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Hypothesis

Unraveling Alzheimer's: Making Sense of the Relationship between Diabetes and Alzheimer's Disease[1]

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Abstract. Numerous studies have documented a strong association between diabetes and Alzheimer's disease (AD). The nature of the relationship, however, has remained a puzzle, in part because of seemingly incongruent findings. For example, some studies have concluded that insulin deficiency is primarily at fault, suggesting that intranasal insulin or inhibiting the insulin-degrading enzyme (IDE) could be beneficial. Other research has concluded that hyperinsulinemia is to blame, which implies that intranasal insulin or the inhibition of IDE would exacerbate the disease. Such antithetical conclusions pose a serious obstacle to making progress on treatments. However, careful integration of multiple strands of research, with attention to the methods used in different studies, makes it possible to disentangle the research on AD. This integration suggests that there is an important relationship between insulin, IDE, and AD that yields multiple pathways to AD depending on the where deficiency or excess in the cycle occurs. I review evidence for each of these pathways here. The results suggest that avoiding excess insulin, and supporting robust IDE levels, could be important ways of preventing and lessening the impact of AD. I also describe what further tests need to be conducted to verify the arguments made in the paper, and their implications for treating AD.

Keywords: Alzheimer disease, amylin, amyloid beta-peptide, dementia, diabetes mellitus, insulin, insulysin, metalloproteases, neprilysin

Alzheimer's disease (AD) is a devastating, fatal disease that affects an estimated 5.2 million Americans, and 44 million people worldwide. It is a disease that is often harder on the families and caregivers of the patient than on the patient themselves. The direct costs to the US of AD in 2014 were estimated to total $214 billion [1]. Adding in the informal costs (the costs of family members and friends providing unpaid care to those with dementia) doubles those figures. The bulk of the financial burden of AD is not due to the cost of drugs or doctor's visits; instead, the vast majority (75–84%) of the expenses go to nursing home care, plus formal and informal home care [2]. The drugs currently available for AD (primarily cholinesterase inhibitors and memantine) offer only incremental improvements in symptoms—they do not stop the progression of the disease [3–6]. Analysts estimate that AD will cost $1.5 trillion per year US by 2050 if a more effective treatment is not developed [7].

[1]New York University Working Paper.

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AD has been a difficult puzzle to solve, in part because of an abundance of seemingly incongruent findings. For example, though many studies have identified a significant association between type 2 diabetes mellitus (T2DM) and AD (see the review provided in Table 1), these studies have often come to different conclusions about the causal mechanism and its implications for treatment. Some studies, for example, have concluded that insulin deficiency is primarily at fault, suggesting that intranasal insulin or inhibiting the insulin-degrading enzyme (IDE) could be beneficial [8–11]. Other research has concluded that hyperinsulinemia is to blame, which implies that intranasal insulin or the inhibition of IDE could exacerbate the disease [12–16]. Similarly, recent studies have found a strong association between AD and amylin, a peptide hormone co-secreted with insulin [17–20]. Jackson et al. and Srodulski et al. found that amylin, like the amyloid-β (Aβ) protein thought to be central to the pathology of AD, forms amyloid plaques in the brain, leading them to conclude that amylin might be another amyloid with a causal role in dementia. Oskarsson et al. similarly found that amylin and Aβ were colocalized in plaques in the brain, leading them to draw similar conclusions. However, two other recent studies came to an opposite conclusion: they obtained results suggesting that amylin provides a neuroprotective effect that reduces the symptoms of AD [21, 22].

Despite these seemingly incongruent results, careful integration of multiple strands of research (with attention to the methods used in different studies) makes it possible to disentangle the research on AD. Such an integration points to the likelihood of a relationship between insulin, IDE, and AD that yields multiple pathways to the disease depending on the where deficiency or excess in the cycle occurs.

I posit that the weight of the evidence suggests that under normal circumstances, insulin upregulates the expression of IDE, which subsequently breaks insulin down [23, 24]. IDE, however, also plays important roles in breaking down Aβ and other amyloidogenic peptides. This system can malfunction and lead to AD in at least four different ways as outlined below (see Fig. 1) Evidence for each of these will be reviewed in turn in the sections that follow:

1) An individual with severe insulin deficiency (e.g., undertreated type 1 diabetes mellitus, T1DM) may have inadequate IDE activity, resulting in the accumulation of Aβ (and other protein aggregates) in the brain [23, 25, 26].

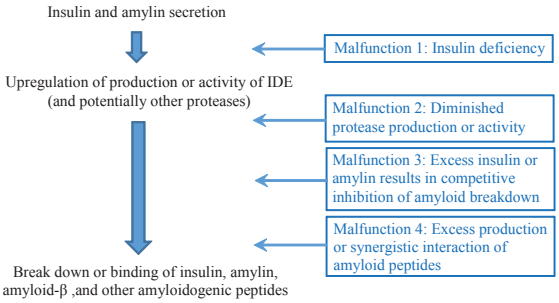

Fig. 1. The insulin-protease-amyloid degradation pathway and its potential malfunctions.

2) An individual with diminished IDE (or similar protease) production may end up with accumulation of Aβ and amylin plaques in the brain [27–32].
3) If an individual has exceptionally high levels of insulin (and amylin) in the body (e.g., due to early stages of T2DM), the insulin and amylin may competitively inhibit the breakdown of Aβ, resulting in AD [30, 33–35].
4) An individual may produce more than a typical level of an amyloidogenic peptide, or experience synergistic interactions between amyloidogenic peptides, leading to deposition that outpaces clearing by IDE and similar proteases [17–19, 36–42].

INSULIN, INSULIN DEGRADING ENZYME, AND ALZHEIMER'S DISEASE

The potential roles of insulin and insulin degrading enzyme in AD and other dementias came under scrutiny because of the strong association between T2DM and AD. I thus begin here by briefly reviewing the research on the relationship between T2DM and AD, and I will then review the evidence (summaries are provided in Table 1) for the pathway proposed in Fig. 1 and its possible malfunctions.

