

Type 2 Diabetes, Cognition, and Dementia in Older Adults: Toward a Precision Health Approach

Brenna Cholerton,¹ Laura D. Baker,² Thomas J. Montine,¹ and Suzanne Craft²

¹Department of Pathology, Stanford University, Palo Alto, CA

²Sticht Center on Aging, Department of Internal Medicine, Wake Forest University, Winston-Salem, NC

Corresponding author: Brenna Cholerton, bchol@stanford.edu

DOI: 10.2337/ds16-0041

©2016 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0> for details.

IN BRIEF There has been a concurrent dramatic rise in type 2 diabetes and dementia in the United States, and type 2 diabetes shares common genetic and environmental risk factors and underlying pathology with both vascular and Alzheimer's dementias. Given the ability to identify this at-risk population and a variety of potential targeted treatments, type 2 diabetes represents a promising focus for a precision health approach to reduce the impact of cognitive decline and dementia in older adults.

A confluence of factors related to dietary changes, sedentary lifestyle, and an aging population in Western cultures has led to a rapid rise in the incidence of type 2 diabetes, a disease that carries enormous burden in terms of health and economic outcomes. Increasingly, type 2 diabetes is recognized as a major contributor to cognitive decline and dementia in older adults. As both

type 2 diabetes and dementia reach epidemic proportions in the United States, the need to identify methods of prevention and treatment grows increasingly important.

Recently, there has been an emphasis on precision medicine, a model of focused identification and treatment of disease based on individual risk, as it applies to dementia. Even more compelling than preci-

sion medicine is the aspirational goal of precision health, through which graded surveillance based on risk discloses preclinical pathophysiological processes that motivate interventions that preserve health and prevent clinical expression of disease. The ability to identify an at-risk population, to detect pathological changes early in the disease process, and to select from a variety of potential targeted treatments make type 2 diabetes an ideal focus for a precision health approach to reducing the impact of dementia.

Type 2 Diabetes and Cognition in Older Adults

Type 2 diabetes is a robust predictor of cognitive impairment and decline in older adults. Multiple population-based studies have reported an association between type 2 diabetes and cognitive impairment (1–4), and older adults with type 2 diabetes experience global cognitive decline at a rate that is double those without type 2 diabetes over a 5-year period (5). General cognitive slowing, thought to be a marker for accelerated brain aging and dementia risk, is related to type 2 diabetes in middle-aged and older adults (6,7), and interactions between type 2 diabetes and genetic risk predict more rapid decline in cognitive speed (8). With regard to specific cognitive domains, associations between type 2 diabetes or even prediabetic levels of insulin resistance are most commonly reported with both episodic memory and decreased executive function, including verbal fluency, working memory, processing speed, cognitive flexibility, and cognitive control (7). Executive function, which may be most predictive of functional performance, also declines more rapidly among older women with type 2 diabetes (9). Conversely, remaining free from diabetes has been associated with preserved cognitive function in women >80 years of age (10).

Several mechanisms may underlie these associations, including peripheral metabolic derangements from

insulin resistance or type 2 diabetes that indirectly damage the brain, vascular brain injury from the vasculopathic consequences of insulin resistance and type 2 diabetes, disruption of the ability of insulin to perform its normal actions in the brain in patients with type 2 diabetes, or some combination of these.

Insulin in the Brain

Sensitivity of target cells in the periphery and in the central nervous system (CNS) to insulin, a peptide hormone secreted by pancreatic β -cells, is suppressed in type 2 diabetes. First recognized as a principle regulator of peripheral glucose, insulin also has been identified as a key factor in memory and other cognitive processes. Insulin is readily transported into the CNS across the blood-brain barrier via a saturable, receptor-mediated process, which likely accounts for the majority of available insulin in the brain (11). Additionally, recent evidence suggests that insulin is also produced in the brain, a process that is potentially regulated by the Wnt/ β -catenin/NeuroD1 pathway in the hypothalamus (12), although this has yet to be verified in human studies. Regardless of source, the CNS is rich with insulin receptors, most prominently in areas important for learning and memory, including the hippocampus, amygdala, parahippocampal gyrus, thalamus, and caudate-putamen (13).

Role of Insulin in Learning and Memory

The salutary effects of acute insulin administration on cognition are well documented. In rats, acute intracerebroventricular insulin administration improves memory on a passive-avoidance task and enhances spatial memory via potentially age-dependent inflammatory reduction processes (14,15). In humans, acute intravenous and intranasal insulin administration (while maintaining euglycemia) consistently improves declarative memory performance (16). Learning also appears to influ-

ence insulin receptor expression and function in the dentate gyrus and CA1 area of the hippocampus (17). Together, these studies support insulin as an important factor in normal memory functioning. Potential mechanisms for the influence of insulin on memory include regional effects of insulin on cerebral glucose metabolism, influence on components of the long-term potentiation cascade, and modulation of acetylcholine and norepinephrine, neurotransmitters that are known to influence cognitive function.

Chronic Effects of Hyperinsulinemia on Cognition

Despite the beneficial effects of acute hyperinsulinemia in the CNS, prolonged elevated levels of circulating insulin may exert an opposing influence on cognition. Sustained peripheral hyperinsulinemia reduces insulin transport into the brain (18). Prolonged insulin resistance, a syndrome characterized by high peripheral insulin and diminished insulin-mediated glucose clearance, underlies the development of type 2 diabetes. Among people with type 2 diabetes, reductions in brain volume (most prominently in the frontal and temporal lobes) and corresponding impairments in cognition are found in comparison to nondiabetic control subjects (19,20). Even in the absence of hyperglycemia, declarative memory impairment has been observed in individuals with chronic hyperinsulinemia (21), consistent with a deleterious role of insulin resistance on cognitive function. Subtle cognitive changes that can accompany early stages of insulin resistance due to aging, type 2 diabetes, and other factors may eventually develop into clinically significant cognitive impairment, including dementia (Figure 1).

