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Beta-Amyloid Monomer and Insulin/IGF-1 Signaling in Alzheimer's Disease

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Abstract Alzheimer's disease is the most common form of dementia among older people and is still untreatable. While β-amyloid protein is recognized as the disease determinant with a pivotal role in inducing neuronal loss and dementia, an impaired brain insulin signaling seems to account in part for the cognitive deficit associated with the disease. The origin of this defective signaling is uncertain. Accumulating toxic species of β-amyloid, the so-called oligomers, has been proposed to be responsible for downregulation of neuronal insulin receptors. We have found that the nontoxic form of β-amyloid, the monomer, is able to activate insulin/insulin-like growth factor-1 (IGF-1) receptor signaling and thus behaves as a neuroprotectant agent. Our suggestion is that depletion of β-amyloid monomers, occurring in the preclinical phase of Alzheimer's disease, might be the cause of early insulin/IGF-1 signaling disturbances that anticipate cognitive decline.

Keywords β-Amyloid · Insulin · Insulin-like growth factor 1 · Alzheimer's disease

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Introduction

Alzheimer's disease (AD) is the most frequent form of dementia and the most common neurodegenerative disease [1]. The two classical lesions of the disease originally described by Alois Alzheimer, namely, senile plaques and neurofibrillary tangles, are made from proteins (β-amyloid and tau, respectively) that have a pivotal role in inducing dementia, with tau alterations occurring downstream of β-amyloid (Aβ) build-up [2]. Early-onset forms of the disease, occurring before the age of 65, have a familiar aggregation and some of these are caused by rare autosomal dominant mutations in the genes encoding the amyloid precursor protein (APP), and presenilin-1 and presenilin-2, which are all involved in Aβ production [3]. The majority of AD cases have a late onset and are sporadic [3], likely resulting from complex interactions of disease determinants with age-related risk factors (e.g., loss of sex hormones [4] or decline of insulin-like growth factor-1 (IGF-1) function [5]) and systemic disease conditions (e.g., hypercholesterolemia [6] or diabetes [7]), which progressively overcome the brain physiological cognitive reserve. Stranahan and Mattson [8] have recently suggested that the cognitive reserve relies on

insulin/neurotrophic factor signaling and glucose metabolism that set the brain metabolic efficiency.

Approximately, 20 % of neurodegenerative disorders have been linked to some sort of altered insulin action. Isolated peripheral insulin resistance is rare (e.g., in ataxia teleangectasia), and either type I (e.g., in Turner's syndrome, Wolfram syndrome, thiamine-responsive megaloblastic anemia syndrome, and maternally inherited diabetes and deafness) or type II (e.g., in narcolepsy, Prader-Willi syndrome, and Werner syndrome) diabetes are observed. An altered peripheral glucose metabolism has been reported also in Parkinson's disease and Huntington's chorea (reviewed in [9]). Apart from those cases in which evident genetic or biochemical factors indicate a unifying mechanism for both diabetes and neurodegeneration (e.g., mutations of mitochondrial tRNAs directly affecting mitochondria metabolism, [9]), overall, the high prevalence of diabetes in people suffering from neurodegenerative disorders points to the relevance of insulin signaling in the brain capacity to compensate for neuropathology.

In the specific case of AD, a relatively high percentage of affected individuals have peripheral insulin resistance or type II diabetes, but the vast majority of AD patients do not have these diseases [10]. Interestingly, even in the absence of a systemic disease, the AD brain shows impairments in insulin/IGF-1 signaling mechanisms [10] and a deficit of glucose metabolism that anticipates the cognitive decline [11].

The present review discusses first the role of insulin/IGF-1 receptors in the adult brain and the possibility that the function of these receptors might exceed mediation of insulin/IGF-1 actions, then suggests that an impairment of insulin/IGF-1 receptor signaling contributes to AD via a disease-specific mechanism involving the loss of receptor activation by monomers of Aβ.