Type 2 diabetes and Alzheimer's disease

There is an abundance of studies suggesting that T2DM has a positive association with AD. Some of the most well known research in this area was based on a large population study in Rotterdam [43, 44]. The longitudinal results from this study suggested that diabetes increased the risk of dementia by 1.9 fold, and that diabetic patients treated with insulin were at even greater risk (4.3 fold). Another longitudinal cohort study from the same time frame

Table 1
Review of literature pertaining to the insulin, insulin degrading enzyme, and Alzheimer's pathways

Citation	Year	Type	Findings
T2DM and Alzheimer's disease			
Ott et al., 1996 [43]	1996	Large population study	6330 participants between 55–90, 11.4% had diabetes at baseline. Of those with dementia, 22.3% had diabetes (1.3 fold increase). In particular, a very strong relationship was found between dementia, and diabetes when treated with insulin (3.2 fold increase).
Leibson et al., 1997 [45]	1997	Longitudinal cohort study	DM was associated with an increased risk of all dementia (1.66 fold), and AD (2.27 for men, 1.37 for women).
Ott et al., 1999 [44]	1999	Longitudinal cohort study	Finds that diabetes almost double the risk of dementia (1.9 RR) and AD (1.9 RR). Patients treated with insulin were at the highest risk of dementia (4.3 RR)
Stewart and Liolitsa, 1999 [107]	1999	Review	
Luchsinger et al., 2001 [48]	2001	Longitudinal cohort study	Study of Black and Hispanic cohort for average of 4.3 years suggested that diabetes (baseline rate of 20%) led to a 1.3 fold increase in AD, a 1.6 fold increase in AD or cognitive impairment without dementia (without stroke).
Peila et al., 2002 [46]	2002	Longitudinal cohort study and postmortems	2,574 Japanese-American men enrolled in study and 216 underwent autopsy.35% were diabetic at baseline. Found that Type 2 diabetes was associated with higher rates of total dementia (1.5 fold), AD (1.8 fold), and vascular dementia (2.3 fold). Those that also had ApoE4 allele had a 5.5 fold risk for AD compared to those with neither risk factor. Risk of neurofibrillary tangles was much higher in presence of both diabetes and ApoE4 allele than with either alone, suggesting an interactive effect.
MacKnight et al., 2002 [53]	2002	Longitudinal cohort study	5,574 subjects of Canadian Study of Health and Aging, Average age of 74; diabetes (baseline rate of 12.1%) found to increase rate of vascular dementia but not AD.
Arvanitakis et al., 2004 [47]	2004	Longitudinal cohort study	Uses cognitive testing to determine AD. Finds that diabetes increases risk of AD by 1.65 fold and increases rate of decline. Found no relationship between diabetes and stroke.
Xu et al., 2004 [49]	2004	Longitudinal cohort study	Diabetes increased the risk of dementia 1.5 fold (1.6 vascular dementia, 1.3 AD). Treatment with oral antidiabetic medications increased risk to 1.7.
Rivera et al., 2005 [108]	2005	Postmortems	Finds that AD brains exhibit lower levels of mRNA for insulin, IGF-1, and IGFII polypeptides and their receptors
Akomolafe et al., 2006 [93]	2006	Longitudinal cohort study	Finds that can only detect that DM increases risk of dementia when looking at groups that are not already at high risk due to ApoE4, etc. (At baseline, finds that 9.13 % have diabetes and 22–24% have ApoE4.)

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Table 1
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Citation	Year	Type	Findings
Arvanitakis et al., 2007 [109]	2006	Longitudinal cohort study	Diabetes was associated with increased risk of cerebral infarction (2.47 fold), but not to increased global AD score. However, subjects had a mean age of 86, "Nearly all subjects had at least some AD pathology: the mean composite measure of AD pathology was 0.71 (SD 0.65; range 0 to 2.88)." Furthermore, sample only had a baseline diabetes rate of 15%. Those without diabetes had a higher ratio of ApoE4 (31%) versus those with diabetes (26%).
Schneider et al., 2007 [51]	2007	Postmortems compared to diagnoses	The majority of older persons have one or more brain pathologies; those with dementia most often have multiple brain pathologies.
Schneider et al., 2009 [50]	2009	Postmortems	Of the 179 people with probable AD, 87.7% were pathologically confirmed to have AD, and 45.8% had mixed pathologies. Of the 134 with MCI, 54.4 % were pathologically confirmed to have AD, and 19.4% had mixed pathologies.
Talbot et al., 2012 [61]	2012	Postmortems	Brain insulin resistance was strongly associated with episodic and working memory deficits, even after controlling for Aβ plaques, neurofibrillary tangles, and ApoE4.
Alzheimer's disease increased by insulin deficiency or hyperinsulinemia?			
Fujisawa et al., 1991 [54]	1991	*In vivo*, humans	People with AD had significantly higher insulin levels in the cerebrospinal fluid both under fasting conditions and in response to a glucose tolerance test.
Razay and Wilcock, 1994 [15]	1994	*In vivo*, humans	Women with AD had higher plasma insulin, higher glucose, and higher body mass index than controls. The differences were not significant for men.
Ott et al., 1996 [43]	1996	Large population study	6330 participants between 55–90; 11.4% had diabetes at baseline. Of those with dementia, 22.3% had diabetes (1.3 fold increase). In particular, a very strong relationship was found between dementia, and diabetes when treated with insulin (3.2 fold increase).
Ott et al., 1999 [44]	1999	Longitudinal cohort study	Finds that diabetes almost double the risk of dementia (1.9 RR) and AD (1.9 RR). Patients treated with insulin were at the highest risk of dementia (4.3 RR).
Carantoni et al., 2000 [13]	2000	*In vivo*, humans	Non-diabetic patients with vascular dementia or AD had significantly higher fasting glucose and insulin levels than healthy controls.
Luchsinger et al., 2004 [55]	2004	Longitudinal cohort study	683 elderly persons were followed over time. Finds that the risk of AD attributable to the presence of hyperinsulinemia or diabetes is 39%.
Fishel et al., 2005 [16]	2005	*In vivo*, humans	Concludes that moderate hyperinsulinemia can elevate inflammatory markets and $A\beta_{42}$ in the periphery and the brain, thereby increasing the risk of AD.
Reger et al., 2006 [57]	2006	*In vivo*, humans	Moderate amounts of intranasal insulin improved some measures of memory in individuals without ApoE4 allele, but impaired performance on some measures of memory in individuals with ApoE4 allele.