Toward a Precision Medicine Model for Dementia: Type 2 Diabetes as a Target Risk Factor

Precision health uses emerging knowledge about specific diseases to identi-

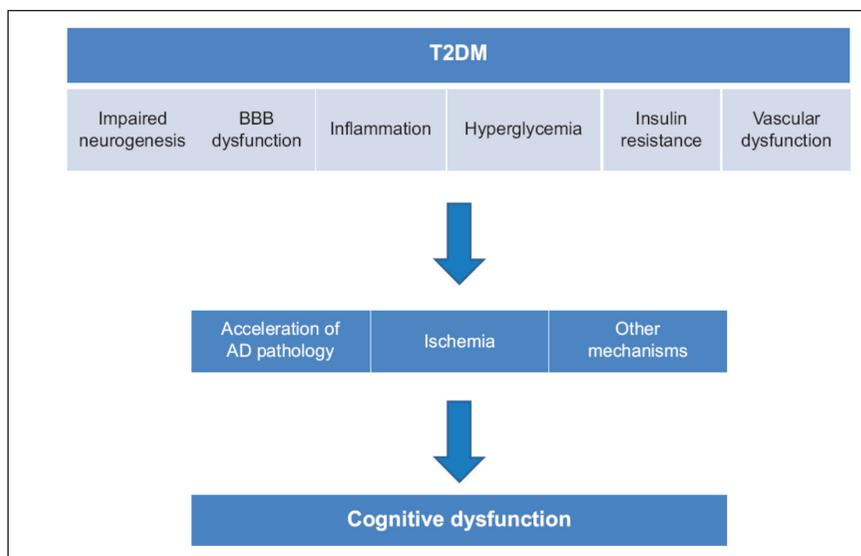


FIGURE 1. Mechanism of type 2 diabetes–associated cognitive dysfunction. AD, Alzheimer’s disease; BBB, blood-brain barrier; T2DM, type 2 diabetes mellitus. Reprinted from Umegaki K. Type 2 diabetes as a risk factor for cognitive impairment: current insights. *Clin Interv Aging* 2014;9:1011–1019. This is an open-access article distributed under the Creative Commons attribution license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

fy optimal and targeted interventions based on individually determined risk factors. To effectively adapt the concept of precision health to cognitive impairment and dementia in older adults, it is imperative to first identify groups of differing risk.

Dementia develops as a result of a complex interplay of clinical and biological factors and is beset by multiple underlying pathological features. People with type 2 diabetes represent an important risk group for cognitive impairment and dementia caused by both Alzheimer’s disease dementia and vascular brain injury. For example, a recent meta-analysis found that type 2 diabetes was associated with a 60% increase in risk for all-cause dementia (22), and a population-based longitudinal study found a 16% increased risk for dementia even among those in which type 2 diabetes onset was recent (23). Furthermore, type 2 diabetes increases the risk of mortality in patients who already have dementia, suggesting that targeted intervention at any point may improve health

outcomes (24). Although many of these studies examined risk related to all-cause dementia, there is evidence that two specific subtypes, Alzheimer’s disease dementia and vascular dementia, are most strongly associated with type 2 diabetes.

Type 2 Diabetes and Alzheimer’s Disease Dementia

The importance of the connection between type 2 diabetes and Alzheimer’s disease dementia is perhaps best captured by the term “type 3 diabetes,” coined to describe a portion of patients who develop Alzheimer’s disease dementia presumably as a result of diabetes-related injury and degeneration (25). Meta-analytic data demonstrate a 56% increased risk for Alzheimer’s disease dementia among individuals with type 2 diabetes (22). Among the studies included in the meta-analysis was the prospective, community-based Rotterdam study, which found that type 2 diabetes significantly increased the risk of Alzheimer’s disease dementia, with greater risk apparent in people who

were treated with insulin (and therefore likely to be in the more severe stages of the disease) at baseline (26). A type 2 diabetes diagnosis appears to raise the risk for Alzheimer’s disease dementia independently (although likely with additive effects) from vascular or other dementias or from *APOE E4* gene status (26,27). Among patients already diagnosed with Alzheimer’s disease dementia, an increased prevalence of type 2 diabetes (35 vs. 18% in nondemented control subjects) and impaired glucose tolerance (46 vs. 24%) was reported (28).

Despite strong results from observational studies, recent explorations into genome-wide associations for type 2 diabetes susceptibility loci, as well as Mendelian randomization (MR) studies that combine genetic factors for type 2 diabetes, have failed to find an association with Alzheimer’s disease dementia (29,30). However, in a follow-up MR study that examined single nucleotide polymorphisms independently according to their specific biological mechanism, Alzheimer’s disease dementia risk correlated negatively with insulin sensitivity only (31), a finding that is not surprising given the wealth of literature that connects insulin dysfunction with Alzheimer’s disease dementia–specific neuropathological changes. In addition, a recent examination of genome-wide association study data found significant overlap between single-nucleotide polymorphisms (SNPs) associated with type 2 diabetes and Alzheimer’s disease, providing initial evidence that the two diseases may indeed share genetic risk. Among the shared type 2 diabetes and Alzheimer’s risk–associated SNPs, those responsible for immune regulation, cell signaling, and long-term potentiation were strongly represented (32). Further investigation into the shared genetic risk profile between type 2 diabetes and Alzheimer’s disease may lead to targeted and more effective prevention and intervention approaches.

There are several potential mechanisms by which type 2 diabetes may induce the neuropathological changes of Alzheimer's disease. Chronic peripheral hyperinsulinemia caused by insulin resistance in type 2 diabetes ultimately lowers brain insulin levels and results in desensitization of neuronal insulin receptors, which may in turn lead to decreased clearance of beta amyloid (A β) peptide (33) and increased hyperphosphorylation of τ protein, which forms neurofibrillary tangles (34). In vivo, insulin modulates A β levels and promotes release of intracellular A β ; thus, reduced sensitivity to insulin in the brain may reduce clearance of A β to extracellular compartments (33). Furthermore, soluble A β binds to the insulin receptor and disrupts its signaling capacity as well as long-term potentiation induction, which forms the basis for learning and memory, an effect that is prevented by insulin pretreatment (35,36). Insulin also inhibits phosphorylation of τ protein, possibly through its regulation of glycogen synthase kinase 3 β , a downstream target in the insulin signaling pathway (37). In a conditional knockout mouse model in which the insulin receptor gene was inactivated in the CNS, phosphorylation of τ and the presence of tangle pathology was significantly increased (38,39). Type 2 diabetes also causes apoptosis in the hippocampus via a number of other dementia-associated processes that are independent of A β and τ , including increased oxidative stress, reduction of caspases, disturbed expression of apoptosis-regulator genes, and defective mitochondrial function (40). Recently, a nontransgenic animal model for Alzheimer's disease dementia was developed that relies on prolonged insulin resistance in the brain (41). In this model, rats are injected with intracerebroventricular streptozotocin to induce insulin resistance and subsequently demonstrate multiple and progressive Alzheimer's disease dementia-like changes in the brain, including accumulation of the

A β peptide and hyperphosphorylated τ , the predominant features in Alzheimer's disease dementia neuropathology, as well as associated structural and cognitive changes.

