblastoma cell lines and primary neurons showed that indeed IGF1-R acts upstream of both receptors [26] (Figure 3). Both genetic silencing of IGF1-R or biochemical inhibition of PI3K, downstream of IGF1-R, were able to block the TrkA to p75^{NTR} switch [26]. Interestingly enough, primary neurons in culture were found to go through a neurotrophin receptor switch reminiscent of that previously observed in the brain of normally aging animals: an expression pattern in which TrkA predominates in day 0–3 (in culture) neurons switches to one in which p75^{NTR} predominates in day 18–24 neurons. This was closely followed by activation of the second messenger ceramide, stabilization of BACE1, and increased production of A β [26]. Gene-silencing approaches directed toward *Igf1-r* were able to block the entire cascade of events, therefore proving that IGF1-R acts upstream. Finally, analysis of both primary neurons and brain tissue (cortex and hippocampus) from p44^{+/+} mice, which have a constitutive hyper-activation of IGF1-R signaling, showed an early and accentuated TrkA to p75^{NTR} switch, together with a parallel activation of ceramide and the events described above. The use of both genetics and biochemistry indicated that these events require the adaptor protein IRS2, PI3K, and conversion of PIP2 into the active second messenger PIP3 (Figure 3).

The above events were found to be under the regulatory control of PTEN and p44: PTEN can block the TrkA to p75^{NTR} switch downstream of IGF1-R by converting PIP3 into its inactive precursor PIP2, whereas p44 can block PTEN, therefore releasing the inhibitory function of PTEN [26]. It is worth noting that AD brains are characterized by decreased levels of PTEN (similarly to p44^{+/+} mice) and hyper-activation of Akt downstream of IGF1-R [1,55,95]. It is also worth mentioning that *ex vivo* studies revealed that the IRS “branch” of IR/IGF1-R signaling can promote tau phosphorylation [93,134], potentially linking the two major hallmarks of AD (A β and tau) to the same upstream molecular pathway. Therefore, the studies implicating IGF1-R signaling to lifespan and aging have now been connected to those that implicate neurotrophin signaling to AD neurobiology, providing a molecular bridge between aging itself and one of the most common forms of age-related diseases.

Even though the main topic of this review is the signaling pathway acting downstream of IGF1-R, and its role in aging and AD neuropathology, we must be aware that IGF1, the preferential ligand for IGF1-R, is also a growth factor with trophic activities that not always require IGF1-R. In fact, IGF1 can protect from cell death *in vitro* (even in cells that do not express IGF1-R) and can exert neuroprotective effects *in vivo* (reviewed in [20]). Some of the neuroprotective effects documented *in vivo* seem to involve the cell-surface receptor megalin/LRP2 [17,19, 21] and/or transport/clearance across the BBB [17,21]. Additionally, plasmatic IGF1 can be naturally cleaved into des-N (1–3)-IGF-1 and the N-terminal tripeptide, glycine-proline-glutamate (GPE-IGF1) [132,167,168,169]. Without interacting with IGF1-R, GPE-IGF1 can cross the BBB, can stimulate dopamine and acetylcholine release *in vitro*, and can protect neurons from hypoxic-ischemic injury [56,57,116]. Finally, some of the anti-apoptotic/pro-survival effects induced by IGF1 *in vitro* do seem to involve signaling molecules that traditionally act downstream of IGF1-R. However, these actions also occur in cells that do not express IGF1-R and must not be confused with IGF1-R signaling. Therefore, we must always be aware of the fact that IGF1 means more than just IGF1-R.

5. PIP3 and ceramide: two different lipids with the ability to act as second messengers

The sequence of events that leads from IGF1-R to A β requires two lipids, PIP3 and ceramide, that share a few similarities, even though they are very different. They both are found –mostly, but not only- in the plasma membrane; they both have a fatty acid moiety that anchors them to the lipid bilayer (Figure 5A and C); they both exist as inactive precursors (PIP2 and SM) under static conditions and are activated only following extracellular signals (Figure 5B and D); and finally, they both can act as second messengers and transduce messages from the extracellular *milieu* to the inside of the cell.