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Table 1
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Citation	Year	Type	Findings
Pedersen et al., 2006 [90]	2006	*In vivo*, mice	Rosiglitazone (an insulin sensitizer) attenuated memory deficits in Tg2576 Alzheimer mice. It appeared to work by lowing glucocorticoid levels (chronically high glucocorticoids have previously been shown to reduce IDE mRNA in the dentate gyrus of the hippocampus, and to reduce IDE activity in the whole hippocampus).
Young et al., 2006 [14]	2006	*In vivo*, humans	Finds that hyperinsulinemia was associated with a significantly lower baseline of delayed word recall, digit symbol subtest, and first letter word fluency. Furthermore, those with hyperinsulinemia had a greater decline over six years in delayed word recall and word fluency.
Reger et al., 2008 [59]	2008	*In vivo*, humans	25 adults with AD or mild cognitive impairment (and NOT diabetes) were assigned randomly to receive intranasal insulin or a placebo. Moderate amounts of intranasal insulin (20 IU) improved immediate recall in older adults with AD or mild cognitive impairment, but not longer term recall. At higher levels of intranasal insulin (40 IU or 60 IU) performance declined to levels below those of placebo. Furthermore, subjects who had the ApoE4 allele showed poorer performance than all other subjects, and that performance did not get better with intranasal insulin.
de la Monte, 2012 [8]	2012	Review	
Craft et al., 2012 [56]	2012	*In vivo*, humans	Finds positive effects of intranasal insulin on memory impaired adults. Again, results more reliably positive for moderate dose (20 IU).
Freiherr et al., 2013 [60]	2013	Review	Concludes that insulin has neuroprotective effect.
Insulin and/or amylin stimulate IDE production/activity			
Zhao et al., 2004 [23]	2004	*In vitro*	Higher levels of insulin resulted in higher levels of IDE protein; insulin –>PI3 kinase –>upregulates IDE (**HOWEVER, it appeared that at very high levels of insulin, it did not continue to increase IDE: 20, 200, and 500 nM; 155.81 ± 14.49% relative to control at 20 nM, 167.86 ± 25.02 at 200 nM, and 157.69 ± 29.39 at 500 nM); IDE levels lower in AD brains; IDE lowest with two copies of ApoE4 allele; second lowest with one copy of ApoE4 allele.
Jolivalt et al., 2010 [24]	2010	*In vivo*, mice	Streptozotocin was used to induce T1DM in mice. Mice who had T1DM performed worse than wild type mice; mice who had both T1DM and AD (APP mice) performed the worst. Brain assays verified increased plaques. Note: T1DM x APP mice expressed significantly less IDE. "IDE upregulation requires insulin-mediated Akt activation (Zhao et al., 2004a). Therefore, insulin deficiency and a decreased signaling via the PI3K pathway may contribute to decreased IDE expression and thus contribute to increased Aβ protein levels as a result of a reduced degradation." (pg. 428)
Kochkina et al., 2015 [71]	2015	*In vivo*, rats	Inducing Type 1 diabetes via streptozotocin caused IDE to go up in liver and striatum, but down in cortex and hippocampus (cortex and hippocampus are the regions where AD effects first begin to show).

(*Continued*)

Table 1
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Citation	Year	Type	Findings
IDE breaks down insulin			
Kuo et al., 1991 [79]	1991	*In vitro*	IDE breaks down insulin
IDE, neprilysin, and potentially other proteases break down Aβ, amylin, and other amyloidogenic peptides			
Kurochkin and Goto, 1994 [110]	1994	*In vitro*	IDE (rat) breaks down Aβ; acidification significantly inhibits IDE's breakdown of Aβ; Aβ links to IDE so fast that is hard to label IDE in presence of Aβ.
Qiu et al., 1996 [111]	1996	*In vitro*	Aβ is broken down by a metalloprotease.
Hamazaki, 1996 [73]	1996	*In vitro*	Cathepsin D purified from rat brain hydrolyzed Aβ.
McDermott and Gibson, 1997 [28]	1997	*In vitro*, postmortem human and rat brains	IDE breaks down Aβ.
Qiu et al., 1998 [30]	1998	*In vitro*	IDE breaks down Aβ.
Kurochkin, 1998 [34]	1998	Review	IDE acts on peptides that share an ability to form amyloid fibrils.
Bennett et al., 2000 [36]	2000	*In vitro*	IDE degrades amylin; insulin inhibited amylin in a dose-dependent manner and insulin degradation was also inhibited by amylin. Excess insulin also inhibits its own degradation. "Normally, a balance exists between deposition and degradation of the amyloidogenic peptide. When the levels of the peptide exceed the capacity of IDE to degrade them, either by increased expression of the peptide, or decreased expression or enzymatic activity of IDE, the balance is shifted from degradation to deposition. In the case of Type 2 diabetes, both insulin and amylin secretion are increased due to peripheral insulin resistance. Because IDE has approximately 4-fold greater affinity for insulin than for amylin, amylin degradation will be proportionately impaired."
Perez et al., 2000 [33]	2000	*In vitro*, postmortem brain tissue, rat IDE	IDE breaks down Aβ and Aβ analogs; IDE breakdown of Aβ inhibited by excess insulin; Aβ also inhibits breakdown of insulin but is less potent than the reverse.
Vekrellis et al., 2000 [112]	2000	*In vitro*	IDE breaks down Aβ.
Farris et al., 2003 [27]	2003	*In vivo*, mice	IDE knockout mice had a greater than 50% decrease in Aβ degradation in both brain membrane fractions and primary neuronal cultures and a similar deficit in insulin degradation in liver. The mice showed an increase in cerebral accumulation of endogenous Aβ (characteristic of AD), hyperinsulinemia, and glucose intolerance. Ergo IDE dysfunction may underlie both AD and T2DM.
Leissring et al., 2003 [82]	2003	*In vivo*, mice	Upregulation of either neprilysin or IDE (via genetic modification) lessened the mortality of APP mice, and increased Aβ degradation. Furthermore, the proteases acted upon the soluble, monomeric Aβ species prior to over deposition. The authors note that "the vast majority of Aβ-degrading activity in these brain membrane samples is attributable to IDE" IDE decreased both soluble and insoluble Aβ, and "... relatively small changes in the activity of IDE and other Aβ-degrading proteases can dramatically impact steady-state cerebral Aβ levels, suggesting that modest increases in proteolytic clearance of Aβ in humans might be sufficient to effect significant changes in the overall economy of brain Aβ" Also, "chronic neuronal overexpression of IDE or NEP beginning postnatally did not itself have obvious deleterious consequences."

