

Type 2 Diabetes and Alzheimer's Disease: From Common Pathologies to Potential New Therapeutics

Daniel E. Levy, Ph.D.

Abstract

Type 2 diabetes constitutes a major health risk in the United States, with over 20% of individuals over the age of 60 currently suffering from this disease and an additional 1.5 million new cases diagnosed in patients over 20 years of age in 2005. Similarly, Alzheimer's disease represents a major risk to the aging population, with recent statistics estimating up to 16 million people diagnosed by 2050 in the United States alone. As type 2 diabetes and Alzheimer's disease are now recognized as members of the broader class of amyloid diseases and because the pathologies of disease progression between these indications is similar, common strategies focused on the design of next-generation therapeutics can be envisioned and are discussed herein.

J Diabetes Sci Technol 2007;1(4):590-594

Throughout history, many plagues and illnesses have ravaged societies around the world. While through medicine, hygiene, and education we have largely been able to control or eliminate infectious and contagious ailments ranging from bubonic plague and leprosy to polio and small pox, we currently see an epidemic increase in diabetes. With over 20% of individuals over the age of 60 currently suffering from this disease and with an additional 1.5 million new cases diagnosed for patients over 20 years of age in 2005, diabetes is now among the greatest threats to public health today.¹

Many factors are known to influence the risk of acquiring type 2 diabetes. Among these are genetic factors such as familial history and health factors including high blood pressure. **Table 1** summarizes key

risk factors associated with type 2 diabetes^{2,3} correlated with Alzheimer's disease (AD) risk factors⁴ and grouped into respective classes. Although little can be done with respect to genetic risk factors and age for both diseases, appropriate lifestyle changes can impact health. Furthermore, the risk factors common to both diseases may allude to an underlying physiological link. Thus, as addressed in the following paragraphs, much interest is focused on the relationship between these diseases and the incidences of developing one once diagnosed with the other.

Regarding therapeutic interventions for diabetes, current standards of care rely on control of blood glucose levels. However, in recent years, attention has focused on pancreatic function as it relates to diabetes.

Author Affiliation: Pharmadyn, Inc., Sunnyvale, California

Abbreviations: (AD) Alzheimer's disease, (PPAR γ) peroxisome proliferator-activated receptor γ

Keywords: Alzheimer's, amyloid, diabetes, insulin, islet, pancreatic, neuronal, plaques

Corresponding Author: Daniel E. Levy, Ph.D., Vice President of Research and Development, Pharmadyn, Inc., 525 Del Rey Avenue, Suite B, Sunnyvale, CA 94085-3515; email address dani@pharmadyn.com

Specifically, as progressive reduction in insulin secretion is a hallmark of type 2 diabetes, the machinery responsible for insulin production and release has attracted significant interest. Looking at the islets of Langerhans (the pancreatic cell structures that produce insulin), researchers found amyloid protein deposits in subjects suffering from type 2 diabetes. Interestingly, in animal models, these deposits were shown to induce diabetes, whereas in humans, amyloid deposits and associated fibrils were linked to diabetes-associated islet dysfunction.⁵

Table 1.
Risk Factors for Type 2 Diabetes^{2,3} and Alzheimer's Disease⁴ Grouped by Class

Class	Risk factors	Type 2 diabetes	Alzheimer's disease
Lifestyle	Poor diet	✓	
	Sedentary activity level	✓	
	Education level		✓
	Sedentary mental activity		✓
Health	Age	✓	✓
	High blood pressure	✓	✓
	High cholesterol	✓	✓
	High triglycerides	✓	
	Low high-density lipoproteins	✓	
	Obesity	✓	
	History of gestational diabetes	✓	
	Diabetes	✓	✓
Genetic	Family history	✓	✓
	Ethnicity	✓	
	Gender		✓