Insulin and the Adult Brain

Both insulin and insulin receptors (IRs) are present in the brain. Concentrations of insulin in the different brain regions range from 10- to 100-fold greater than in plasma [12], from where insulin is transported in the cerebrospinal fluid through an IR-based saturable transport occurring mostly in the olfactory bulb and in the hypothalamus [12]. Evidence for insulin synthesis in the CNS is less solid; neuronal synthesis has been found in animals [13], but it is unknown whether brain-derived insulin has a significant role in the adult human brain. IRs are highly abundant and localized on both astrocytes and neurons. Glial cells express typical IRs, whereas a brain-specific IR is present in neurons [12]. This brain-specific IR is an IR-A isoform that is less glycosylated than the corresponding peripheral receptor [14]. As different from the IR-B isoform, which has exquisite metabolic actions, IR-A also has mitogenic and anti-apoptotic actions during development [14]. This predominant expression of the IR-A is peculiar to the adult brain, since IR-B is the main receptor in all adult peripheral tissues that depend on insulin for glucose metabolism [14]. The evidence that IR-A, but not IR-B, is a low specificity receptor that is activated with high affinity by ligands other than insulin (i.e., IGF-1 and IGF-2) [15] suggests that many of the effects observed with insulin administration (e.g., neuronal survival or memory enhancement [16, 17]) may physiologically depend on locally produced substances. Accordingly, IR density and insulin contents do not correlate well in the different brain areas [12]. Based on the evidence that dendritic areas receiving rich synaptic inputs have a high IR density [18], a possible correlation between IRs and synaptic activity has been suggested [19]. The obvious functional sequel would be the cognition-enhancing properties of insulin. There are several mechanisms by which insulin may affect memory; these include modulation of neurotransmitter release and enhanced expression of postsynaptic NMDA receptors, which are responsible for the induction of long-term potentiation, the molecular substrate of learning, and memory [20]. Mechanisms directly related to the modulation of glucose uptake have also been suggested. Insulin does not affect whole-brain glucose use, but it increases glucose metabolism in selected brain regions [21, 22] where discrete neuronal populations express insulin-sensitive glucose transporters, namely, GLUT4 and GLUT8 [12, 23, 24]. Because of their somatic cellular localization [25], GLUT4 and GLUT8 are likely to support the metabolic requirements of neuronal cell bodies, but the fact remains that an insulin-insensitive glucose transporter, GLUT3, is present in the neuropil [25] and is likely to uphold synaptic energy provision.

Another level of complexity is added by the evidence that IR is highly homologous to IGF-1R [14], with nearly identical signal transduction pathways potentially leading to the same neuronal effects. The two receptors are receptor tyrosine kinases that, after ligand-induced autophosphorylation, associate with insulin receptor substrate (IRS) adapter proteins. IRS proteins bind to tyrosine phosphate docking sites on the activated receptors, undergo phosphorylation themselves, and then recruit additional SH2-containing signaling proteins. Among these, the phosphatidylinositol-3 kinase (PI-3K), via phosphorylation of protein kinase B (PKB)/AKT, leads to the translocation of facilitative GLUTs from the intracellular pool to the plasma membrane (reviewed in [14]). AKT/PKB also induces the inhibitory serine phosphorylation of glycogen synthase kinase-3β (GSK-3β), which relieves the inhibition of the glycogen synthase and the translation initiation factor eIF2B, thus promoting glycogen and protein synthesis [26]. In addition, PI-3K/AKT

activation may result into: (1) an activation of regulatory-associated protein of mammalian target of rapamycin–mTOR pathway, which regulates cell growth and metabolism [27]; (2) an inhibition of the pro-apoptotic BAD functions; and (3) a suppression of the transcriptional program of FoxO proteins (reviewed in [14]). Finally, another signal transduction protein interacting with IRS proteins is GRB2, an adaptor that in turn elicits the activation of the extracellular-regulated kinase (ERK) cascade leading to mitogenic responses (reviewed in [14]).

IR and IGF-1R expression overlaps in many brain regions [28], and also hybrid insulin/IGF-1 receptors, with an unclear physiological role, are highly present in the brain [29]. Noteworthy, insulin has a low affinity for both IGF-1R and hybrid receptors that, instead, are bounded by IGF-1 with higher affinity than insulin (reviewed in [14]). Specifically, at least in purified receptors from human placenta, the concentration of unlabeled IGF-I for half-maximal inhibition of ^{125}I-IGF-I binding appears to be 0.1–0.2 nM for hybrids and 0.05–0.01 nM for IGF-1R. By contrast, unlabeled insulin required for half-maximal inhibition of ^{125}1-insulin binding is 3–5 nM for hybrids and 0.3–0.5 nM for IRs, confirming the relatively low affinity of hybrids for insulin [30]. The evidence that IGF-1 inhibits 1^{25}1-insulin binding to hybrid receptors or IGF-1R more effectively than insulin (1 and 0.04 nM (IGF-I) vs. 4 and 4 nM (insulin) for hybrid receptors and IGF-IR, respectively) [30] and also stimulates the kinase activity of hybrid receptors more significantly than insulin [31] suggests that hybrid insulin/IGF-1 receptors might have the functional properties of an IGF-1R.

