COMMENTARY

# Advanced glycation end products, dementia, and diabetes

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It is becoming abundantly clear that the insight into the pathological process of Alzheimer's disease (AD) provided through autosomal dominant variants of the condition is only a partial one. The formation and aggregation of Aβ and the phosphorylation and aggregation of tau are clearly part of the core pathogenesis. However, although these may be necessary processes, and indeed in familial forms of the condition possibly also sufficient processes, they are not the whole story in the common late-onset forms of the disease. Here, mixed pathologies are the norm and at post mortem the plaques and tangles formed by Aβ and tau are accompanied also by inflammation and by vascular disease. This finding is congruent with the epidemiology that has long pointed to only three substantial factors that alter risk of dementia other than age: head injury, anti-inflammatory drugs, and diabetes. It is reasonably clear why head injury and anti-inflammatory drugs might affect risk but the relationship between diabetes and dementia has been far less clear. It could be that diabetes simply increases risk of vascular and related damage to the brain as it does to limbs, kidneys, and other organs. More interesting to molecular scientists are the observations that insulin signaling modifies amyloid precursor protein (APP) metabolism and tau phosphorylation in cells and in animal models, suggesting a possible influence of metabolic pathways on the canonical pathway of AD. Most intriguing of all is the observation that such pathways and processes are related not only to metabolic disease and to AD, but also to aging or longevity itself. In PNAS, Cai et al. (1) shed light on these complex interactions and point to possible clinical implications, including both biomarkers and potential therapeutics.

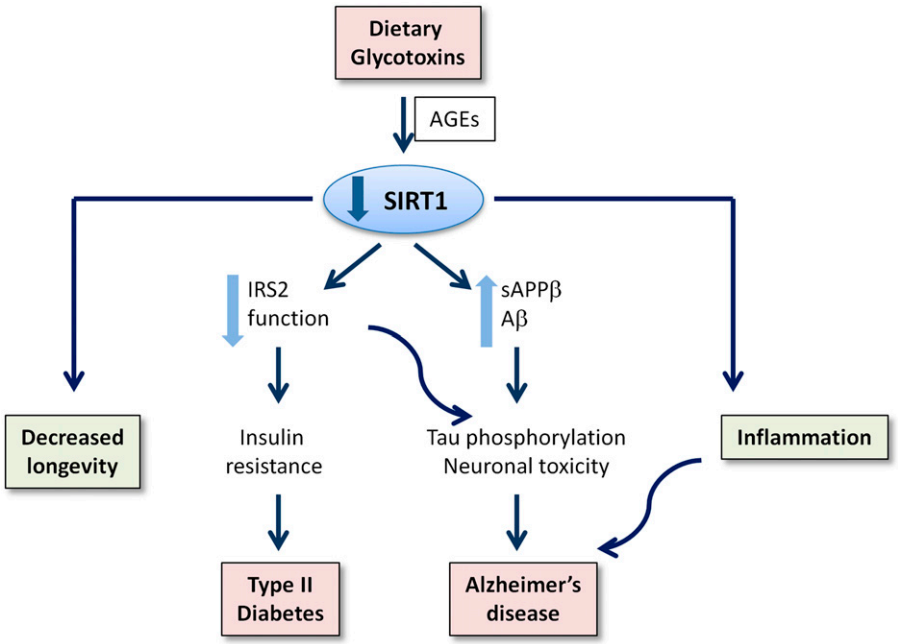


**Fig. 1.** Glycotoxin-induced dementia and diabetes pathways. Cai et al. (1) show that dietary glycotoxins reduce SIRT1 expression and increase amyloidogenic APP metabolism. This theory suggests SIRT1 as the link between pathways that induce insulin resistance and diabetes, as well as Alzheimer's and inflammation and possibly also aging itself.

In line with the considerable evidence for an oxidant-mediated pathogenic effect, Cai et al. show that a pro-oxidant diet in mice induces β-cleaved APP and Aβ generation. At the same time these mice, fed methyl-glyoxyl (MG) derivatives, had increased weight and systemic insulin resistance. In both the mice and also in a human cohort, dietary MG levels and accompanying advanced glycation end products (AGEs) correlated positively with cognitive deficits or decline and inversely with survival factor sirtuin-1 (SIRT1) levels and other markers of insulin sensitivity.

The most striking, and sometimes neglected, observation in relation to risk of AD is that age increases it. This might be a simple inconsequential coincidence; it takes a lifetime of insult to result in neuronal dysfunction. However, the results of Cai et al. (1) hint at a more substantial possibility. The sirtuins, of which there are seven in mammals, have long been implicated as factors involved in longevity (2, 3). The most studied—SIRT1, -3 and -6—are all increased as a consequence of caloric restriction (CR), and CR increases both longevity and insulin sensitivity and also reduces certain features of AD pathology (4). It may indeed be the effect of CR on SIRT expression or function that is the critical factor, as mice lacking SIRT1 had a shortened lifespan even in the context of CR (5). These data suggest that the positive effects of CR are, at least in part, mediated by the induction of sirtuins.

Cai et al. (1) add another element to this growing story in showing that an oxidative diet of MG derivatives (MG+) decreases SIRT1 protein in mouse brain and, in man, there is evidence of increased MG in blood correlated with decreased SIRT1 mRNA levels in circulating monocytes. There is an apparent anomaly here though: in Cai et al. increased MG is associated with cognitive decline and decreased SIRT1, whereas in mouse models of neurodegeneration SIRT1 levels are generally increased (6). A plausible explanation for this otherwise puzzling observation

Author contributions: S.L. and U.S. wrote the paper.