The noninsulin hypoglycemic agents used to treat type 2 diabetes stimulate either increased release of insulin or increased sensitivity to insulin. Relating diabetes to AD, thiazolidinediones such as Avandia (rosiglitazone, GlaxoSmithKline) and Actos (pioglitazone, Takeda/Eli Lilly) act through stimulation of peroxisome proliferator-activated receptor γ (PPAR γ). These drugs are known to control glucose and lipid metabolism through modulation of transcription of insulin-sensitive genes and to reduce hepatic insulin resistance. Finally, of the thiazolidinediones, rosiglitazone is currently being studied for use in treating AD.⁶ A recent study links

this effect to the ability of PPAR γ agonists to induce neuronal mitochondrial biogenesis while also improving cellular glucose utilization.⁷

While the various disorders associated with AD have probably been known for centuries, this ailment was characterized for the first time in the early 20th century by German psychologist Alois Alzheimer and his colleague Emil Kraepelin. While Kraepelin had classified and grouped the symptoms, it was Alzheimer who had discovered the plaques and fibrils presenting in the brains of those succumbing to the fatal end point of this disease.⁸ Today, like diabetes, AD represents a significant and growing influence on our aging population. In fact, recent statistics estimate that by 2050, up to 16 million people will suffer from this devastating disease in the United States alone.⁹

Risk factors believed to contribute to development of AD are listed in **Table 1**. While not confirmed conclusively for all factors, primary influences include age, level of mental activity, family history, female gender, and diabetes. Less established influences include high blood pressure and high cholesterol. With respect to diabetes, recent studies allude to neuronal insulin resistance (brain diabetes) as a causative factor in the development of AD.¹⁰ Finally, as a factor directly linking diabetes to AD, decreased catalytic activity of insulin-degrading enzyme, an enzyme responsible for the degradation of amyloid peptides, was demonstrated in AD patients with familial histories of the disease.¹¹ A recent review extensively covers the importance of insulin resistance as it relates to both diabetes and AD.¹²

Patients suffering from AD generally present with progressive dementia, neurodegeneration, memory loss, cognitive decline, and behavioral dysfunction. As the disease progresses, these symptoms are correlated with pathogenic features in cranial tissue, which include aggregates of β -amyloid protein and neurofibrillary tangles made up of τ -protein filaments. Aggregates of β -amyloid are known to be toxic to neurons,¹³ and τ -protein filaments have been implicated in mediating β -amyloid-induced neurotoxicity.¹⁴ AD researchers at the University of Virginia demonstrated that prefibrillar β -amyloid induces τ -dependent microtubule disassembly, leading to neuronal cell toxicity.¹⁵ Ultimately, while disease progression is because of the presence of amyloid plaques and neurofibrillary tangles, leading to excessive loss of neuronal cells, early symptoms of cognitive impairment are linked to a measurable decline in acetylcholine levels.¹⁶

Because of the link between AD symptoms and neurotransmitter levels, first-line therapeutic interventions focus on preserving neuronal levels of acetylcholine through inhibition of acetylcholinesterase. Such therapeutics, listed in **Table 2**, include Aricept (donepezil HCl, Eisai/Pfizer), Razadyne (galantamine HBr, Ortho-McNeil), and huperzine A.¹⁷ Of these compounds, Aricept is approved by the Food and Drug Administration for the treatment of AD symptoms. Similarly, Razadyne is approved for use in 29 countries, including the United States. Finally, huperzine A has undergone clinical trials in China and is being evaluated by the National Institute on Aging for use in improving cognitive function in AD patients. Additional acetylcholinesterase inhibitors that have been studied include Synapton (physostigmine salicylate, Forest Laboratories), Metrifonate (Bayer), and Memric (sabcomeline, GlaxoSmithKline)—all of which have been discontinued for various reasons. Unfortunately, while acetylcholinesterase inhibitors are known to improve cognitive function, they do not impact the progressing pathology of AD and their long-term efficacy is not robust.