Despite evidence from in vitro and animal studies that insulin resistance modulates the predominant pathological features of Alzheimer's disease dementia, along with the consistently reported increased risk for Alzheimer's disease dementia associated with type 2 diabetes, recent imaging studies have produced somewhat conflicting results. For example, among nondemented participants in the Mayo Clinic Study of Aging (42), type 2 diabetes and elevated A1C levels were associated with brain hypometabolism in Alzheimer's disease dementia-specific brain regions; however, these factors did not correlate with significant amyloid accumulations (42). Similarly, among participants enrolled in the Alzheimer's Disease Neuroimaging Initiative, type 2 diabetes was associated with lower bilateral frontal and parietal cortical thickness, but not with cerebrospinal fluid (CSF) A β 42 levels or with amyloid accumulations by neuroimaging (43). Conversely, total and phosphorylated CSF τ proteins were negatively associated with type 2 diabetes. These findings may support a pathway to Alzheimer's disease dementia that is less dependent on A β in people with type 2 diabetes. Future studies that incorporate human τ imaging will help to clarify whether the typical course of Alzheimer's pathology is altered in the insulin-resistant brain.

Type 2 Diabetes and Vascular Dementia

Vascular disease represents a principle factor in accelerated brain aging, and vascular brain injury is an important contributor to cognitive dysfunction in older adults (44). Type 2 diabetes is a known risk factor for cardiovascular and cerebrovascular disease and may increase susceptibility to large and small caliber vessel-mediated

injury to the brain, including hypoxic events, ischemia, and blood-brain barrier leakage. Dysfunction of vascular endothelial cells secondary to insulin resistance and inflammation is a characteristic consequence of type 2 diabetes, and disruption of white matter networks is seen on neuroimaging in patients with type 2 diabetes (45–47). Furthermore, white matter dysfunction is associated with poorer cognitive performance in patients with type 2 diabetes (46–48).

Type 2 diabetes is frequently reported to be more strongly correlated with vascular dementia than with other types, including Alzheimer's disease dementia. Indeed, a recent meta-analysis of prospective studies that examined the risk of dementia in patients with type 2 diabetes reported a pooled relative risk of 2.27 for vascular dementia (22). Interestingly, new evidence suggests the increased risk for vascular dementia may be especially prominent in women; women with type 2 diabetes had a 19% greater chance of vascular dementia than men (49). In addition, those with longer duration and earlier age of onset of type 2 diabetes were more likely to develop vascular dementia.

Vascular burden in dementia is substantial but often co-occurs with other pathology (50). It is important to note that vascular risk factors may interact synergistically to amplify the effects of the Alzheimer's disease cascade. For example, vascular dysfunction may be associated with progression of both amyloid and τ pathology (51). In patients already diagnosed with Alzheimer's disease dementia and mild cognitive impairment, both cognitive and affective dysfunction were increased among those with insulin resistance (52,53), and treating vascular risk factors helped to slow cognitive decline (54). The strong association between type 2 diabetes and vascular contributions to dementia should be carefully considered when implementing treatment and prevention measures.

Precision Health: Early Detection

To effectively target and treat dementia associated with type 2 diabetes, such treatment would be most effective when implemented as early as possible, preferably during a latent or prodromal phase when the neuropathological changes are not yet significant enough to result in significant overt clinical symptoms (55). Importantly, both type 2 diabetes and dementia are associated with prolonged prodromal phases, and although symptoms may not be overt, current advances permit early identification of both syndromes.

It is now established that the pathophysiological processes underlying dementia may begin years or even decades before clinical manifestation of symptoms (56,57). Similarly, the insulin resistance syndrome is associated with a silent phase before the onset of frank diabetes, during which the pancreas is able to compensate by producing adequate levels of insulin to lower peripheral glucose levels. Midlife is thus frequently identified as a potentially crucial period of intervention. Impaired glucose tolerance and other cardiovascular risk factors during midlife may be particularly associated with impaired cognition and, later, dementia risk (58). Thus, this period may be an important point for widespread intervention in pursuit of precision health for the aging brain. For example, a recent study of late-middle-aged participants demonstrated a positive association between elevated insulin resistance and amyloid deposition (59). Thus, developing wide-scale prevention and treatment methods early in the course of insulin resistance may lead to substantial reductions in the burden of both type 2 diabetes and dementia in later years.

Precision Health: Approaches to Intervention

The precision medicine model assumes that innovative treatments will target specific risk factors based

on individuals' disease risk. Currently, approved pharmacological treatments for Alzheimer's disease are prescribed comprehensively, regardless of specific disease risk and despite known limited effectiveness. Given the impact of type 2 diabetes on risk for both vascular and Alzheimer's diseases, interventions that target insulin resistance may have significant potential to affect the clinical symptomatology associated with Alzheimer's disease dementia.

Diet

A typical Western diet consists of high levels of saturated fats and simple carbohydrates, a pattern of consumption that substantially raises the risk of insulin resistance and type 2 diabetes and related cognitive impairment. Conversely, improving the dietary profile may produce protective effects on cognitive functioning and Alzheimer's disease dementia risk (60). In animals, diets high in either saturated fat or sucrose modify processing of the amyloid precursor protein, elevate A β -related cerebrovascular disturbance, and reduce brain insulin signaling and expression of insulin-degrading enzyme (61,62). Evidence from population-based studies generally supports that an improved dietary profile, in particular, a Mediterranean diet, leads to a reduced risk of age-related cognitive decline and dementia (63). In an intervention trial (64) aimed at examining the effects of diet on cognitive function and CSF biomarkers in older adults with and without cognitive impairment, subjects were assigned to a 4-week isocaloric diet that consisted of either high saturated fat/high simple carbohydrates (HIGH; a pattern associated with type 2 diabetes and insulin resistance) or low saturated fat/low simple carbohydrates (LOW). In this study, diet intervention influenced insulin sensitivity, Alzheimer's disease dementia biomarker profile, level of oxidative stress, and cognition. The confluence of population-based evidence, animal models, and initial

intervention trials suggests that increasing insulin sensitivity via dietary modification may play a key role in overall dementia risk reduction.

