Insulin-like peptides signaling in Alzheimer’s disease: on the road to alternative therapeutics
Angel Trueba-Saiz and Ignacio Torres Aleman

Several decades ago, the observation that Alzheimer’s disease (AD) presents early disturbances in brain glucose metabolism prompted the notion of insulin dysregulation in this condition. Since then, abundant epidemiological evidence has associated AD to insulin resistance as in type 2 diabetes mellitus (T2DM). However, because the role of insulin in brain glucose handling is not clear, it cannot yet be firmly stated whether a T2DM-like condition in the brain might be cause or consequence of AD pathology. Additionally, it is becoming apparent that insulin and the closely related insulin-like peptides (i.e. IGF-I and IGF-II) modulate cognition in normal physiology, whereas robust evidence indicates central impairment of insulin/IGF-I signaling in AD patients. This may provide new leads into the pathology, even though there is still controversy on the role of these hormones in the pathogenesis of Alzheimer’s dementia. At any rate, preliminary clinical trials using either intranasal insulin or IGF-I stimulating therapy show promising results. The present review summarizes major findings in the field during the last years, an intense period of research in this area.

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Central versus peripheral insulin-like signaling in cognition

Although ILPs, including insulin at low levels [13], are locally synthesized in the adult brain, a substantial contribution to brain ILP levels arises from the periphery, as discussed elsewhere [1]. A mechanism for the entrance of serum IGF-I into the brain has been described [14]. However, much less is known about how serum insulin gets into the brain [15]. As for IGF-II, because it is produced by the choroid plexus, a direct secretion into the CSF may explain its presence in the brain [16]. A summary of the different sources of brain ILPs and mechanisms of entrance into the brain of circulating ILPs is shown in Figure 1. From these data we may state that...
ILPs are able to exert endocrine and paracrine modulation of neuronal activity that may eventually differentially impinge on learning and memory processes (Figure 2).

As recently reviewed [17], there are many mechanisms responsible for the positive effects of insulin on cognition including synaptogenesis, synapse remodeling, LTP enhancement, regulation of acetylcholine and norepinephrine expression, and increased cerebral glucose metabolism. Many pilot trials have demonstrated cognitive benefits of insulin either in healthy subjects or in patients with MCI or AD [18]. As for IGF-I, reported mechanisms linking it to cognition involve angiogenesis, enhanced neuronal excitability, synaptic and neuronal plasticity, neurogenesis, enhancement of brain insulin sensitivity or modulation of different neurotransmitters [1]. Likewise, hippocampal IGF-II has been noted to play a key role in memory consolidation [19], and more recently, to improve memory retention when administered systemically [20]. Collectively, the actions of ILPs on cognitive processes may be summarized in their ability to modulate neuronal plasticity [21], neurotransmitter function [22] and tissue remodeling [1,16]. However, whether pro-cognitive roles of ILPs may vary depending on their source is not (yet) a matter of debate. Tacitly, insulin actions in the brain are ascribed to systemic insulin [23], while IGF-II actions are usually ascribed to local production [24*] given that most brain IGF-II may derive from the choroid plexus and meninges. The observation that IGF-I exert pro-cognitive actions from both local and endocrine sources opens the possibility that for insulin and IGF-II this might also be the case [1].

**Diabetes and AD**

Currently, there is a tremendous effort to identify the ultimate mechanistic link, if any, between diabetes and AD. Insulin dysfunction may either predispose to AD [25], or alternatively, AD may increase the susceptibility to develop diabetes [26*,27]. It is also possible that both diseases share common pathogenic processes [28], although genetic factors for T2DM do not relate to AD risk [29]. At any rate, numerous reviews summarize evidence of a link between T2DM and cognitive deterioration. Mechanistic explanations range from indirect microvascular [30] or cholesterol-related impairments [31], to direct actions of insulin resistance on brain cells.
The latter is known to induce tau hyperphosphorylation, a toxic alteration generally considered downstream of amyloidosis in AD [33]. However, abnormal phosphorylation of tau may be produced by insulin resistance independently of Aβ [34–36], although this is still a matter of debate. Although previous studies and newer ones detect abnormal tau phosphorylation after exposure to unhealthy diets leading to insulin resistance [34], others either have failed to confirm it [37], or argue that insulin resistance only worsens pre-existing tauopathy [35].