5.1 Ceramide

The initial step in ceramide biosynthesis occurs in the endoplasmic reticulum with the condensation of serine and palmitoyl-CoA, followed by reduction of 3-ketosphinganine, acylation of the amide group of sphinganine, and final dehydrogenation of dihydroceramide. The predominant long-chain base of ceramide is sphingosine (shown in red in Figure 5A), although sphinganine is also found in very low amounts. Once these initial steps are completed, ceramide is transported to the Golgi apparatus by two different mechanisms: one protein-mediated, which requires a ceramide-specific transfer protein (CERT), and another vesicular-mediated [61, 88]. The ceramide that will serve as substrate for the generation of sphingomyelin is transported by CERT, whereas the one that will serve as substrate for glycosylation is translocated by the vesicular-mediated mechanism, indicating that the biosynthesis of glycosphingolipids is segregated and compartmentalized very early in the pathway (for review, see also [48, 62, 114]).

The initial step in the biosynthesis of major glycosphingolipids requires the generation of glucosylceramide by a ceramide-specific glucosyltransferase, which then will serve as backbone for further glycosylation. All these glycosylation steps occur in the Golgi apparatus. In contrast, the biosynthesis of sphingomyelin (SM), which also occurs in the Golgi apparatus, requires only the addition of choline. The donor of the choline moiety is phosphatidylcholine (PC) and the enzyme that carries out the reaction is the sphingomyelin synthase [47]. Even though most of the SM is generated very early in the Golgi apparatus (*cis*- and *medial*-Golgi), a SM synthase activity has also been described at the plasma membrane (PM), which could account for as much as 10–15% of total cell SM synthase [47,48]).

Following its biosynthesis in the Golgi apparatus, SM is translocated to the PM, where it is mostly clustered into lipid rafts in tight association with cholesterol. At the PM, SM can undergo hydrolysis and liberate ceramide plus choline. The enzyme that carries out this reaction is called neutral sphingomyelinase 2 (nSMase2) [69,104,177] and is different from the lysosomal-based SMase that is active at low pH (hence the name acid SMase) and involved in the catabolism of ceramide-containing sphingolipids in the lysosomal compartment [130, 159].

The ceramide generated at the cell surface following hydrolysis of SM has signaling abilities and acts as a lipid second messenger. It is not clear whether SM hydrolysis occurs on the outer or inner leaflet of the PM bilayer. However, ceramide can rapidly equilibrate (“flip-flop”) across the membrane bilayer; therefore this issue does not pose any topographical obstacle to the activity of the second messenger [159]. Cell surface ceramide can then recycle back to SM. Whether this step requires retro-translocation to the Golgi apparatus is not clear yet. However, the fact that both the donor of choline, PC, and the enzyme, SM-synthase, are found in the PM may suggest a local form of regulation of the “ceramide cycle” [48]. Even though the above cycle is regarded as the main pathway for the metabolism and regulation of the signaling

activities of ceramide, it is important to stress that local pools of SM/ceramides are also found in other cellular membranes. Whether they can elicit signaling events limited to a specific organelle is still under debate.

When dealing with the signaling activities of ceramide, it is always important to consider the fact that the transfer of the choline phosphate head group from PC to ceramide by SM synthase results in the formation of SM and diacylglycerol (DAG). In addition, following SM hydrolysis, ceramide can be converted to sphingosine, which can be phosphorylated to sphingosine-1-phosphate (S1P). Since DAG, sphingosine, and S1P can also act as signal transducers, it is not difficult to conceive how one or more of the enzymatic steps delineated above (and schematically shown in Figure 5B) can result in very complex (and sometimes opposite) biological responses (reviewed in [171]). Indeed, it is not unusual to consider ceramide, DAG, sphingosine, and S1P as a “biostat sensor” system that allows the cell to adapt and respond to very diverse situations.