IGF-1 and the Adult Brain

The insulin homolog, IGF-1, is highly produced in the developing brain by IGF-1R-expressing neurons, suggesting local autocrine/paracrine actions of neuronal IGF-1 [32]. In the adult brain, the local production of IGF-1 is low, but serum IGF-1 gets access to the brain through the blood–brain barrier (BBB) [33]. Thus, the first question arises of whether brain IGF-1 and peripheral IGF-1 play different roles in the nervous tissue. Genetic manipulation of IGF-1 contents in transgenic mice has determined the fundamental role of neuronal IGF-1 in the regulation of brain growth and glucose utilization during development [34]. In contrast, brain IGF-1 actions in the adult, and particularly in the control of cerebral glucose metabolism, are not fully understood. Brain IGF-1 does not seem to participate in glucose utilization under normal condition in the adult; however, IGF-1 induction (both neuronal and glial) in response to injury correlates with increases in local glucose utilization [34], suggesting that brain IGF-1 functions at least to provide glucose for biosynthetic and reparative processes. Under these conditions, IGF-1 is believed to substitute for insulin by promoting GLUT4 activity [34]. More ample effects have been reported for serum IGF-1, including modulation of adult neurogenesis [35], neuronal excitability [36], neuroprotection by exercise [37], and cognitive functions [38]. Because of the need for serum IGF-1 in the brain, a peculiar mechanism of regulated passage through the BBB (beside a tonic input) exists, according to which neuronal activity is coupled to the entrance of serum IGF-1 and, in turn, this peripheral input of IGF-1 to the brain might sustain the activity of already active neurons [39]. This feedforward mechanism has been named "neurotrophic coupling" and suggested to be a determinant of the cognitive reserve of the brain [33].

The interrelationship between IGF-1 and insulin actions remains to be established. As in the periphery, brain insulin signaling could depend on proper IGF-1 signaling via hybrid receptors [40], and/or direct facilitation of insulin signaling could occur via IGF-1 co-stimulation of IRs [41]. Interpretation remains open until a more comprehensive analysis will be available, which includes the potential context-specific role of IGF-binding proteins [42] in setting IGF-1 activity with respect to insulin, the specific properties of hybrid insulin/IGF-1 receptors, and pathophysiological conditions that may affect hybrid assembly [29].

Insulin, IGF-1, and the AD Brain

Possible defects in insulin/IGF-1 signaling have been investigated in postmortem AD brains mainly by immunohistochemical analysis [43, 44]. Hoyer et al. first reported a reduction of IRs and receptor-kinase activity markers in the tissue [45]. Recently, a more detailed analysis carried by Moloney et al. [46] has revealed that the localization of both IRs and IGF-1Rs in AD neurons is away from the plasma membrane and concentrated in the cytosol, suggesting that these neurons become resistant to insulin/IGF-1 signaling in the course of the disease. Accordingly, decreased levels of IRS-1 and IRS-2, key adaptors for both IR and IGF-1R signaling, are disease stage-related and correlate strongly with neurofibrillary tangle pathology [46]. Since insulin and IGF-1 engage the same downstream adaptors (i.e., IRS-1/IRS-2 and Shc) to drive the activation of PI-3 kinase and Ras/ERK kinase pathways [14], determining the relative contribution of IRs and IGF-1R to this defective signaling system is particularly challenging. One difference stays in the evidence that IGF-1R is highly expressed in AD astrocytes, and increasing

IGF-1R levels, but not IR levels, accumulate within and around plaque pathology both in the AD brain and in 18-month-old Tg2576 mice, a transgenic model of AD [46]. This finding is consistent with a reparative role of IGF-1 under injury conditions [34] and might reflect the AD brain attempt to cope with progressing neuropathology by activating the IGF-1 signaling system.

Genetically engineered model targeting either the IGF-1 or the insulin signaling might help to identify relevant steps for AD pathology in the absence of a systemic disease condition (i.e., diabetes). Heterozygous inactivation of IGF-1R in the mouse brain has confounding effects resulting from a reduced somatotopic tone with ensuing decelerated animal growth and delayed mortality [47]. Even so, it is interesting that the IGF-1R-deficient brain shows a compensatory overactivation of the remaining IGF-1Rs so that the animals exhibit only a subtle impairment of exploratory behavior [47]. On the other hand, brain-specific IR knockout mice exhibit the features of reduced insulin signaling, including the lack of activated PI-3K and the presence of activated GSK-3β and phosphorylated tau protein, but not cognitive dysfunctions [48].