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Citation	Year	Type	Findings
Farris et al., 2004 [31]	2004	*In vivo*, mice	Partial loss-of-function mutations in the IDE gene can impair regulation of Aβ levels without early debilitating dementia, consistent with it having a potential role in late onset AD
Madani et al., 2006 [91]	2006	*In vivo*, mice	Neprilysin knockout mice exhibit Alzheimer's-like behavior impairment and increased Aβ deposits.
de Tullio et al., 2008 [84]	2008	*In vitro*	Aβ binds to IDE very strongly.
Miners et al., 2011 [83]	2011	Review	Neprilysin (NEP), insulin-degrading enzyme, and endothelin-converting enzyme reduce Aβ levels and protect against cognitive impairment in mouse models of AD.
Steneberg et al., 2013 [87]	2013	*In vivo*, mice	Deficiency in IDE leads to deficiency in insulin because IDE is needed to replenish the pool of insulin granules. "We find that glucose-stimulated insulin secretion (GSIS) is decreased in Ide KO mice due to impaired replenishment of the releasable pool of granules and that the Ide gene is haploinsufficient." Also finds that alpha synuclein and IDE levels are inversely correlated, and finds evidence that alpha synuclein suppresses insulin secretion.
Quan et al., 2013 [86]	2013	*In vivo*, rat	Ginsenoside Rg1 upregulates proliferator-activated receptor y (PPARy); PPARγ can upregulate IDE expression and IDE can degrade $A\beta_{1\text{-}42}$.
Vingtdeux et al., 2015 [85]	2015	*In vitro* and *in vivo*, mice	CALHM1 potentiates IDE activity, facilitating degradation of Aβ. Calhm1 knockout mice had roughly a 50% increase in endogenous Aβ concentrations in the whole brain and primary neurons.
Sharma et al., 2015 [88]	2015	*In vitro*	IDE binds to alpha synuclein oligomers, thereby preventing them from forming amyloids. Furthermore, the presence of alpha synuclein intensified IDE's proteolytic activity on another fluorogenic substrate, "substrate V." The researchers also found that adding APP to the mix competitively inhibited the breakdown of "substrate V."
IDE has preferential affinity for insulin; insulin, amylin, Aβ competitive inhibit each other's breakdown			
Qui et al., 1998 [30]	1998	*In vitro*	Finds that IDE is secreted endogeneously by the microglial cell line (suggesting that it is IDE that breaks down Aβ rather than other potential proteases). Also demonstrates that 110-kDA IDE was present in fresh lumbar CSF obtained from living patients, indicating that this protease exists extracellularly under *in vivo* conditions. IDE breaks down Aβ; degradation of Aβ was completely inhibited by competitive IDE substrate, insulin.
Perez et al., 2000 [33]	2000	*In vitro*, postmortem brain tissue, rat IDE	IDE breaks down Aβ and Aβ analogs; IDE breakdown of Aβ inhibited by excess insulin; Aβ also inhibits breakdown of insulin but is less potent than the reverse.
Bennett, et al., 2000 [36]	2000	*In vitro*	IDE degrades amylin; insulin inhibited amylin in a dose-dependent manner and insulin degradation was also inhibited by amylin. Excess insulin also inhibits its own degradation. "Normally, a balance exists between deposition and degradation of the amyloidogenic peptide. When the levels of the peptide exceed the capacity of IDE to degrade them, either by increased expression of the peptide, or decreased expression or enzymatic activity of IDE, the balance is shifted from degradation to deposition. In the case of Type 2 diabetes, both insulin and amylin secretion are increased due to peripheral insulin resistance. Because IDE has approximately 4-fold greater affinity for insulin than for amylin, amylin degradation will be proportionately impaired."