Physical Exercise

An increasingly sedentary lifestyle present in Western cultures is likely also a key factor in the rise in type 2 diabetes in recent years. Aerobic exercise, which is known to be an effective treatment for diabetes and related conditions, also has potent salutary effects in the brain. Increased physical activity is consistently linked with improved learning and memory, both in humans and in animal models (65). The benefits of exercise on cognitive function have been demonstrated in healthy older adults and in adults with cognitive impairment, and exercise appears to have positive implications for the reduction of dementia risk (66–69). The favorable effects of exercise likely are exerted through multiple pathways known to be influenced by insulin, including improved cardiovascular and cerebrovascular function, anti-inflammatory processes, and enhanced insulin-dependent energy metabolism. Thus, aerobic exercise has the potential to modify multiple processes compromised in pathological brain aging.

Regular exercise during midlife, when many pathological disease processes likely begin, has been linked to reduced dementia risk and improved cognitive profile in older adults (70,71). Among older adults, those who exercised for at least 30 minutes per day, 5 days per week, for at least 10 years demonstrated lower brain A β deposition (using Pittsburgh compound B on positive emission tomography [PET] scan) (72). Given its multiple beneficial effects in the brain, regular physical exercise is recommended to help reduce the negative cognitive effects of type 2 diabetes.

Intranasal Insulin

Augmenting insulin in the CNS via intranasal insulin administration is one promising and innovative ap-

proach currently under investigation. Animal models and human studies support that insulin may be transported effectively into the CNS via intranasal administration without substantially affecting peripheral insulin levels (73–75). Initial studies examining younger adult participants found that acute intranasal administration improved both verbal memory and mood (76). Subsequently, intranasal insulin was found to improve verbal memory acutely in nondiabetic subjects with Alzheimer's disease dementia or amnesic mild cognitive impairment (MCI) without affecting plasma insulin or glucose (77,78). Research into the chronic effects of regular and long-acting formulations demonstrated improved general cognitive abilities, declarative memory, and aspects of executive function, including verbal and non-verbal working memory and selective attention, among healthy control subjects and participants with MCI and early Alzheimer's disease (79–81). In addition, changes in CSF A β 42 and τ /A β 42 ratios over the course of treatment were associated with cognitive and functional changes for insulin-treated participants. On fluorodeoxyglucose PET imaging, the intranasal insulin-treated group showed reduced progression of hypometabolism in the bilateral frontal, right temporal, bilateral occipital, and right precuneus/cuneus regions over a 4-month treatment period (80). Cumulative results to date thus support intranasal insulin administration as a potentially effective intervention in older adults with cognitive impairment or type 2 diabetes. A phase 3 clinical trial is underway to examine the effectiveness of intranasal insulin in people with early cognitive changes associated with Alzheimer's disease.

Type 2 Diabetes Treatments

Although early treatment of type 2 diabetes may reduce the risk for complications, including cognitive decline, there may be differential effects in the brain related to the type of phar-

macological intervention employed. Metformin, the typical first-line therapy for treatment of type 2 diabetes, has been both lauded for potential cognition-enhancing effects (82,83) and identified as a potential risk factor in increased cognitive impairment (84) among patients with type 2 diabetes. However, the association between metformin and cognition is murky because of multiple factors, including the fact that those taking metformin for many years may be at higher risk for cognitive impairment as a function of the disease process rather than the medication per se. Conversely, treated versus untreated type 2 diabetes may confer a differing risk for cognitive decline due to vascular injury versus amyloid deposition (85). A recent meta-analysis found no significant effect of treatment type across multiple cognitive domains among older adults with type 2 diabetes, although there appeared to be protective effects on verbal learning, working memory, and executive function for those who only used metformin (86).

Peroxisome proliferator-activated receptor- γ (PPAR- γ) agonists, which act specifically to reduce insulin resistance, may help to normalize A β levels in the brain and to improve associated behavioral symptoms. Ongoing in vitro and animal studies show beneficial effects of these agents via reduced inflammation, enhanced clearance of A β , reductions in hyperphosphorylation of τ , and improved synaptic plasticity (Figure 2) (87–89).

However, clinical trials using these medications have been less convincing. Although early pilot studies suggested improved cognition, a more favorable plasma A β 40/42 ratio, and enhanced regional cerebral blood flow in patients with MCI or early Alzheimer's disease (90), subsequent phase 3 clinical trials using rosiglitazone failed to show cognitive improvement in patients with mild to moderate Alzheimer's disease dementia (91,92). Pioglitazone has produced similarly mixed results.

Treatment with pioglitazone in patients with both type 2 diabetes and Alzheimer's disease dementia produced improvement in general cognitive status and declarative verbal memory, as well as improved regional cerebral blood flow in the parietal lobe, after 6 months of treatment (93,94). However, another trial that was designed primarily to assess the safety of pioglitazone in nondiabetic patients with Alzheimer's disease dementia failed to show any improvements on secondary cognitive and functional outcome measures (95).

Interestingly, a recent in vitro model suggested that a subclinical dose of rosiglitazone may produce more beneficial effects on A β clearance than higher doses (96). Thus, follow-up studies that use lower doses may be illuminating. Furthermore, the larger trials above included patients with clinically diagnosed Alzheimer's disease dementia; it is possible that treating insulin resistance before the onset of clinically significant dementia (e.g., MCI) may produce more favorable cognitive results.