Both spontaneous and experimentally induced animal models of diabetes have been used to search for the presence of AD-like pathology [49]. The limit of this approach is that mice, due to the intrinsic nature of their own Aβ, cannot produce the extracellular Aβ aggregates [50] that have a pivotal role in AD; therefore, all data are biased by the lack of evident Aβ-related neuronal pathology.

Instead, the induction of both type 1 and type 2 diabetes in transgenic mouse models of AD appears to exacerbate brain pathology [49], confirming the notion that diabetes-related metabolic disturbances are intervening promoting factors in the pathogenic cascade leading to AD [51].

The diabetogenic substance streptozotocin has been found to induce an isolated insulin-resistant brain state (IRBS) months after a single intracerebroventricular (i.c.v.) injection in rats [52]. After STZ i.c.v. administration, regionally specific alterations have been reported in the rodent brain, including a reduced IGF-1R gene expression in the cortex and striatum [53], a reduced IR gene expression in the frontoparietal cerebral cortex and hippocampus [54], and an increase in the non-phosphorylated active GSK-3 in the hippocampus [52]. Interestingly, when the IRBS is induced in AD transgenic mice by the i.c.v. injection of streptozotocin, mice neuropathology is exacerbated [55].

A unifying interpretation of the data is that the impairment of IRs and IGF-1Rs, which per se represents a neuronal stressor, is a contributing factor in the pathogenesis of AD (see after). That said, we still need to determine what is directly responsible for the defects in the insulin/IGF-1 system, which have been found in postmortem AD brains.

The Nature of Aβ

Aβ (a 40–42 amino acid peptide) is normally produced by neuronal cells through the endoproteolytic cleavage of APP [56] and is exported outside the brain by the low density lipoprotein receptor-related protein-1. Aβ is also synthesized in the periphery and gets into the brain via the receptor for advanced glycation end-products [57]. This tightly regulated bidirectional trafficking of Aβ across the blood–brain barrier, together with Aβ clearance by different metalloproteases [58, 59], is aimed at maintaining the peptide into a specific range of concentrations. As other aggregation-capable molecules, Aβ has a defined equilibrium state between monomers and oligomers such that it is primarily monomeric below a certain concentration [60]. Thermodynamic studies predict that, at the estimated in vivo concentrations [61], soluble Aβ is mainly monomeric [60], and thus oligomers must originate in localized compartments (e.g., cell membranes) and under pathological conditions. In vitro, many different types of Aβ assembly forms, including protofibrils, annular structures, paranuclei, Aβ-derived diffusible ligands, and globulomers have been described [62]. In vivo, pre-fibrillar assemblies of Aβ, known as soluble Aβ oligomers, have been demonstrated to correlate better with dementia than plaques [63], suggesting that oligomers represent the primary neurotoxic species in AD. Natural oligomers of human Aβ disrupt synaptic functions when added in vitro to hippocampal slices [64] or microinjected in living rats [65], where they also interfere rapidly and reversibly with the memory of a learned behavior [66]. The neurotoxicity of Aβ oligomers has been confirmed by distinct experimental approaches, including the use of synthetic or native Aβ peptides, cell cultures overexpressing APP, and APP transgenic mice [65, 67].

Mechanisms of Aβ toxicity have been largely investigated [68, 69]. However, since the majority of the reviews on the topic of cell death in AD are largely focused on the toxic actions of Aβ, there is no need to repeat the knowledge here. On the contrary, few studies have addressed the physiological activities of Aβ, although indirect evidence for the implication of Aβ in the normal neuronal metabolism occasionally appears in published papers. Thus, the in vitro inhibition of either β- or γ-secretase (the two enzymes required for APP metabolism and Aβ production) has been reported to affect the viability of cortical neurons, which are rescued by adding picomolar concentrations of Aβ [70]. The addition of Aβ to cultured neurons has been shown to enhance metabolism via the induction of hypoxia-inducible factor-1 [71]. Finally, the finding that the 1–28 fragment of Aβ has a neurotrophic activity [72] dates back to 1989.

More recent findings provide hints towards the concept of a physiological role for Aβ. β-Amyloid precursor protein cleavage enzyme (BACE 1) knockout mice, which lack Aβ

formation, have behavioral deficits [73] and synaptic dysfunctions [74, 75]. Along this line, picomolar concentrations of synthetic Aβ, which likely approximate the endogenous level of the peptide, have been shown to enhance synaptic plasticity and memory in the rat hippocampus [76].