To address concerns regarding the long-term utility of symptomatic treatments for AD, many groups are now focused on its underlying progressing pathology. In this arena, attention is directed at inhibiting production of β -amyloid, inhibiting β -amyloid aggregation, or inducing disaggregation and clearing of β -amyloid plaques. The latter of these strategies is an interesting approach because symptomatic reversal due to accumulation of β -amyloid plaques has not been considered viable. However, research has demonstrated that β -amyloid aggregation and memory loss in the Tg2567 mouse model system may both be reversible.^{18,19}

Drugs designed to interfere with the cascade leading to β -amyloid aggregation are now in late-stage clinical trials and are included in **Table 2**. Among these is Alzhemed (tramiprosate, Neurochem), which is currently in phase III clinical trials and acts by inhibiting the formation of β -amyloid fibrils while also reducing levels of soluble β -amyloid. Additionally, Flurizan (MPC-7869, Myriad Genetics) is in phase III clinical trials as an agent that also reduces β -amyloid levels. Regarding the formation of β -amyloid, γ -secretase accomplishes this through cleavage of a larger protein. Thus, LY450139 (Eli Lilly) is in phase II clinical trials as a γ -secretase inhibitor. Furthermore, AAB-011 (Elan Pharmaceuticals/Wyeth), a monoclonal antibody that binds to and clears β -amyloid, is currently in phase II clinical trials.

As alluded to in the preceding paragraphs, both AD and type 2 diabetes belong to a class of diseases linked to amyloid proteins. The term “amyloid” refers to a family of proteins deposited in various tissues and identifiable using aromatic dyes such as Congo red. Historically, these proteins were mischaracterized and thus named amyloids after the Latin word for starch.²⁰ Amyloid proteins are generally found extracellularly and are known to recruit additional factors, leading to large and indefinable structures.²¹ Additionally, amyloid-like deposits have been identified in intracellular space.²²

While amyloid proteins are widely found throughout nature and, particularly, in mammalian systems, diseases associated with amyloid plaque deposition are generally the result of misfolding of these proteins. Identification of such diseases began with the realization that scrapie was caused by the transmission of infectious misfolded proteins now known as prions. Ultimately, prions were recognized as being composed of amyloids and allowed

Table 2.
Therapeutic Agents for AD

Drug	Manufacturer	Status	Mechanism of action
Aricept	Eisai	Marketed	Acetylcholinesterase inhibitors
Razadyne	Ortho-McNeil	Marketed	
Huperzine A		Clinical studies	
Synapton	Forest Laboratories	Discontinued	
Metrifonate	Bayer	Discontinued	
Memric	GlaxoSmithKline	Discontinued	
Alzhemed	Neurochem	Phase III	Lowers β -amyloid levels
AAB-011	Elan	Phase II	
LY450139	Eli Lilly	Phase II	γ -Secretase inhibitor

the classification of scrapie as a member of this family of transmissible neurologic disorders that include kuru, bovine spongiform encephalopathy, and Creutzfeldt–Jakob disease.²³ Moving from the infectious class of amyloid-related disorders to those neurologic disorders that develop based on currently unknown mechanisms, we find Huntington's disease,²⁴ Parkinson's disease,²⁵ and AD. Finally, amyloids are now associated with nonneurological disorders, including type 2 diabetes and some instances of heart failure.²⁶ Although amyloids have been identified as causes for many of these diseases, it is important to remember that there is still much debate whether, for all of these diseases, amyloids are the cause or simply an observable pathologic outcome. Nevertheless, with amyloid plaque deposition being recognized as a component of so many diseases with limited treatment options, a reasonable expectation now exists that, for at least some of these indications, targeting amyloid pathology will lead to therapeutically beneficial outcomes.