Practical Treatment Considerations

Given the relationship between type 2 diabetes and subsequent clinical effects on vascular or Alzheimer's pathology, it is reasonable to provide guidelines to patients at multiple levels of intervention. Primary prevention of type 2 diabetes and other metabolic and vascular diseases may ultimately be crucial to curtailing the rapid increase in the cognitive disorders of aging. Thus, instituting dietary and exercise guidelines at midlife or before, particularly among those most at risk for cardiovascular disease or diabetes, is particularly important. Once diabetes has been diagnosed, targeted secondary prevention methods designed to reduce or even reverse the impact of the disease early on, including diet, exercise, and any necessary medical treatments, should

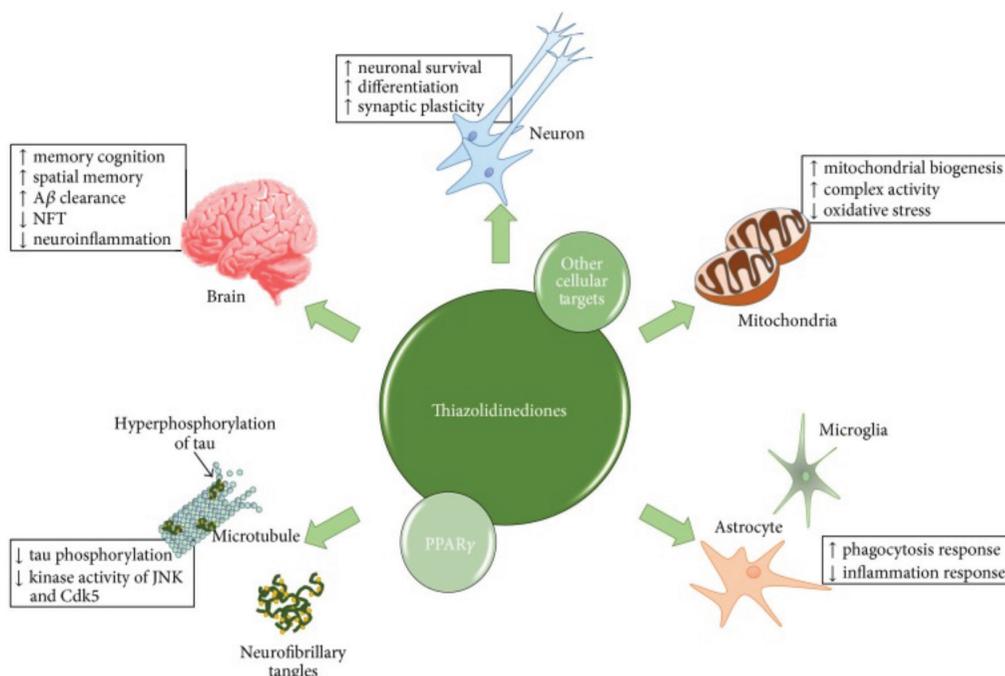


FIGURE 2. Targets of thiazolidinedione (TZD) drugs in Alzheimer’s disease. TZDs can bind to PPAR- γ receptors and other pathways that regulate energy metabolism in cellular and animal models of Alzheimer’s disease. In cognition and behavioral tests, these drugs increase the memory performance of the animals and also decrease A β deposits, accelerating amyloid plaque clearance. At more cellular levels, TZDs promote neuronal survival, differentiation, and synaptic plasticity and also increase phagocytosis and reduce neuroinflammation in both astrocytes and microglia. In the mitochondria, TZDs induce biogenesis and enhance the mitochondrial function observed by a rise in respiratory complex activities and decrease in oxidative stress. Finally, TZDs are capable of reducing τ phosphorylation through the inhibition of different kinase activities and the later formation of the neurofibrillary tangles presented in Alzheimer’s disease. Reprinted from Pérez MJ, Quintanilla RA. Therapeutic actions of the thiazolidinediones in Alzheimer’s disease. *PPAR Res* 2015;2015:957248. This is an open-access article distributed under the Creative Commons attribution license, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

be considered. In particular, those at risk for cognitive decline, including patients with a family history of dementia, additional vascular risk factors, or a diagnosis of MCI, may be best targeted for education and intervention. Referral for detailed cognitive assessment and intervention should be considered for those who express concerns about changes in cognition. Baseline cognitive assessment may be useful for older adults diagnosed with diabetes to identify those at high cognitive risk (e.g., MCI) and to adequately track subsequent cognitive changes over time. Finally, for those who have already developed clinically significant cognitive symptoms, treatments now in development such as those described above may eventually represent viable options for tertiary prevention.

Summary

With an aging population and concurrent rise in chronic health conditions has come a rapid escalation in the incidence of both type 2 diabetes and dementia. The risk for cognitive impairment and dementia is increased among those with type 2 diabetes, and insulin resistance represents a potential mechanism by which both Alzheimer’s and vascular disease can develop. Fortunately, type 2 diabetes is amenable to intervention, and promising therapeutic interventions are under investigation. The abilities to establish risk among specific populations, identify and perhaps prevent progression of the disease early in its process, and institute targeted interventions help to establish type 2 diabetes as an ideal candidate for a precision health approach in dementia.

Acknowledgments

This work was supported by National Institutes of Health grants P50AG005135 and P50NS062684.

Duality of Interest

No potential conflicts of interest relevant to this article were reported.

References

- Hassing LB, Grant MD, Hofer SM, et al. Type 2 diabetes mellitus contributes to cognitive decline in old age: a longitudinal population-based study. *J Int Neuropsychol Soc* 2004;10:599–607
- Strachan MW. R. D. Lawrence Lecture 2010: The brain as a target organ in type 2 diabetes: exploring the links with cognitive impairment and dementia. *Diabet Med* 2011;28:141–147
- Yaffe K, Blackwell T, Kanaya AM, Davidowitz N, Barrett-Connor E, Krueger K. Diabetes, impaired fasting glucose, and development of cognitive impairment in older women. *Neurology* 2004;63:658–663