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Table 1
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Citation	Year	Type	Findings
Qiu and Folstein, 2006 [35]	2006	Review	Reviews studies that show that insulin competitively inhibits the breakdown of Aβ.
Amylin and Pramlintide and AD			
Jackson et al., 2013 [17]	2013	Postmortems	Subjects with AD and diabetes, or AD alone, both showed large amylin plaque deposits in the brain. They also found mixed amylin and Aβ plaques. "Amylin deposition in AD brains suggests undiagnosed insulin resistance in these patients, which is common to aging."(p.521)
Srodulski et al., 2014 [18]	2014	*In vivo*, rats	Rats genetically modified to overexpress human amylin accumulated amylin oligomers in their brains and exhibited neurological deficits.
Adler et al., 2014 [21]	2014	*In vivo*, humans and mice	AD and MCI patients exhibited significantly lower plasma amylin. Pramlintide injections to accelerated senescence mice improved their memory.
Qiu and Zhu, 2014 [100]	2014	*In vivo*, mice	Amylin and pramlintide helped reduce neurological deficits in mice that were engineered to have AD. Also found that in humans, amylin increases the Aβ42 in the blood and CSF.
Zhu et al., 2015 [99]	2015	*In vivo*, mice	Pramlintide improved neurological symptoms in APP mice.
Oskarsson et al., 2015 [19]	2015	*In vivo*, mice; postmortem, humans	Amylin fibrils promote an increase in the formation of amylin fibrils (self-reinforced seeding). Also found that amylin fibrils cross-seeded Aβ fibrils, and amylin and Aβ were found to be colocalized in plaques in AD patient brains.
Lutz and Meyer, 2015 [20]	2015	Review	Discusses the similarities between amylin and Aβ, and reviews research suggesting that amyloid may constitute a "second amyloid" that plays an important role in neurodegenerative disorders.
Excess production of amyloidogenic proteins or synergistic interactions of amyloidogenic proteins can increase Aβ deposition			
Giasson et al., 2003 [42]	2003	Review	Alpha synuclein readily self-polymerizes; tau does not. However, Giasson et al demonstrated (*in vitro*) that alpha-synuclein could initiate the polymerization of tau *in vitro* and that tau and alpha synuclein synergistically promote and propagate the polymerization of each other.
Yin et al., 2007 [38]	2007	*In vitro*	APP mutations enhance the preference of γ-secretase for the 42-site over the 40-site cleavage; higher γ-secretase substrate concentrations result in higher ratios of $A\beta_{42}/A\beta_{40}$.
Morale et al., 2009 [39]	2009	Review	The infectious agent in prion disease is thought to be the misfolded protein structure. Because this misfolded protein structure is also common to the other amyloid proteins, they may be infectious as well.
Morales et al., 2009 [40]	2009	Review	Morales et al. review considerable evidence (epidemiological, *in vitro*, *in vivo*) that different protein misfolding disorders can cross-seed each other. Particular focus is paid to cross-seeding between Aβ, amylin, and alpha-synuclein.
Oskarsson et al., 2015 [19]	2015	*In vivo*, mice; postmortem, humans	Amylin fibrils promote an increase in the formation of amylin fibrils (self-reinforced seeding). Also found that amylin fibrils cross-seeded Aβ fibrils, and amylin and Aβ were found to be colocalized in plaques in AD patient brains.
IDE inhibition may make T2DM worse			
Farris et al., 2003 [27]	2003	*In vivo*, mice	IDE knockout mice exhibit hyperinsulinemia, glucose intolerance, and increased Aβ.

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Table 1
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Citation	Year	Type	Findings
Abdul-Hay et al., 2011 [113]	2011	*In vivo*, mice	Although Ide (-/-) mice have elevated insulin levels, they exhibit impaired, rather than improved, glucose tolerance that may arise from compensatory insulin signaling dysfunction.
Deprez-Poulain et al., 2015 [32]	2015	*In vivo*, mice	Inhibiting IDE results in glucose intolerance.
Promotors and inhibitors of IDE secretion or IDE breakdown of Aβ			
Kurochkin and Goto, 1994 [110]	1994	*In vitro*	IDE (rat) breaks down Aβ; acidification significantly inhibits IDE's breakdown of Aβ.
Perez et al., 2000 [33]	2000	*In vitro*, postmortem brain tissue, rat IDE	Bacitracin, phenanthroline, and N0ethylmaleimide each inhibit IDE.
Cook et al., 2003 [95]	2003		ApoE4 associated with reduced IDE expression.
Zhao et al., 2004 [23]	2004	*In vitro*	ApoE4 associated with reduced IDE expression.
Zhao et al., 2009 [114]	2009		It is not well understood what promotes IDE secretion.
Cordes et al., 2009 [89]	2009		Nitric Oxide inhibits insulin degrading enzyme.
Yin et al., 2012 [115]	2012		Geniposide promotes IDE breakdown of Aβ; bacitracin inhibits insulin degrading enzyme.
Quan et al., 2013 [86]	2013	*In vivo*, rat	Ginsenoside Rg1 upregulates proliferator-activated receptor y (PPARy); PPARγ can upregulate IDE expression and IDE can degrade $A\beta_{1\text{-}42}$.

found that T2DM was associated with an increased risk for all dementias (1.66), and AD in particular (2.27 fold for men, 1.37 fold for women) [45]. Several other longitudinal cohort studies followed, with nearly all concluding that T2DM increased the risk of AD between 1.3 fold and 1.8 fold [46–49].

When cognitive testing is used to assess AD, there is a risk that other types of dementias (notably vascular dementia) will be labeled AD. A diagnosis of AD may often be the result of multiple pathologies [50]. Using autopsies, Schneider et al., for example, found that of 179 probable AD cases, almost half exhibited mixed pathologies—most commonly vascular dementia as a result of cerebral infarctions or neocortical Lewy bodies [51]. Notably, many studies have also implicated T2DM in an increased risk of vascular dementia [46, 52, 53], and, as I will explain later, we have reason to suspect that T2DM could also increase the risk of Lewy bodies.

As noted previously, there is considerable disagreement about the mechanism by which T2DM increases the risk of AD. One line of research posits that it is the excess of insulin or glucose from T2DM that leads to AD. Several studies have found that people with AD have significantly higher levels of insulin and glucose than healthy controls [13, 15, 54]. In a large sample longitudinal study of elderly subjects, Luchsinger et al. conclude that 39% of AD in their sample was attributable to hyperinsulinemia or diabetes [55]. This is also consistent with earlier findings of Ott et al. that diabetics that were treated with insulin had far greater risk of AD [43, 44].