With the common pathological progressions linking type 2 diabetes with AD, research has focused on the risk of developing one disease once diagnosed with the other. In addressing this issue, one study indicated that cognitively impaired subjects had elevated levels of both insulin and A β 42, the amyloid protein responsible for plaque deposition in neuronal tissue, as compared to cognitively normal subjects.²⁷ In an additional study, expression of insulin was found to decline as a function of the progression of AD.²⁸ Finally, one review addressed many of the factors linking AD to type 2 diabetes with concluding remarks alluding to the possible future ability of treating both diseases with common therapeutics.²⁹

As discussed previously, progress toward the advancement of treatments for AD is reflected in ongoing studies and late-stage clinical trials for drugs targeting amyloid plaque deposition and destruction of associated fibrils. With the common pathologies linking AD with type 2 diabetes, the development of agents capable of interrupting the progression of pancreatic amyloid deposition and facilitating destruction of associated plaques represents a currently unavailable strategy for the treatment of diabetes. While the recent launches of Symlin (pramlintide, amylin) and Byetta (exenatide, amylin) present new approaches for the control of diabetes, their novel mechanisms of action, like current therapies, target control of blood glucose levels and not the underlying pathology leading to pancreatic dysfunction. However, if deteriorating pancreatic function can be stabilized through preservation of islet activity, and if clearance of pancreatic amyloid plaques can result

in restored production of insulin, then this strategy offers new opportunities to improve the quality of life for millions suffering from the progression of diabetes and its associated debilitating complications.

References:

1. www.diabetes.org/diabetes-statistics/prevalence.jsp
2. diabetes.about.com/od/symptomsdiagnosis/tp/riskfactors.htm
3. www.nlm.nih.gov/medlineplus/ency/article/002072.htm
4. www.mayoclinic.com/health/alzheimers-disease/DS00161/DSECTION=4
5. Jaikaran ET, Clark A. Islet amyloid and type 2 diabetes: from molecular misfolding to islet pathophysiology. *Biochim Biophys Acta*. 2001 Nov 29;1537(3):179-203.
6. Risner ME, Saunders AM, Altman JFB, Ormandy GC, Craft S, Foley IM, Zvartau-Hind ME, Hosford DA, Roses AD; Rosiglitazone in Alzheimer's Disease Study Group. Efficacy of rosiglitazone in a genetically defined population with mild-to-moderate Alzheimer's disease. *Pharmacogenomics J*. 2006 Jul-Aug;6:246-54.
7. Strum JC, Shehee R, Virley D, Richardson J, Mattie M, Selley P, Ghosh S, Nock C, Saunders A, Roses A. Rosiglitazone induces mitochondrial biogenesis in mouse brain. *J Alzheimers Dis*. 2007 Mar;11(1):45-51.
8. www.medopedia.com/alzheimers/history
9. Hebert LE, Scherr PA, Bienias JL, Bennett DA, Evans DA. Alzheimer disease in the U.S. population: prevalence estimates using the 2000 census. *Arch Neurol*. 2003 Aug;60(8):1119-22.
10. de la Monte SM, Wands JR. Review of insulin and insulin-like growth factor expression, signaling, and malfunction in the central nervous system: relevance to Alzheimer's disease. *J Alzheimers Dis*. 2005 Feb;7(1):45-61.
11. Kim M, Hersh LB, Leissring MA, Ingelsson M, Matsui T, Farris W, Lu A, Hyman BT, Selkoe DJ, Bertram L, Tanzi RE. Decreased catalytic activity of the insulin-degrading enzyme in chromosome 10-linked Alzheimer disease families. *J Biol Chem*. 2007 Mar 16;282(11):7825-32.
12. Craft S. Insulin resistance and Alzheimer's disease pathogenesis: potential mechanisms and implications for treatment. *Curr Alzheimer Res*. 2007 Apr;4(2):147-52.
13. McGowan E, Pickford F, Kim J, Onstead L, Eriksen J, Yu C, Skipper L, Murphy MP, Beard J, Das P, Jansen K, Delucia M, Lin WL, Dolios G, Wang R, Eckman CB, Dickson DW, Hutton M, Hardy J, Golde T. A β 42 is essential for parenchymal and vascular amyloid deposition in mice. *Neuron*. 2005 Jul 21;47(2):191-9.
14. Park SY, Ferreira A. The generation of a 17 kDa neurotoxic fragment: an alternative mechanism by which tau mediates β -amyloid-induced neurodegeneration. *J Neurosci*. 2005 Jun 1;25(22):5365-75.
15. King ME, Kan HM, Baas PW, Erisir A, Glabe CG, Bloom GS. Tau-dependent microtubule disassembly initiated by prefibrillar β -amyloid. *J Cell Biol*. 2006 Nov 20;175(4):541-6.
16. Perry EK. The cholinergic hypothesis—ten years on. *Br Med Bull*. 1986 Jan;42(1):63-9.
17. Tang XC, He XC, Bai DL. Huperzine A. a novel acetylcholinesterase inhibitor. *Drugs of the Future* 1999;24(6):647-63.
18. Kotilinek LA, Bacskaï B, Westerman M, Kawarabayashi T, Younkin L, Hyman BT, Younkin S, Ashe KH. Reversible memory loss in a mouse transgenic model of Alzheimer's disease. *J Neurosci*. 2002 Aug 1;22(15):6331-5.