To date, several lines of evidence indicate that Aβ is released in normal brains during synaptic activity. Kamenetz and colleagues first reported that Aβ is secreted from neurons in response to neuronal activity and that, in turn, it downregulates excitatory synaptic transmission [77], thus providing a physiological homeostatic control of neuronal activity. In rodent hippocampal cells and slices, acute increases in Aβ levels expand reversibly the number of active synapses [78]. In the same system, enduring inhibition of Aβ clearance results in a reduction in the number of synapses [78], suggesting that Aβ functions at least as a modulator of synaptic activity requiring a fine balance between production and clearance. Although the nature of the endogenous released Aβ has not been determined, it seems reasonable to assume that it is released in its nontoxic monomeric state.

Aβ and the Insulin/IGF-1 System in AD

The existence of different Aβ forms (i.e., nontoxic monomers and toxic oligomers) adds complexity to the understanding of the link between the dysregulation of the insulin/IGF-1 signaling, which has been reported in AD [44], and Aβ peptide itself. One level of interaction is established by the fact that insulin and IGF-I have a direct effect on the metabolism and clearance of Aβ. Insulin directly increases Aβ secretion from neurons by accelerating peptide trafficking to the plasma membrane [79] and promotes Aβ degradation by regulating the expression of the insulin-degrading enzyme (IDE), a metalloprotease that catabolizes both