4. Shaik MA, Chan QL, Xu J, et al. Risk factors of cognitive impairment and brief cognitive tests to predict cognitive performance determined by a formal neuropsychological evaluation of primary health care patients. *J Am Med Dir Assoc* 2016;17:343–347
5. Tilvis RS, Kahonen-Vare MH, Jolkkonen J, Valvanne J, Pitkala KH, Strandberg TE. Predictors of cognitive decline and mortality of aged people over a 10-year period. *J Gerontol A Biol Sci Med Sci* 2004;59:268–274
6. Mehrabian S, Raycheva M, Gateva A, et al. Cognitive dysfunction profile and arterial stiffness in type 2 diabetes. *J Neurol Sci* 2012;322:152–156
7. McCrimmon RJ, Ryan CM, Friar BM. Diabetes and cognitive dysfunction. *Lancet* 2012;379:2291–2299
8. McFall GP, Wiebe SA, Vergote D, Anstey KJ, Dixon RA. Alzheimer's genetic risk intensifies neurocognitive slowing associated with diabetes in non-demented older adults. *Alzheimer's Dement* 2015;1:395–402
9. Yaffe K, Peltz CB, Ewing SK, et al. Long-term cognitive trajectories and mortality in older women. *J Gerontol A Biol Sci Med Sci* 2016;71:1074–1080
10. Goveas JS, Rapp SR, Hogan PE, et al. Predictors of optimal cognitive aging in 80+ women: the Women's Health Initiative Memory Study. *J Gerontol A Biol Sci Med Sci* 2016;71(Suppl. 1):S62–S71
11. Banks WA, Jaspan JB, Kastin AJ. Selective, physiological transport of insulin across the blood-brain barrier: novel demonstration by species-specific radioimmunoassays. *Peptides* 1997;18:1257–1262
12. Lee J, Kim K, Yu SW, Kim EK. Wnt3a upregulates brain-derived insulin by increasing NeuroD1 via Wnt/beta-catenin signaling in the hypothalamus. *Mol Brain* 2016;9:24
13. Ghasemi R, Haeri A, Dargahi L, Mohamed Z, Ahmadiani A. Insulin in the brain: sources, localization and functions. *Mol Neurobiol* 2013;47:145–171
14. Adzovic L, Lynn AE, D'Angelo HM, et al. Insulin improves memory and reduces chronic neuroinflammation in the hippocampus of young but not aged brains. *J Neuroinflammation* 2015;12:63
15. Park CR, Seeley RJ, Craft S, Woods SC. Intracerebroventricular insulin enhances memory in a passive-avoidance task. *Physiol Behav* 2000;68:509–514
16. Freiherr J, Hallschmid M, Frey WH 2nd, et al. Intranasal insulin as a treatment for Alzheimer's disease: a review of basic research and clinical evidence. *CNS Drugs* 2013;27:505–514
17. Zhao W, Chen H, Xu H, et al. Brain insulin receptors and spatial memory: correlated changes in gene expression, tyrosine phosphorylation, and signaling molecules in the hippocampus of water maze trained rats. *J Biol Chem* 1999;274:34893–34902
18. Schwartz MW, Figlewicz DF, Kahn SE, Baskin DG, Greenwood MR, Porte D Jr. Insulin binding to brain capillaries is reduced in genetically obese, hyperinsulinemic Zucker rats. *Peptides* 1990;11:467–472
19. Moran C, Phan TG, Chen J, et al. Brain atrophy in type 2 diabetes: regional distribution and influence on cognition. *Diabetes Care* 2013;36:4036–4042
20. Brundel M, Kappelle LJ, Biessels GJ. Brain imaging in type 2 diabetes. *Eur Neuropsychopharmacol* 2014;24:1967–1981
21. Vanhanen M, Koivisto K, Kuusisto J, et al. Cognitive function in an elderly population with persistent impaired glucose tolerance. *Diabetes Care* 1998;21:398–402
22. Gudala K, Bansal D, Schifano F, Bhansali A. Diabetes mellitus and risk of dementia: a meta-analysis of prospective observational studies. *J Diabetes Invest* 2013;4:640–650
23. Haroon NN, Austin PC, Shah BR, Wu J, Gill SS, Booth GL. Risk of dementia in seniors with newly diagnosed diabetes: a population-based study. *Diabetes Care* 2015;38:1868–1875
24. van de Vorst IE, Koek HL, de Vries R, Bots ML, Reitsma JB, Vaartjes I. Effect of vascular risk factors and diseases on mortality in individuals with dementia: a systematic review and meta-analysis. *J Am Geriatr Soc* 2016;64:37–46
25. Mittal K, Katare DP. Shared links between type 2 diabetes mellitus and Alzheimer's disease: a review. *Diabetes Metab Syndr* 2016;pii:S1871-4021: 30070-9. Electronically published ahead of print (DOI: 10.1016/j.dsx.2016.01.021)
26. Ott A, Stolk RP, van Harskamp F, Pols HA, Hofman A, Breteler MM. Diabetes mellitus and the risk of dementia: the Rotterdam Study. *Neurology* 1999;53:1937–1942
27. Maher PA, Schubert DR. Metabolic links between diabetes and Alzheimer's disease. *Expert Rev Neurother* 2009;9:617–630
28. Janson J, Laedtke T, Parisi JE, O'Brien P, Petersen RC, Butler PC. Increased risk of type 2 diabetes in Alzheimer disease. *Diabetes* 2004;53:474–481
29. Ostergaard SD, Mukherjee S, Sharp SJ, et al. Associations between potentially modifiable risk factors and Alzheimer disease: a Mendelian randomization study. *PLoS Med* 2015;12:e1001841; discussion e1001841
30. Chung SJ, Kim MJ, Kim J, et al. Association of type 2 diabetes GWAS loci and the risk of Parkinson's and Alzheimer's diseases. *Parkinsonism Relat Disord* 2015;21:1435–1440
31. Walter S, Marden JR, Kubzansky LD, et al. Diabetic phenotypes and late-life dementia risk: a mechanism-specific Mendelian randomization study. *Alzheimer Dis Assoc Disord* 2016;30:15–20
32. Hao K, Di Narzo AF, Ho L, et al. Shared genetic etiology underlying Alzheimer's disease and type 2 diabetes. *Mol Aspects Med* 2015;43–44:66–76
33. Gasparini L, Gouras GK, Wang R, et al. Stimulation of beta-amyloid precursor protein trafficking by insulin reduces intraneuronal beta-amyloid and requires mitogen-activated protein kinase signaling. *J Neurosci* 2001;21:2561–2570
34. Ahmed S, Mahmood Z, Zahid S. Linking insulin with Alzheimer's disease: emergence as type III diabetes. *Neurol Sci* 2015;36:1763–1769
35. Townsend M, Mehta T, Selkoe DJ. Soluble Abeta inhibits specific signal transduction cascades common to the insulin receptor pathway. *J Biol Chem* 2007;282:33305–33312
36. De Felice FG, Vieira MN, Bomfim TR, et al. Protection of synapses against Alzheimer's-linked toxins: insulin signaling prevents the pathogenic binding of Abeta oligomers. *Proc Natl Acad Sci U S A* 2009;106:1971–1976
37. Hong M, Lee VM. Insulin and insulin-like growth factor-1 regulate tau phosphorylation in cultured human neurons. *J Biol Chem* 1997;272:19547–19553
38. Schubert M, Brazil DP, Burks DJ, et al. Insulin receptor substrate-2 deficiency impairs brain growth and promotes tau phosphorylation. *J Neurosci* 2003;23:7084–7092
39. Schubert M, Gautam D, Surjo D, et al. Role for neuronal insulin resistance in neurodegenerative diseases. *Proc Natl Acad Sci U S A* 2004;101:3100–3105
40. Vincent AM, Brownlee M, Russell JW. Oxidative stress and programmed cell death in diabetic neuropathy. *Ann N Y Acad Sci* 2002;959:368–383
41. Knezovic A, Osmanovic-Barilar J, Curlin M, et al. Staging of cognitive deficits and neuropathological and ultrastructural changes in streptozotocin-induced rat model of Alzheimer's disease. *J Neural Transm* 2015;122:577–592
42. Roberts RO, Knopman DS, Cha RH, et al. Diabetes and elevated hemoglobin A1c levels are associated with brain hypometabolism but not amyloid accumulation. *J Nuclear Med* 2014;55:759–764
43. Moran C, Beare R, Phan TG, Bruce DG, Callisaya ML, Srikanth V. Alzheimer's Disease Neuroimaging I: Type 2 diabetes mellitus and biomarkers of neurodegeneration. *Neurology* 2015;85:1123–1130
44. Kapasi A, Schneider JA. Vascular contributions to cognitive impairment, clinical Alzheimer's disease, and dementia in older persons. *Biochim Biophys Acta* 2016;1862:878–886
45. Reijmer YD, Leemans A, Brundel M, Kappelle LJ, Biessels GJ, Utrecht Vascular Cognitive Impairment Study Group. Disruption of the cerebral white matter