5.2 PIP3

Phosphoinositides (PtdIns) are low abundant lipids (less than 5% of total membrane phospholipids) that are mainly found in the cytoplasmic leaflet of cellular membranes. They can be phosphorylated in three different positions –3, 4, and 5- of their inositol head group (Figure 5C), generating different species (Figure 5D) that have different biological functions. PtdIns(3)P and PtdIns(4,5)P₂ (also known as PIP₂) are the most abundant and seem quite static. They are mostly found in the PM, endosomes, and, although in smaller amounts, in the Golgi apparatus, where they serve as an anchor for the sorting/targeting of proteins containing the pleckstrin homology (PH) domain and as regulators of endocytosis [154]. The bis-phosphoinositide, PtdIns(3,4)P₂, and the tris-phosphoinositide, PtdIns(3,4,5)P₃ (also known as PIP₃) are not abundant and seem to be very dynamic, showing rapid changes in response to extracellular stimuli.

The critical phosphorylation of the inositol head group at position 3 requires a specific set of enzymes collectively called phosphatidylinositol-3-kinases (PI3Ks) or phosphoinositide 3-kinases (reviewed in [35]). Depending on their subunit structure and substrate selectivity, PI3Ks are normally categorized as class I, II, and III. The conversion of PtdIns into PtdIns(3)P is mainly performed by class III PI3Ks, whereas the conversion of PtdIns(4)P into PtdIns(3,4)P₂ can be performed by both class I and class II PI3Ks. Finally, class I are the only capable of converting PIP₂ into the critical and better characterized second messenger PIP₃ (Figure 5D). PI3K is a heterodimer composed of a catalytic and regulatory subunit. The catalytic subunit exists in three isoforms (p100α, p110β, and p110δ), whereas the regulatory subunit exists in five different isoforms (p85α, p85β, p55α, p55γ, and p50α) produced by differential splicing of three genes (reviewed in [35]). When inactive, PI3K is found in the cytoplasm while its substrate, PI(4,5)P₂, resides on the cytoplasmic leaflet of the PM. Upon binding to its extracellular ligand, IGF1-R associates and phosphorylates IRS proteins. The phosphorylated-Tyr-X-X-Met sequence on IRS proteins then serves to recruit and activate the regulatory subunits of PI3K. This event is followed by the assembly of the active PI3K heterodimer that phosphorylates PI(4,5)P₂ to produce the second messenger PI(3,4,5)P₃.

In addition to the above and more studied PI3K-mediated pathway, PIP₃ can also originate following phosphorylation at position 5 of the inositol group on PtdIns(3,4)P₂ by type I phosphatidylinositol phosphate kinase (PIPK) (reviewed in [52]). This previously unknown biochemical reaction can occur both *in vitro* [174] and *in vivo* [59], and seems to act downstream of oxidative stress rather than classical growth factors, potentially providing signal specificity to the signal transduced by PIP₃. PIPK seems to be more promiscuous than PI3K and could be involved in the phosphorylation of additional positions of the inositol head group, playing an even more complex regulatory role [67].

The levels of PIP2 and PIP3 are tightly controlled by a dynamic equilibrium between the rate of phosphorylation (by PI3Ks) and dephosphorylation (by PTEN) at position 3 (Figure 5D). PTEN has both protein [94, 146] and lipid [101, 115, 142] phosphatase activities; however, most of the functions in signal transduction ascribed to PTEN seem to be mediated by its lipid phosphatase activity, which dephosphorylates position 3 of the inositol head group of PIP3 [101, 115, 142]. In addition, PIP3 can also be dephosphorylated at position 5 by SH2-containing inositol 5'-phosphatase proteins (SHIP), which counteract PIPK (Figure 5D). The recognition/binding capacity of SHIP seems to require the Src homology 2 (SH2) domain, which mediates binding of several additional proteins to PIP3 [9]. Therefore, generation of PIP3 not only recruits proteins that will transduce the signal, but also proteins that will limit the signal by deactivating PIP3 itself.

Mutations in PTEN and SHIP generate non-overlapping phenotypes, therefore underscoring the importance and differential roles played by the above lipids and enzymes [9,101,128]. The importance of the dynamic equilibrium between the different PtdIns species is also stressed by the fact that PIP2 is slowly emerging as a previously unrecognized signal transducer, rather than a simple inert molecule [34,66,75]. This is further complicated by the fact that phosphatidylinositols can be cleaved at the *myo*-inositol group, producing the soluble inositol phosphate and the lipid anchored DAG (Figure 5D), which can also act as signal transducer [7].