Another line of research, however, suggests that it is insulin deficiency (either by the relative deficiency that results from insulin resistance in early stages of T2DM, or absolute deficiency that occurs when beta cell dysfunction occurs in full-blown T2DM) that causes AD by impairing insulin's ability to perform its roles in the brain [8, 56–61]. Insulin and its signaling pathways have been found to affect learning and memory [62, 63]. For example, some research has found that administering insulin growth factors in rats and mice enhances memory retention [63, 64], and depleting it impairs learning [65]. However, the mechanisms of insulin's roles in the brain remain poorly understood [66]. The potential roles of insulin deficiency in AD has led some researchers to conclude that administration of intranasal insulin, or insulin sensitizers, would attenuate neurological deficits. For example, in several studies, Reger et al. found that moderate doses of intranasal insulin improved some memory symptoms in older adults

with AD or mild cognitive impairment [57–59]. However, it is important to note first that patients with diabetes were excluded from the study, and second that the results were nonmonotonic in the dosages of insulin. That is, at higher levels, insulin administration impaired performance.

If insulin deficiency is one of the main culprits in AD, then we would expect a very strong relationship between undertreated T1DM (whereby an individual does not produce insulin or amylin at all) and AD. However, T1DM is much rarer than T2DM, and in the past it often resulted in much earlier mortality. Furthermore, survival of T1DM requires individuals to be treated with insulin, confounding our ability to analyze its relationship with AD. In a few studies, T1DM was induced in mice via administration of streptozotocin, and these mice exhibited AD (or AD-like) pathology [11, 24, 67, 68][1]. For example, in the study by Wang et al., inducing T1DM in mice via administration of streptozotocin resulted in increased Aβ generation, neuritic plaque formation, and spatial memory deficits in mice engineered to exhibit AD [11]. Similarly, a study by Clodfelder-Miller et al. found that within three days of insulin depletion by streptozotocin, mice exhibited a five-fold increase in tau phosphorylation [68]. There is also some evidence to suggest that having a severe insulin deficiency, as in T1DM, could result in inadequate upregulation of proteases that break down Aβ [71]. This leads, then, to the first malfunction pathway proposed above.

MALFUNCTION 1. SEVERE INSULIN DEFICIENCY MAY LEAD TO INADEQUATE PROTEASE PRODUCTION OR ACTIVITY

There is a paucity of information about what stimulates IDE and other amyloid proteases, however, the studies that do exist suggest that insulin is a primary regulator of IDE [23, 24, 26]. For example, in one study, Zhao et al. conclude that IDE upregulation requires insulin-mediated Akt (also known as protein kinase B) activation [23], and mice induced to have T1DM (and thus do not produce insulin) expressed significantly less IDE [24]. Rezende et al. also found that when insulin secretion levels were dramatically reduced in mice through protein secretion, there was a concomitant dramatic decrease in IDE expression in the liver [72]. This suggests that a severe insulin deficiency could possibly be accompanied by an IDE deficiency that could lead to or exacerbate AD. However, because severe insulin deficiency is typically fatal if untreated, this malfunction pathway is probably the least likely to be observed *in situ*. Furthermore, there are other proteases known to act upon Aβ (e.g., cathepsin D, endothelin-converting enzyme, neprilysin [73–77]) that may not be as reliant upon insulin, and we know relatively little about how these proteases are stimulated, which ones act on Aβ *in vivo*, and how they may compensate for each other. This area thus requires much further research.

MALFUNCTION 2. DIMINISHED PROTEASE PRODUCTION OR ACTIVITY RESULTS IN AMYLOID ACCUMULATION

IDE is one of the most widely studied proteases in studies of the relationship between insulin and Aβ. It is a ubiquitously expressed zinc metalloprotease that breaks down or irreversibly binds insulin [27, 33, 36, 78, 79], amylin [36], Aβ [27–31, 33, 80–86], and other amyloidogenic peptides [34, 36], including alpha synuclein [87, 88], which is implicated in Parkinson's disease and Lewy body dementia. An individual with diminished IDE production (for example, due to the excess of an IDE inhibitor such as nitric oxide [89], or an inadequacy of zinc) might thus end up with accumulation of Aβ, amylin plaques, and alpha synuclein in the brain.

There are numerous studies showing that diminished IDE can result in accumulation of Aβ and memory deficits [27, 90, 91]. For example, Farris et al. found that IDE knockout mice had a greater than 50% decrease in Aβ degradation in both brain membrane fractions and primary neuronal cultures. [27] The mice exhibited an increase in cerebral accumulation of endogenous Aβ (consistent with AD), hyperinsulinemia, and glucose intolerance. Madani et al. found that neprilysin knockout mice had increased Aβ deposition [91], and Miller et al. found that IDE knockout mice had significantly increased levels of Aβ in the brain [92]. Vingtdeux et al. found that CALHM1 potentiates IDE activity, and CALHM1 knockout mice exhibited roughly a 50% increase in endogenous Aβ concentrations in the whole brain and primary neurons [85].

There is also research suggesting that deficiency in IDE might lead to an accumulation of insulin

[1]It should be noted that there is disagreement about the validity of a Type 1 diabetes model based on the administration of streptozotocin. Some studies have suggested that streptozotocin is neurotoxic *per se* [69] while others have found that streptozotocin is not directly neurotoxic [70].

in the brain (hyperinsulinemia), leading to insulin resistance and glucose intolerance [27, 32]. Though the possibility of IDE regulating insulin in the brain remains to be directly tested, this possibility suggests that one of the reasons that AD and T2DM are closely associated might be because they can be caused by the same mechanism.

Diminished IDE production may also account for at least part of the association between the ApoE4 allele and AD. ApoE4 is a well-established risk factor for AD; most estimates suggest that roughly 20–25% of the population has the ApoE4 allele, yet roughly 50% of the AD population has the ApoE4 allele [21, 93, 94]. Furthermore, in their longitudinal study of 2,574 Japanese-American men (and 216 autopsies), Peila et al. found that the combination of diabetes and having one or more copies of the ApoE4 allele resulted in a dramatically higher risk of AD—5.5 fold—than either risk alone [46]. Having a single copy of the allele is thought to triple the risk for late-onset AD; having two copies of the allele is thought to increase the risk of AD 12 fold [94]. Importantly, Cook et al. found that AD patients with the ApoE4 allele had a 50% reduction in expression of IDE compared to AD patients without the ApoE4 allele, suggesting that the ApoE4 allele may play a role in IDE deficiency leading to AD [95]. The mechanisms that underlie ApoE4's relationship to AD remain to be more fully explored, however.