In parallel, low CSF insulin has been reported in early AD [38], which may indicate impaired passage of serum insulin through the blood–brain-barrier (BBB). Lower input of serum IGF-I into the brain has also been detected in these patients [39,40]. In a different cohort, IGF-II was found to be higher in the CSF and lower in the plasma of AD patients, whereas IGF-I remained stable [41]. Besides possible alterations in BBB traffic of these peptides, other types of potential pathogenic processes of insulin resistance impinging in AD pathology include glucotoxicity, cardiovascular compromise, or inflammation [42]. Relationships between disturbed peripheral glucose handling and early cognitive deterioration [43] or even AD have also been reported [44]. Based on all these observations, the use of anti-T2DM drugs for AD has been favored [45].

**Resistance to ILPs as a cause and/or consequence of Alzheimer’s disease**

The proposal that a combined resistance to both IGF-I and insulin may initiate AD pathology [46] was later supported by observations based on biomarkers and...
direct stimulation of brain tissue [6**,47,48]. In AD mice, treatment with insulin sensitizers normalized these markers and improved symptoms [5]. However, these perturbations in ILP signaling were described in already diseased brains and in other neurodegenerative conditions [48], precluding its significance in the development of AD. Nevertheless, there is additional evidence supporting that AD is caused by ILP resistance. For instance, an AD-like brain glucose hypometabolism is associated with greater insulin resistance and subtle cognitive deterioration in apparently normal subjects [49*], suggesting that metabolic impairment precedes cognitive deterioration. In this vein, it has been reported that neuronal insulin resistance triggers behavioral deficits commonly associated to AD [50]. The default mode network of functional brain connectivity, that is altered in AD [51], is disturbed in cognitively normal women with pre-symptomatic insulin resistance [52]. In addition, low serum IGF-I, also associated to T2DM [53], is related to deterioration of cognitive (mild cognitive impairment) and physical function (gait), two common co-morbidities of human aging [54]. Prior work had extensively documented a link between serum IGF-I and cognitive performance [55]. Furthermore, reduced passage of serum IGF-I into the brain, probably the result of IGF-I resistance at the BBB, has been suggested as an early marker for AD [40]. The proposed experimental approach of associating metabolic impairment related to insulin/IGF-I function with AD pathology [56] has yielded abundant valuable information in later years. For example, impaired insulin function increases Aβ accumulation through increased BACE1 activity and APP levels [57], while reduced IGF-I [58] or insulin function due to high fat diet [59] accelerates AD in mouse models. Further, insulin dampens exacerbated AD pathology induced by high fat diet [60]. It is important to stress out that energy deprivation alone can also produce AD-like pathology, including increased BACE1 levels or tau phosphorylation [61,62]. Other candidate mechanisms linking deteriorated cognition with ILP dysfunction may involve lipoprotein receptor associated protein 1 (LRP1), which is a risk factor for AD and interacts with both insulin and IGF-I signaling, even controlling its BBB traffic. LRP1 participates in brain glucose handling, and is actively involved in APP metabolism, Aβ clearance, and even AD pathology [63*,64].

Alternatively, other observations suggest that ILP resistance is originated by AD pathology [65]. Examples abound; ILP resistance arises after injection of Aβ in normal monkey brains [66] or rats [67]. A similar procedure elicits peripheral metabolic impairment [26*]. Because insulin does not appear to control brain glucose uptake [2], glucose hypometabolism in AD may be independent of insulin dysfunction and, in that case, could be placed as an upstream mechanism of insulin resistance [68]. So far, deteriorated glucose uptake by brain endothelium associated to brain amyloidosis has been shown to contribute to ongoing AD pathology [69*], and has even been proposed as a biomarker of the transformation of amnesic MCI into AD [70].