6. Conclusion

The last decade has surprisingly shown that the lifespan of an organism can be modulated by the signaling pathway that acts downstream of the IGF1-R, indicating that there is a "program" that drives the process of aging. New studies have now shown that the same pathway can regulate neurotrophin signaling, the neurogenic capacity of the brain, and the rate of A β generation. Therefore, a complex molecular cascade seems to link the normal process of aging to one (or more) of the initial events involved with the pathogenesis of AD. Obviously, we still need to identify all the signaling molecules that act downstream of PIP3 and ceramide (Figure 3). This might be easier for PIP3, since many target molecules that are activated/recruited by PIP3 are already known. In addition, the presence of the PH domain can serve to screen for new potential targets that have not yet been linked to PIP3 signaling. In contrast, ceramide signaling is still mostly uncertain; specifically, it is not known how the signal is transferred and whether ceramide requires a specific targeting sequence/domain(s) to recruit downstream molecules. In addition, the mechanism(s) that allow p75^{NTR} itself, which is devoid of any catalytic activity, to activate nSMase are still completely unknown. This might require initial dissection of the function(s) of the cytosolic tail of the receptor. For example, the identification of the specific sequence that is responsible for the p75^{NTR}-mediated activation of ceramide might lead to the identification of the adaptor protein(s) responsible for the recruitment/activation of nSMase.

Finally, the specific mechanism that leads to the TrkA-to-p75^{NTR} switch downstream of IGF1-R remains to be determined. In theory, the expression levels of p75^{NTR} could be regulated at three different levels: increased transcription/translation, reduced clearance, and increased molecular stability. The last two events are intimately related because a reduction in clearance would also lead to increased half-life of p75^{NTR}. On this regard, the fact that TrkA can stimulate the proteolysis of p75^{NTR} [83] seems to support a possible post-translational event. Indeed, the down-regulation of TrkA would reduce the proteolytic clearance of p75^{NTR}. However, transcriptional regulation is normally regarded as the primary mechanism used by aging to control the expression levels of a certain protein. Therefore, the primary mechanism could still involve an independent transcriptional regulation of TrkA and p75^{NTR}; the downregulation of

TrkA, in turn, would further potentiate the effects on p75^{NTR} by reducing the proteolysis of the receptor.

One additional argument that needs to be addressed –the role of IGF1-R in the progression of AD pathology- will require the generation of appropriate mouse models. In fact, even though the connection between IGF1-R and A β has been identified and characterized at the molecular level, we still need to analyze whether hyper-activation of IGF1-R signaling can accelerate the progression of AD-like pathology in a mouse model. This approach, if successful, would also allow testing possible biochemical strategies aimed at the modulation of IGF1-R signaling for the prevention of AD. Such a strategy cannot be performed with the current mouse models of AD, since they harbor human genes (APP and/or presenilins) carrying mutations associated with familial-forms of AD, and, therefore, not under the control of the aging program.

The main focus of this review was to bring together the findings that implicate IGF1-R in the regulation of lifespan to those that connect IGF1-R to neurotrophin signaling, the progressive loss of neurogenic capacity of the aging brain, and to the pathogenesis of AD. This connection is particularly relevant because aging itself is acknowledged as the single most important risk factor for AD. In fact, the prevalence of AD increases sharply after the age of 60 and doubles with every decade of life reaching ~50% in individuals that are 85 years of age or older [64, 149]. In addition, with increasing age, the frequency of higher neurofibrillary stages and higher A β stages in non-demented individuals increases as well, underscoring a strong relationship between aging and AD pathology [149]. However, we still must remember that, by definition, risk factors (in this case, age) are neither necessary nor sufficient for the development of a disease. Indeed, approx. 50% of the individuals that are 85 years of age or older are not affected by any sign of dementia, proving that a successful aging is possible. Additional risk factors (either environmental or genetic) might be required to develop the disorder. Obviously, protective factors might also be involved in the protection of certain individuals. Therefore, a broad combination of different approaches (both age- and disease-oriented), combining different areas of biomedical research, including biochemistry, molecular biology, and genetics will be required to completely resolve the rise of the tragic and devastating disease described by Alois Alzheimer a century ago.