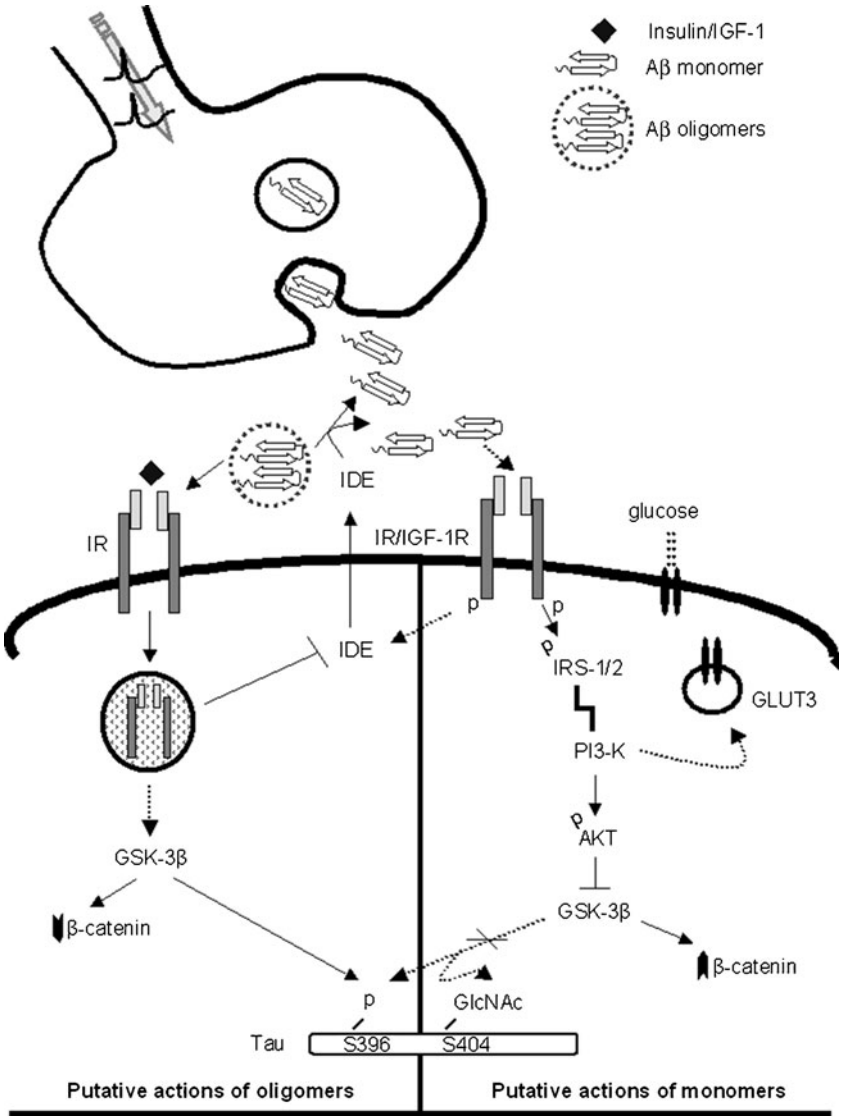

Fig. 1 Possible interactions between Aβ and the insulin/IGF-1 receptor signaling. Aβ monomers released at the synapse (*right panel*) promote the activation of the insulin/IGF-1 signaling pathway, resulting into: (1) self-maintained levels of Aβ monomers (via the activity of the insulin-degrading enzyme, IDE), (2) sustained neuronal survival (via β-catenin-regulated gene transcription), and (3) decreased tau phosphorylation (via GSK-3β inhibition). Aβ monomers could also be responsible for synaptic glucose provision (via GLUT3 translocation) and increased *O*-GlcNAcylation of tau protein, which opposes tau hyperphosphorylation. On the other side, accumulating Aβ oligomers (*left panel*) induce the downregulation of insulin/IGF-1 receptors that will exacerbate Aβ oligomerization with ensuing neurotoxicity. *Dashed lines* refer to proposed but not proven mechanisms

insulin and Aβ [80, 81]. On its side, IGF-1 increases Aβ clearance from the brain by enhancing transport of Aβ-carrier proteins (e.g., albumin and transthyretin) into the brain [82]. Hence, insulin and IGF-1 seem to act in conjunction as regulators of brain Aβ content, and systemic conditions altering their interplay could indirectly promote Aβ oligomerization. For example, aging (the main risk factor for AD) is a associated with low serum levels of IGF-1 [5], and type 2 diabetes is associated with peripheral hyperinsulinemia and low brain insulin levels that could result in reduced Aβ clearance [83].

Another level of interaction is at the receptor level. Zhao and coworkers have suggested that the state of insulin resistance observed in the AD brain is a response to Aβ oligomers, which downregulate neuronal surface IRs [84]. In contrast, IR activation would promote the reduction of oligomers to monomers via the IDE activity [85]. Our own contribution to the field is the demonstration that Aβ monomers support the survival of developing neurons under conditions of trophic deprivation and protect mature neurons against excitotoxic death. Both effects result from the stimulation of a receptor of the insulin/IGF-1 system and are mediated by the activation of the PI-3K pathway [86]. Among the survival pathways that are stimulated by insulin/IGF-1, such as the ERK1/2 pathway and the PI-3K pathway [14], Aβ monomers appear to specifically activate the last one, thus leading to an enhanced phosphorylation of Akt and also to an enhanced Ser9 phosphorylation (inhibition) of the Akt substrate, GSK-3β [86]. Inhibition of GSK-3β promotes cell survival through a variety of mechanisms including a reduced degradation of β-catenin, which activates the transcription of protective genes [87]. Accordingly, the neuronal levels of β-catenin show a rapid and substantial increase in response to Aβ monomers [86]. By inhibiting GSK-3β, Aβ monomers could also decrease the overall phosphorylation of tau [88], a process that appears to be facilitated by decreased tau *O*-GlcNAcylation [89]. Interestingly, *O*-GlcNAcylation processes depend on glucose metabolism and a reduced *O*-GlcNAcylation seems to be the link between low brain glucose metabolism and tau pathology in AD [89]. Whether or not Aβ monomers can increase the *O*-GlcNAcylation of tau protein, by supporting neuronal glucose provision, remains to be established.

A possible model of interaction between the different Aβ species and the IR/IGF-1R system could be the following: accumulating Aβ oligomers impair insulin/IGF-1 signaling, which exacerbates Aβ oligomerization and toxicity within a feedfoward mechanism. Aβ monomers, by sustaining the insulin/IGF-1 signaling, promote survival, impede oligomerization, and contribute to the homeostatic control of the system (Fig. 1).

At present, it is unknown whether Aβ monomers bind directly to IRs and/or IGF-1Rs, although evidence suggests that monomers have specific recognition sites on the neuronal surface [86]. The unheralded importance of the finding that Aβ monomers are able to activate IRs/IGF-1Rs would be the evidence that the peptide is produced and released to sustain transient needs in synaptic modeling, neuronal energy provision, and protection in the absence of brain insulin/IGF-l fluctuations.

Conclusion

The nontoxic form of Aβ, the monomer, appears to behave as a brain protective factor able to regulate synaptic activity and to activate insulin/IGF-1 receptor signaling. Depletion of Aβ monomers in the preclinical phase of AD, resulting from pathological Aβ aggregation, could be responsible for early defects of insulin/IGF-1 receptor signaling (including the deficit of glucose metabolism that anticipates cognitive decline [11]), thus participating to the overall AD pathology.

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