Therapeutic use of ILPs in AD

Current therapies for AD patients, based mostly on acetylcholinesterase inhibition, offer modest benefits [71]. However, as there are no other available approaches they constitute the mainstream treatment, even though disease progression is unaltered. This is the reason why the search for new compounds is restless.

Numerous mechanisms have been invoked in the beneficial actions of restoring ILP function on AD-related pathology [72,73]. An important mechanistic insight in this regard can be gathered by analyzing the impact of life-style factors on ILP function and its relation to AD risk factors. Using this approach it was predicted that risk factors in AD related to life-style could all be explained by their impact on ILP homeostasis [46]. Recent clinical intervention studies addressing life-style factors have yielded promising results, opening the possibility of practical preventive measures for AD based in behavioral modification [74*]. At any rate, recent observations confirm prior findings of a therapeutic potential of ILPs. Clinical trials using intranasal insulin or its analogs in aging subjects confirm them as a feasible therapeutic alternative for cognitive loss [8**]. Intriguingly, increments of brain insulin levels after intranasal application only reach the pM range, which is far below the concentration needed to activate IRs [18]. This poses the question of how insulin could be affecting cognition. Despite this, evidence supporting its therapeutic use keeps accumulating. Studies in animal models provide additional details. For instance, intranasal insulin normalized Ca2+-dependent hippocampal after-hyperpolarization in aging rats, an electrophysiological alteration found in aged animals [75]. Conversely, intranasal insulin improved memory after brain inflammatory challenge only in young rats [76]. In addition, short-term treatment with intranasal insulin ameliorated pathology in a mouse model of AD, including reduced Aβ levels [77], and even an acute bolus of insulin was able to reverse worsening of Aβ pathology by a high fat diet in mice [60]. Mechanistic insight is also obtained from human studies. Resting-state hippocampal connectivity in humans is reduced in AD and under conditions of insulin resistance [52], whereas intranasal insulin enhanced it in diabetic patients [78]. Also, insulin increases odor memory in young healthy adults [79] and cerebral blood flow [80], two processes early altered in AD.

Conversely, the therapeutic potential of IGF-I for cognitive disorders is controversial. Animal studies demonstrated that increasing serum IGF-I was helpful against AD symptoms [81], whereas others found no such an effect.
Table 1

Past, present & future of clinical trials using ILPs to treat AD. Data was collected through a systematic search (dating back 5 years) on Pubmed & Clinicaltrials.gov using the terms ‘insulin’ (or ‘IGF’ or ‘GHRH’) & ‘Alzheimer’ (& also ‘trial’ in Pubmed). Due to space limitations, other ILP-based strategies such as diet interventions or anti-diabetic agents (e.g. metformin, rosiglitazone, among others) were not included. AD: Alzheimer’s disease, CA: cross-over assignment, CBF: cerebral blood flow, CSF: cerebrospinal fluid, DB: double-blinded, FDG-PET: fluorodeoxiglucose positron emission tomography, geno: genotype, ILP: insulin-like peptide, IU: international units, MC: multi-center, MCI: mild cognitive impairment, MRI: magnetic resonance imaging, N/A: non-available, oGTT: oral glucose tolerance test, PA: parallel assignment, PIC: Placebo-controlled, R: randomized, SC: single-center, yo: years old. Note: the exact controlled co-morbidities may vary along the studies. *: estimate number of participants.