Qiu et al.'s study, and a review by Qiu and Folstein, suggest that IDE is likely to be an important protease involved in Aβ degradation [30, 35]. Furthermore, since the IDE gene plays a significant role also in diabetes, this would help to explain the strong relationship between the two pathologies. However, it is important to note that are other proteases that appear to play roles in breaking down or binding Aβ such as neprilysin, endothelin-converting enzyme, cathepsin B, or cathepsin D [73, 83, 96]. The role of these proteases in Aβ degradation and AD pathology have thus far received far less attention and warrant further study.

MALFUNCTION 3. EXCESS INSULIN OR AMYLIN COMPETITIVELY INHIBITS BREAKDOWN OF Aβ

Though IDE can break down a range of amyloidogenic peptides [34], it has a preferential affinity for insulin [33, 36]. This suggests the possibility that, consistent with Qiu et al.'s hypothesis, one of the causal mechanisms leading to sporadic AD may be the competitive inhibition of Aβ by insulin or amylin [30]. Numerous studies have shown that insulin completely competitively inhibits the breakdown of both Aβ [30, 33, 35] and amylin [36]. Furthermore, though insulin upregulates the expression of IDE, it has been shown that its ability to increase IDE diminishes at high levels [23]. This suggests that in the hyperinsulinemia of early T2DM (or obesity) [97, 98], insulin levels could outstrip IDE's ability to break it down. If IDE preferentially targets insulin and insulin levels are outpacing IDE production, IDE's ability to breakdown other amyloidogenic proteins will be markedly reduced. As eloquently stated in Bennett et al., "Normally, a balance exists between deposition and degradation of the amyloidogenic peptide. When the levels of the peptide exceed the capacity to degrade them, either by increased expression of the peptide, or decreased expression of the enzymatic activity of IDE, the balance is shifted from degradation to deposition." [36] The chronic hyperinsulinemia of early T2DM and its potential to competitively inhibit the breakdown of Aβ thus likely explains a large portion of the association between T2DM and AD.

This competitive inhibition of degradation among different IDE substrates brings us to the recent amylin studies. In 2013, Jackson et al. found patients with AD had large amylin plaque deposits and mixed amylin and Aβ deposits in their brains [17]. They concluded that amylin may play a causal role in AD. Then in 2014, Srodulski et al. found that rats that were genetically modified to express human amylin accumulated amylin oligomers in their brains, and exhibited neurological deficits [18]. Oskarsson et al. also found that amylin and Aβ were colocalized in the brains of human AD patients [19]. If amylin, which is co-secreted with insulin, competes with Aβ for degradation, promotes the deposition of Aβ, or accumulates in plaques on the brain itself, this is another strong mechanism by which T2DM and dementia may be linked.

Remarkably, another set of recent studies appeared to directly counter this conclusion by finding that amylin exhibited a neuroprotective effect [21, 99, 100]. These studies found that injection of pramlintide (an amylin analog), or rat/mouse amylin, appeared to improve memory symptoms in mice engineered to exhibit AD or accelerated senescence. Furthermore, administration of pramlintide to humans appeared to improve some learning and memory measures. However, two important features of these recent stud-

ies must be noted. First, the studies used rat/mouse amylin, or pramlintide (synthetic amylin), both of which have proline substitutions at positions 25, 28, and 29 that limit amylin's self-aggregating properties, thus rendering it non-amyloidogenic. Second, in all the studies except for Qiu et al.'s study of homebound elderly [22], the subjects were diabetes free, and thus likely had no deficiency in their IDE system or excess of competing insulin. In the Qiu et al. study of homebound elderly, the researchers found some differences in memory scores across quartiles of amylin levels across all subjects (including those with diabetes), however these differences were not monotonically increasing. Furthermore, the significant differences they report in amylin levels across AD patients, mild cognitive impairment patients, and healthy persons were only for patients without diabetes.

The preceding suggests that pramlintide might have beneficial effects for people without diabetes. This could be due to its role in preventing post-prandial glucose spikes or by inhibiting glucagon, both of which would collectively lessen insulin demand. These mechanisms of potential benefit, however, are speculative; the mechanism of pramlintide's potential neuroprotective effect is unclear. For people with diabetes, however, pramlintide seems far less likely to be beneficial in AD. In people with diabetes, insulin and amylin levels are already high, and may have already exhausted their capacity for stimulating IDE production and activity.

MALFUNCTION 4. EXCESS PRODUCTION OF AN AMYLOIDOGENIC PROTEIN, OR POSITIVE INTERACTIONS BETWEEN AMYLOIDOGENIC PROTEINS, RESULT IN AMYLOID ACCUMULATION

Excess production of an amyloidogenic protein can result in amyloid deposition outpacing amyloid degradation, resulting in amyloid accumulation [36]. For example, mutations in the amyloid precursor protein gene (the gene associated with early-onset AD) can increase the relative production of $A\beta_{42}$, leading to amyloid deposition [37, 38]. Similarly, excess production of amylin (as in T2DM) may directly cause a build-up of amylin plaques on the brain [17]. There is also growing evidence that some amyloidogenic proteins can foster the formation of amyloids of other proteins, in a process known as "cross-seeding" [39–41]. For example, alpha synuclein can initiate tau amyloid formation, and then the two peptides can increase the polymerization of each other [42]. Similarly, amylin may interact with Aβ to increase its formation of plaques [17–19].