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While preparing the reference section, I tried to maintain a balance between original papers and reviews on selected topics. The reviews provide additional breadth for those who wish to gain more insights, whereas the original papers acknowledge and describe the original findings. However, due to the large number of references, I apologize to those whose work could not be included in the final version of this manuscript.

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Figure 1. Schematic view of A β generation from APP

APP is a type 1 membrane protein with a large extracellular domain, a single membrane-spanning domain, and a short cytoplasmic tail. The A β region of APP (in yellow) includes the first 12–14 amino acids of the membrane domain. The initial enzymatic step for the generation of A β requires proteolysis of APP at β site (amino acid 1 of the A β region). This event liberates a large N-terminal fragment (s β APP) that is rapidly secreted into the extracellular *milieu* and a small C-terminal fragment (β -APP-CTF) of 99 amino acids [25,126,136]. The removal of s β APP most likely induces a conformational change and/or a shift of the β -APP-CTF from the lipid bilayer allowing subsequent cleavage by the γ -secretase multimeric complex. The shift from the bilayer might be necessary to allow the cleavage of the peptide bond, which requires a molecule of water. However, the structure of the active γ secretase complex, which has recently been resolved by electron microscopy, shows a central aqueous chamber with two exit ports [90,120], suggesting that the cleavage could occur without involving a shift of the β -APP-CTF outside of the lipid bilayer. Once generated, the A β peptides aggregate in the brain in the form of plaques. Further cleavage of β -APP-CTF at the ϵ site liberates the signaling active APP intracellular domain (AICD). In addition to the above β/γ pathway, APP can also be cleaved at the α site (between amino acids 16–17 of the A β region), precluding the generation of A β [25,126,136].

Figure 2. Schematic diagram of IGF1-R signaling in mammals and *C. elegans*

The description of the signaling pathway is in the text. The common elements in mammals and worms are shown in red.

Figure 3. IGF1-R acts upstream of p75^{NTR} in regulating Aβ generation during aging

The progressive activation of IGF1-R expression levels and signaling activity in the brain that characterizes aging leads to a switch in the expression levels of neurotrophin receptors TrkA and p75^{NTR} [25,26]. This event requires the adaptor protein IRS2 and class I PI3Ks, which phosphorylate PIP2 at position 3 of the inositol head group activating the second messenger PIP3. The activation of p75^{NTR} leads to a progressive and age-associated activation of nSMase, which results in hydrolysis of SM and liberation of the active second messenger ceramide [25]. Ceramide, in turn, is responsible for the molecular stabilization of BACE1, the rate-limiting enzyme for the generation of Aβ [125]. The question marks indicate the signaling cascades that act downstream of PIP3 and ceramide, which are still unknown. Similarly, the adaptor protein that allows p75^{NTR} to activate nSMase has not been identified yet.

Figure 4. The stoichiometry of binding with NGF influences the signals transduced by TrkA and p75^{NTR}

TrkA can bind NGF both as homo- (TrkA + TrkA; *left panel*) or hetero- (TrkA + p75^{NTR}; *right panel*) dimer [63,82,173]. In contrast, the crystal structure of the p75^{NTR}/NGF complex indicates that the functional NGF dimer binds a single p75^{NTR} monomer (*middle panel*) –even though it does not rule out the possibility for NGF to engage p75^{NTR} as a homodimer [63]. The affinity binding of the NGF dimer: TrkA homodimer does not differ from the NGF dimer:p75^{NTR} monomer (or homodimer). However, the TrkA + p75^{NTR} complex has a higher affinity ($K_d \sim 10^{-10} - 10^{-11}$ vs $K_d \sim 10^{-8} - 10^{-9}$) for NGF (discussed in the text). Therefore, expression of p75^{NTR} on a TrkA background may facilitate the generation of bimolecular (1 TrkA + 1 p75^{NTR}) signaling complexes transducing TrkA –and not p75^{NTR}– signals.

Figure 5. Schematic view of the ceramide and PIP3 “cycles”
The full description of the structures and pathways is in the text.