- network is related to slowing of information processing speed in patients with type 2 diabetes. *Diabetes* 2013;62:2112–2115
46. Reijmer YD, Brundel M, de Bresser J, Kappelle LJ, Leemans A, Biessels GJ, Utrecht Vascular Cognitive Impairment Study Group. Microstructural white matter abnormalities and cognitive functioning in type 2 diabetes: a diffusion tensor imaging study. *Diabetes Care* 2013;36:137–144
47. Zhang JH, Xu HZ, Shen QF, et al. Nepsilon-(carboxymethyl)-lysine, white matter, and cognitive function in diabetes patients. *Can J Neurol Sci* 2016;43:518–522
48. Yau PL, Javier D, Tsui W, et al. Emotional and neutral declarative memory impairments and associated white matter microstructural abnormalities in adults with type 2 diabetes. *Psychiatry Res* 2009;174:223–230
49. Chatterjee S, Peters SA, Woodward M, et al. Type 2 diabetes as a risk factor for dementia in women compared with men: a pooled analysis of 2.3 million people comprising more than 100,000 cases of dementia. *Diabetes Care* 2016;39:300–307
50. Flanagan M, Larson EB, Latimer CS, et al. Clinical-pathologic correlations in vascular cognitive impairment and dementia. *Biochim Biophys Acta* 2016;1862:945–951
51. Kamal A, Biessels GJ, Gispen WH, Ramakers GM. Synaptic transmission changes in the pyramidal cells of the hippocampus in streptozotocin-induced diabetes mellitus in rats. *Brain Res* 2006;1073–1074:276–280
52. Hishikawa N, Fukui Y, Sato K, Yamashita T, Ohta Y, Abe K. Clinical features of incidental mild cognitive impairment and dementia in a population-based study. *Geriatr Gerontol Int* 2016. Electronically published ahead of print (DOI: 10.1111/ggi.12778)
53. Hishikawa N, Fukui Y, Sato K, et al. Cognitive and affective functions in Alzheimer's disease patients with metabolic syndrome. *Eur J Neurol* 2016;23:339–345
54. Deschaintre Y, Richard F, Leys D, Pasquier F. Treatment of vascular risk factors is associated with slower decline in Alzheimer disease. *Neurology* 2009;73:674–680
55. Cholerton B, Larson EB, Quinn JF, et al. Precision medicine: clarity for the complexity of dementia. *Am J Pathol* 2016;186:500–506
56. Masdeu JC, Kreisl WC, Berman KF. The neurobiology of Alzheimer disease defined by neuroimaging. *Curr Opin Neurol* 2012;25:410–420
57. Sperling RA, Aisen PS, Beckett LA, et al. Toward defining the preclinical stages of Alzheimer's disease: recommendations from the National Institute on Aging–Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimer's Dement* 2011;7:280–292
58. Tolppanen AM, Solomon A, Soininen H, Kivipelto M. Midlife vascular risk factors and Alzheimer's disease: evidence from epidemiological studies. *J Alzheimer's Dis* 2012;32:531–540
59. Willette AA, Johnson SC, Birdsill AC, et al. Insulin resistance predicts brain amyloid deposition in late middle-aged adults. *Alzheimer's Dement* 2015;11:504–510
60. Solfrizzi V, Panza F, Frisardi V, et al. Diet and Alzheimer's disease risk factors or prevention: the current evidence. *Expert Rev Neurother* 2011;11:677–708
61. Schroeder JE, Richardson JC, Virley DJ. Dietary manipulation and caloric restriction in the development of mouse models relevant to neurological diseases. *Biochim Biophys Acta* 2010;1802:840–846
62. Takechi R, Galloway S, Pallegage-Gamarallage MM, Lam V, Mamo JC. Dietary fats, cerebrovasculature integrity and Alzheimer's disease risk. *Prog Lipid Res* 2010;49:159–170
63. Smith PJ, Blumenthal JA. Diet and neurocognition: review of evidence and methodological considerations. *Curr Aging Sci* 2010;3:57–66
64. Bayer-Carter JL, Green PS, Montine TJ, et al. Diet intervention and cerebrospinal fluid biomarkers in amnesic mild cognitive impairment. *Arch Neurol* 2011;68:743–752
65. Archer T. Physical exercise alleviates debilities of normal aging and Alzheimer's disease. *Acta Neurol Scand* 2011;123:221–238
66. Kramer AF, Hahn S, Cohen NJ, et al. Ageing, fitness and neurocognitive function. *Nature* 1999;400:418–419
67. Kramer AF, Erickson KI, Colcombe SJ. Exercise, cognition, and the aging brain. *J Appl Physiol* 2006;101:1237–1242
68. Baker LD, Frank LL, Foster-Schubert K, et al. Aerobic exercise improves cognition for older adults with glucose intolerance, a risk factor for Alzheimer's disease. *J Alzheimer's Dis* 2010;22:569–579
69. Lautenschlager NT, Cox KL, Flicker L, et al. Effect of physical activity on cognitive function in older adults at risk for Alzheimer disease: a randomized trial. *JAMA* 2008;300:1027–1037
70. Geda YE, Roberts RO, Knopman DS, et al. Physical exercise, aging, and mild cognitive impairment: a population-based study. *Arch Neurol* 2010;67:80–86
71. Andel R, Crowe M, Pedersen NL, Fratiglioni L, Johansson B, Gatz M. Physical exercise at midlife and risk of dementia three decades later: a population-based study of Swedish twins. *J Gerontol A Biol Sci Med Sci* 2008;63:62–66
72. Liang KY, Mintun MA, Fagan AM, et al. Exercise and Alzheimer's disease biomarkers in cognitively normal older adults. *Ann Neurol* 2010;68:311–318
73. Born J, Lange T, Kern W, McGregor GP, Bickel U, Fehm HL. Sniffing neuropeptides: a transnasal approach to the human brain. *Nat Neurosci* 2002;5:514–516
74. Francis GJ, Martinez JA, Liu WQ, et al. Intranasal insulin prevents cognitive decline, cerebral atrophy and white matter changes in murine type I diabetic encephalopathy. *Brain* 2008;131:3311–3334
75. Thorne RG, Pronk GJ, Padmanabhan V, Frey WH 2nd. Delivery of insulin-like growth factor-I to the rat brain and spinal cord along olfactory and trigeminal pathways following intranasal administration. *Neuroscience* 2004;127:481–496
76. Benedict C, Hallschmid M, Hatke A, et al. Intranasal insulin improves memory in humans. *Psychoneuroendocrinology* 2004;29:1326–1334
77. Reger MA, Watson GS, Green PS, et al. Intranasal insulin administration dose-dependently modulates verbal memory and plasma amyloid-beta in memory-impaired older adults. *J Alzheimer's Dis* 2008;13:323–331
78. Reger MA, Watson GS, Frey WH 2nd, et al. Effects of intranasal insulin on cognition in memory-impaired older adults: modulation by APOE genotype. *Neurobiol Aging* 2006;27:451–458
79. Claxton A, Baker LD, Hanson A, et al. Long-acting intranasal insulin detemir improves cognition for adults with mild cognitive impairment or early-stage Alzheimer's disease dementia. *J Alzheimer's Dis* 2015;44:897–906
80. Craft S, Baker LD, Montine TJ, et al. Intranasal insulin therapy for Alzheimer disease and amnesic mild cognitive impairment: a pilot clinical trial. *Arch Neurol* 2012;69:29–38
81. Reger MA, Watson GS, Green PS, et al. Intranasal insulin improves cognition and modulates beta-amyloid in early AD. *Neurology* 2008;70:440–448
82. Ng TP, Feng L, Yap KB, Lee TS, Tan CH, Winblad B. Long-term metformin usage and cognitive function among older adults with diabetes. *J Alzheimer's Dis* 2014;41:61–68
83. Mostafa DK, Ismail CA, Ghareeb DA. Differential metformin dose-dependent effects on cognition in rats: role of Akt. *Psychopharmacology* 2016;233:2513–2524
84. Moore EM, Mander AG, Ames D, et al. Increased risk of cognitive impairment in patients with diabetes is associated with metformin. *Diabetes Care* 2013;36:2981–2987
85. Sonnen JA, Larson EB, Brickell K, et al. Different patterns of cerebral injury in dementia with or without diabetes. *Arch Neurol* 2009;66:315–322
86. Herath PM, Cherbuin N, Eramudugolla R, Anstey KJ. The effect of diabetes medication on cognitive function: evidence from the PATH Through Life study. *Biomed Res Int* 2016;2016:7208429