IMPLICATIONS

The implications of the preceding are very important, because the mechanism by which AD arises strongly determines what treatments are likely to be effective. If insulin deficiency is the main culprit, for example, then intranasal insulin might be of significant benefit. If, however, hyperinsulinemia and/or competitive inhibition of degradation of Aβ by a degrading protease is the main cause, then administering intranasal insulin could exacerbate the disease. Furthermore, there is evidence that hyperinsulinemia precedes the hyperglycemia of T2DM by many years and it is likely the chronic overstimulation of insulin receptors that leads to insulin resistance [35, 97, 101]. This suggests that extreme caution should be exercised in giving a diabetic or pre-diabetic individual extra insulin—it may just add fuel to the fire.

The evidence overwhelmingly suggests that testing for glucose tolerance should occur early and often. There is no downside to glucose tolerance testing other than minor cost, and the upside could be the earlier identification and treatment of pre-diabetes and diabetes. Given the evidence of a very strong association between hyperinsulinemia and AD (and other forms of dementia), every patient with AD or mild cognitive impairment should be regularly tested for glucose intolerance. Furthermore, obesity is also strongly associated with hyperinsulinemia [97] and diabetes [102], and thus, not surprisingly, increases the risk of AD [103]. Given the widespread prevalence of obesity, pre-diabetes, and diabetes, glucose intolerance testing should become a standard part of regular health screening in the broader population. According to the American Diabetes Association, of the 29.1 million Americans with diabetes in 2012, 8.1 million (28%) were undiagnosed. Furthermore, 86 million Americans are estimated to be pre-diabetic (i.e., have impaired glucose tolerance) and most will have no symptoms that are recognizable without medical testing [104]. Early identification of, and intervention for, diabetes and prediabetes could significantly lessen the impact of both diabetes and AD.

The review and arguments here suggest a few necessary future studies:

1. Insulin Deficiency versus Hyperinsulinemia

First, to test the competing hypotheses that it is insulin deficiency versus hyperinsulinemia that create or exacerbate AD (and thus the appropriateness of administering intranasal insulin) mice (including wild type, mice altered to develop AD, and mice altered to develop both AD and hyperinsulinemia) should be given chronic intranasal insulin and then subjected to both cognitive testing and quantification of amyloid burden and tauopathy. If the pathways to AD posed in this paper are correct, intranasal insulin should make AD in hyperinsulinemic mice worse. Its effects on the other mice should be very informative: if it yields moderate neurological improvements in the AD mice, this would support its use in non-hyperinsulinemic AD patients. It might, however, induce hyperinsulinemia and insulin resistance leading to T2DM in the wild type mice, and both T2DM and worsening of AD in the AD mice by competitively inhibiting the breakdown of Aβ. Ideally a range of doses of insulin will be used to assess potential curvilinear effects.

2. Neuroprotective versus Competitive Inhibition Effects of Amylin and Pramlintide

Next, to assess the neuroprotective versus competitive inhibition effects of amylin and pramlintide, *in vitro* studies should first be conducted to assess the degree to which pramlintide (rather than human amylin) competitively inhibits the breakdown of Aβ. If IDE responds primarily to the amyloidogenic motif rather than particular amino acid sequences, as suggested by Kurochkin [34] and others, perhaps pramlintide competes less for breakdown of IDE compared to human amylin. Next different groups of mice (wild type, mice altered to develop AD and hyperinsulinemia, mice altered to develop AD but without hyperinsulinemia, and IDE knockout mice altered to develop AD) should be chronically treated with different amylins (pramlintide, human amylin), at different dosage levels to observe the potential differential effects of amylin and pramlintide depending on the state of the insulin-IDE system of the subject. IDE inhibitors that can decrease (rather than eliminate) IDE could also be used to more precisely explore the relationships between intranasal insulin, pramlintide, IDE, and AD [32, 105]. This should be followed by cognitive testing and quantification of amyloid burden and tauopathy. If the arguments about competitive inhibition presented earlier are correct, the administration of human amylin should exacerbate AD in all but the wild-type mice. I was unable to find any studies of whether pramlintide competitively inhibits the breakdown of Aβ, so it is impossible to predict the outcome of the tests with pramlintide. If, however, it turns out that pramlintide does competitively inhibit the breakdown of Aβ, then its administration should also exacerbate AD in all but the wild-type mice.

If the results of the first set of studies above find that hyperinsulinemia rather than insulin deficiency exacerbates AD, then this implies that we should be able to significantly lower rates of AD through educating people about how to better manage their blood sugar and insulin. A very large portion of the population has little understanding of the glycemic index of carbohydrates. Furthermore, very few people know that some artificial sweeteners produce an insulin response. This also yields a potential policy implication that perhaps food should be labeled with a measure of its effect on insulin. The results of the second study should help us to identify any AD risks of administering pramlintide (which is already given to many diabetic patients in addition to insulin sensitizers) and help us to assess the overall reliability, efficacy, and safety of administering these drugs.

If the results of future studies support the arguments made in this paper, then this suggests that much more research should be done to identify the different proteases that degrade Aβ *in vivo*, to better understand their promoters and inhibitors, and to evaluate the safety and efficacy of increasing the availability of such proteases in both AD and diabetes. Relatedly, it would be valuable to develop easily administered diagnostic tests to identify protease deficiencies.

Finally, the work here hints at some very fruitful opportunities for extending the findings in AD to better understand other neurodegenerative diseases that involve protein aggregation in the brain. For example, many of the studies cited here with IDE knockout or IDE upregulated mice should be adapted for studies of Parkinson's disease, Lewy body dementia, and Huntington's disease. These latter diseases have longer peptide sequences than IDE is thought to degrade (IDE has been shown to only cleave peptides of 50 amino acids or shorter [106]), but recent studies indicate that IDE nonproteolytically inhibits alpha synuclein fibril formation by binding to alpha synuclein oligomers and preventing them from forming amyloids [88], suggesting there could be great promise in this research pathway.

DISCLOSURE STATEMENT

The author's disclosure is available online (http://j-alz.com/manuscript-disclosures/15-0980r2).

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