19. Cruz L, Urbanc B, Buldyrev SV, Christie R, Gomez-Isla T, Havlin S, McNamara M, Stanley HE, Hyman BT. Aggregation and disaggregation of senile plaques in Alzheimer disease. *Proc Natl Acad Sci U S A*. 1997 Jul;94(14):7612-6.
20. Kyle RA. Amyloidosis: a convoluted story. *Br J Haematol* 2001 Sep;114(3):529-38.
21. Sipe JD, Cohen AS. History of the amyloid fibril. *J Struct Biol*. 2000 Jun;130(2-3):88-98.
22. Paulsson JF, Andersson A, Westermark P, Westermark GT. Intracellular amyloid-like deposits contain unprocessed pro-islet amyloid polypeptide (proIAPP) in beta cells of transgenic mice overexpressing the gene for human IAPP and transplanted human islets. *Diabetologia*. 2006 Jun;49(6):1237-46.
23. Liberski PP. Amyloid plaques in transmissible spongiform encephalopathies (prion diseases). *Folia Neuropathol*. 2004;42 Suppl B:109-19.
24. McGowan DP, van Roon-Mom W, Holloway H, Bates GP, Mangiarini L, Cooper GJ, Faull RL, Snell RG. Amyloid-like inclusions in Huntington's disease. *Neuroscience*. 2000;100(4):677-80.
25. Mollenhauer B, Trenkwalder C, von Ahsen N, Bibl M, Steinacker P, Brechlin P, Schindehuetter J, Poser S, Wiltfang J, Otto M. Beta-amyloid 1-42 and tau-protein in cerebrospinal fluid of patients with Parkinson's disease dementia. *Dement Geriatr Cogn Disord*. 2006;22(3):200-8.
26. Shah KB, Inoue Y, Mehra MR. Amyloidosis and the heart: a comprehensive review. *Arch Intern Med*. 2006 Sep 25;166(17):1805-13.
27. Odetti P, Piccini A, Giliberto L, Borghi R, Natale A, Monacelli F, Marchese M, Assini A, Colucci M, Cammarata S, Tabaton M. Plasma levels of insulin and amyloid β 42 are correlated in patients with amnesic mild cognitive impairment. *J Alzheimers Dis*. 2005 Dec;8(3):243-5.
28. Rivera EJ, Goldin A, Fulmer N, Tavares R, Wands JR, de la Monte SM. Insulin and insulin-like growth factor expression and function deteriorate with progression of Alzheimer's disease: link to brain reductions in acetylcholine. *J Alzheimers Dis*. 2005 Dec;8(3):247-68.
29. Haan MN. Therapy insight: type 2 diabetes mellitus and the risk of late-onset Alzheimer's disease. *Nat Clin Pract Neurol*. 2006 Mar;2(3):159-66.