<table>
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<tr>
<th>Trial ID</th>
<th>ILP/analog</th>
<th>Phase</th>
<th>Trial design</th>
<th>Demographics</th>
<th>Diagnostic Other parameters</th>
<th>Treatment Route</th>
<th>Groups &amp; dose</th>
<th>Length</th>
<th>Results</th>
<th>Publications</th>
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<td>NCT02503501</td>
<td>Insulin glulisine (rapid acting)</td>
<td>II</td>
<td>SC, PA, PIC, DB, R</td>
<td>Both genders. Age 50–90 yo. No relevant co-morbidities. Includes non-insulin dependent diabetics. Biomarkers: CSF (Aβ, tau, p-tau), FDG-PET.</td>
<td>Intranasal (twice daily)</td>
<td>Placebo, 40 IU: 2 × 20 IU/day</td>
<td>6 months</td>
<td>Negative. Status: not yet recruiting. Study Director: Michael H Rosenbloom, MD</td>
<td>Estimated end date September 2017</td>
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<td>Trial ID</td>
<td>ILP/analog</td>
<td>Phase</td>
<td>Trial design</td>
<td>Demographics</td>
<td>Treatment</td>
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<td>NCT01595646</td>
<td>Regular insulin</td>
<td>II</td>
<td>SC, PA, PIC, DB, R</td>
<td>36 MCI &amp; AD (mild/mod)</td>
<td>Both genders. Age 50–89 yo. ApoE geno No relevant co-morbidities. Excludes diabetics. Biomarkers: oGTT, CBF, plasma &amp; CSF (Aβ, tau, p-tau, inflammation)</td>
<td>Intranasal (twice daily)</td>
<td>Placebo, 40 IU Regular: 2 x 10 IU/day 40 IU Detemir: 2 x 20 IU/day</td>
<td>120 days</td>
<td>Negative. Status: active, not recruiting. Study Director: Suzanne Craft, PhD Estimated end date: September 2015</td>
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<td>NCT01547169</td>
<td>Insulin-detemir (long acting)</td>
<td>II</td>
<td>SC, PA, PIC, DB, R</td>
<td>MCI (39), AD (21) MMSE &gt; 15</td>
<td>No relevant co-morbidities. Excludes diabetics. No intergroup differences in: age (50–89), education, BMI, cognition, gender (both), treatment, ApoE geno</td>
<td>Intranasal (twice daily)</td>
<td>Placebo, 20 IU &amp; 40 IU</td>
<td>21 days</td>
<td>Positive. Positive effects for the 40 IU group. Improvement of overall verbal memory (only in ApoE-ε4 carriers), and verbal and visuospatial working memory Claxton et al., 2015</td>
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<td>NCT01145482</td>
<td>Insulin aspart (rapid acting)</td>
<td>N/A</td>
<td>SC, CA, PIC, DB, R</td>
<td>AD (probable) MMSE &gt; 15</td>
<td>Both genders. Age over 21. No relevant co-morbidities. Excludes diabetics</td>
<td>Intranasal (one dose)</td>
<td>20 IU — PI 20 IU washout: N/A</td>
<td>Acute (15 min, 2 sessions)</td>
<td>Positive. Inconclusive. No comprehensive analysis provided for data on cerebral glutamate concentration or cognitive performance. Study Director: Andreaa P Haley, PhD Not found. Completion date: April 2014</td>
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<td>SC, CA, PIC, DB, R</td>
<td>Mild to mod AD MMSE 18 to 26 ApoE-ε4 carriers</td>
<td>Both genders. Age 65–85 yo No relevant co-morbidities. Excludes diabetics</td>
<td>Intranasal (one dose)</td>
<td>20 IU — PI 20 IU washout: 7 days</td>
<td>Acute (20 min, 2 sessions)</td>
<td>Rosembloom et al., 2014</td>
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### Table 1 (Continued)

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<td>SC, CA, PIC, DB, R</td>
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<td>40 IU → Pl PI → 40 IU washout: 48 h</td>
<td>Acute (30 min)</td>
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<td>GHRH analog (IGF-1 inducer)</td>
<td>II</td>
<td>SC, PA, PIC, DB, R</td>
<td>Healthy older adults (76) &amp; aMCI (61)</td>
<td>Subcutaneous</td>
<td>Placebo GHRH (1 mg/day)</td>
<td>20 weeks</td>
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Diet, behavior and brain function