87. Lan LF, Zheng L, Yang X, Ji XT, Fan YH, Zeng JS. Peroxisome proliferator-activated receptor-gamma agonist pioglitazone ameliorates white matter lesion and cognitive impairment in hypertensive rats. *CNS Neurosci Ther* 2015;21:410–416
88. Kariharan T, Nanayakkara G, Parameshwaran K, et al. Central activation of PPAR-gamma ameliorates diabetes induced cognitive dysfunction and improves BDNF expression. *Neurobiol Aging* 2015;36:1451–1461
89. Liu LP, Yan TH, Jiang LY, et al. Pioglitazone ameliorates memory deficits in streptozotocin-induced diabetic mice by reducing brain beta-amyloid through PPARgamma activation. *Acta Pharmacol Sin* 2013;34:455–463
90. Watson GS, Cholerton BA, Reger MA, et al. Preserved cognition in patients with early Alzheimer disease and amnesic mild cognitive impairment during treatment with rosiglitazone: a preliminary study. *Am J Geriatr Psychiatry* 2005;13:950–958
91. Harrington C, Sawchak S, Chiang C, et al. Rosiglitazone does not improve cognition or global function when used as adjunctive therapy to AChE inhibitors in mild-to-moderate Alzheimer's disease: two phase 3 studies. *Curr Alzheimer Res* 2011;8:592–606
92. Gold M, Alderton C, Zvartau-Hind M, et al. Rosiglitazone monotherapy in mild-to-moderate Alzheimer's disease: results from a randomized, double-blind, placebo-controlled phase III study. *Dement Geriatr Cogn Disord* 2010;30:131–146
93. Hanyu H, Sato T, Kiuchi A, Sakurai H, Iwamoto T. Pioglitazone improved cognition in a pilot study on patients with Alzheimer's disease and mild cognitive impairment with diabetes mellitus. *J Am Geriatr Soc* 2009;57:177–179
94. Sato T, Hanyu H, Hirao K, Kanetaka H, Sakurai H, Iwamoto T. Efficacy of PPAR-gamma agonist pioglitazone in mild Alzheimer disease. *Neurobiol Aging* 2011;32:1626–1633
95. Geldmacher DS, Fritsch T, McClendon MJ, Landreth G. A randomized pilot clinical trial of the safety of pioglitazone in treatment of patients with Alzheimer disease. *Arch Neurology* 2011;68:45–50
96. Moon JH, Kim HJ, Yang AH, et al. The effect of rosiglitazone on LRP1 expression and amyloid beta uptake in human brain microvascular endothelial cells: a possible role of a low-dose thiazolidinedione for dementia treatment. *Int J Neuropsychopharmacol* 2012;15:135–142