[82], or even proposed that IGF-IR antagonists [83] or IGF-IR reduction [84] should be used. Interestingly, the latter study observed high serum IGF-I levels when the IGF-IR is eliminated in forebrain neurons [84]. Thus, more research is needed to identify when and how much IGF-I, if any, must be supplemented to fight AD; for example, when given early in the course of the disease, abnormally high brain IGF-IR levels are normalized [85]. This agrees with previous suggestions that IGF-I treatment is only beneficial to normalize pre-existing deficits in IGF-I signaling [86]. In fact, time of treatment may be crucial in AD; one of the reasons adduced to explain the failure of many clinical trials evaluating anti-amyloid therapies during the last decade was the advanced degree of pathology of the patients used in the studies [87]. Indeed, a pilot clinical trial with growth hormone releasing hormone, which increased circulating IGF-I within the physiological range, improved cognitive function in MCI and healthy older adults [10], whereas the use of a potent GH/IGF-I secretagogue in subjects with mild to moderate AD showed no slowing of disease progression [88]. As pointed out above, the use of IGF-II seems an encouraging alternative due to its potent cognitive enhancing properties in pre-clinical studies. Other approaches include the use of anti-diabetic drugs to prevent or modify the course of AD, such as glucagon-like peptide 1 (GLP 1) agonists (e.g. exenatide, liraglutide) or dipeptidyl peptidase 4 inhibitors (that increase GLP 1 levels) that are oriented to increase insulin-like signaling by circumventing ILP resistance and readily cross the BBB [11,89]. A summary of current trials with ILPs is shown in Table 1.

Conclusion

Alzheimer’s disease (AD) presents early disturbances in brain glucose handling. Based on this, a role for insulin dysregulation in AD was proposed over twenty years ago, but until recently this idea has gained full credit. Two major facts account for this new appreciation of the pathogenic role of brain insulin (and IGF-I) resistance in AD. First, amyloid-based theories of AD pathology have yet to deliver, so new or revisited hypothesis are flourishing. Second, a role of insulin and insulin-like peptides (IGFs) in human cognition is starting to emerge. Although the evidence of a link between glucose intolerance, insulin/IGF-I resistance and AD is now overwhelming, the search for mechanisms underlying a common thread between T2DM and AD is still open. The fact that glucose disturbances are found in other neurodegenerative conditions opens the question of a central role for brain insulin/IGF-I signaling in neurodegenerative processes in general. Because there is still no firm evidence that dysregulation of insulin and insulin-like factors are downstream of the amyloid cascade, operationally we still favor the idea that these alterations constitute pathogenic triggers of sporadic AD.

Conflict of interest statement

Nothing declared.

Acknowledgments

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References and recommended reading

Papers of particular interest, published within the period of review, have been highlighted as:

- of special interest
- - of outstanding interest


This work provided robust evidence of insulin and IGF-I resistance in the brain of Alzheimer’s patients.


This is one of the latest studies documenting beneficial actions of intranasal insulin in AD patients.


A mechanism linking serum IGF-I and brain activity is provided in this work.

A recent review carefully documenting the striking lack of data on how serum insulin reaches the brain.


This work describes a mechanism for the pro-cognitive actions of IGF-II.

One of the latest studies from a group that is decisively contributing to our knowledge on the insulin/Alzheimer connection.


Type 2 diabetes mellitus is not associated with increased risk for Alzheimer's disease.

Proteins that increase risk for type 2 diabetes mellitus are not associated with increased risk for Alzheimer's disease.


50. Of many of one of many studies from a group that has taken insulin treatment to the clinic.


64. A new mechanism linking glucose metabolism with insulin function in the brain through the multisecalphase transporter LR1P1 is described in this work.


Insulin peptides and Alzheimer disease