The authors declare no conflict of interest.

See companion article on page 4940.

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would be that mice are able to respond protectively to the disease process. This theory has been suggested before and one of the earlier experiments to find such a protective factor pointed to a substantial increase in the insulin-signaling pathway that occurs in the brain of APP transgenic mice (7), a not unexpected effect if SIRT1-induced insulin sensitivity is part of a protective pathway.

If a decrease in the sirtuins, whether induced by diet or by some other factor, increases risk of both AD pathogenesis and insulin resistance, might this be the underlying mechanism to the undoubted link between AD and diabetes (8)? In line with such a hypothesis, in mice, SIRT1 increased insulin sensitivity through acetylation and phosphorylation of insulin receptor substrate-2 (IRS2) (5), whilst loss of IRS2, as well as resulting in insulin resistance, increased Aβ-induced tau phosphorylation (9). Some recent evidence, however, suggests the effect of SIRT1 on insulin signalling might be different in neurons (10). The generation of AGEs is a common process in both diabetes and AD and might also stimulate the inflammatory response of both conditions (11).

The findings of Cai et al. (1), together with a substantial preceding literature, suggest a process whereby diet—and an excess of glycotoxins in particular—suppresses SIRT1 with adverse consequences for both systemic insulin sensitivity and AD pathogenic processes, including APP metabolism and the response of tau-kinase–regulating pathways leading to the phosphorylation of tau. Increased tau phosphorylation disrupts binding to microtubules resulting in a translocation from the axon, a loss of microtubule stability and function, and a tendency to increased aggregation (12), all of which are part of the tau-related toxicity of the disease (13). Taking these data together, our current understanding of the effect of glycotoxins is that they are able to cross-talk with pathways involved in glucose regulation and response to insulin, as well as with pathways of cytokine response and innate immunity (14), and so bring together in a network three of the four known environmental influences on AD: diabetes, inflammation, and age itself (Fig. 1). In fact, there is increasing evidence for glycotoxins being the lynchpin of the wheel of disease that includes diabetes, AD, and immunity; diets (such as those in the Mediterranean) that decrease glyocotoxins reduce risk not only of metabolic disease (15), but also of AD (16), as well as the inflammatory correlates of disease (17).

There are some fairly obvious practical considerations that follow from this integrative hypothesis; most obvious of these are public health measures to reduce calorie intake, obesity, and its associated complications, including type 2 diabetes. Another important step to consider now is to build credibility for the concept that it is not necessarily only increased caloric intake but, more specifically, increased intake of glycotoxins in the diet that plays an important role for these common human disorders. This process requires the initiation of sufficiently large controlled clinical trials specifically addressing the role of the glycotoxins, and the time seems ripe to consider this now. Might there also be other ways to build on the growing findings around glycotoxin-induced loss of sirtuin expression and function? One way might be to increase sirtuin expression directly, but which SIRT gene and in which target tissue? Another way might be to increase sirtuins indirectly, such as through resveratrol, a phytocompound found in, among other things, red wine. There is some evidence linking resveratrol directly and indirectly to the prevalence of dementia (18) and trials in man are underway. Another approach would be to target the signaling pathways downstream of SIRT1. These pathways include peroxisome proliferator-activated receptor-γ (PPARγ), and Cai et al. (1) observe, as would be expected, PPARγ suppression alongside a decrease in SIRT1 in glycotoxin-fed animals. Although trials of the PPARγ agonist Rosiglitazone did not prove efficacious in AD (19), this may be because they were conducted too late in the disease course to test the concept properly.

All of this points to an important piece of the jigsaw that many are searching for: a good biomarker of risk. If a marker, ideally a peripheral fluid marker, could be identified that would act as a herald of preclinical or incipient pathology, then secondary prevention trials in preclinical phases would become possible. There is now some evidence that the glycotoxin-induced pathway might be such a biomarker. Sirtuin 1 may be increased in serum in AD (20) and PPARγ gene variation might modify age of onset (21). AGEs and their receptors may be both risk factors and biomarkers.

It is probably too much to ask for a simple explanation of a complex disease, such as AD. Nonetheless, there is a growing body of work, substantially enhanced by Cai et al.'s report (1), that not only suggests an incidental link between metabolic disease and AD but begins to tease out the underlying molecular pathways. Specifically, the finding that a diet rich in glycotoxins increases the β-cleavage of APP, resulting in Aβ generation, and is accompanied by a decrease in SIRT1 does offer sight of a unifying hypothesis that is in line with previous evidence. More importantly, this finding offers some obvious experiments to test the hypothesis. Would a MG-rich diet have the same effects on learning and memory and on Aβ generation in mice overexpressing sirtuins? Indeed, is an effect mediated simply by SIRT1 or are some of the other six mammalian sirtuins also involved? In man do these findings replicate; and might PPARγ agonism be more efficacious in a population not only early in disease but stratified by biomarkers relevant to this pathway including AGE, RAGE, and sirtuins; and might dietary change be additive to PPARγ agonists? These and other questions follow from these data, but for now another piece of evidence has been added to the link between diabetes, AD, inflammation, aging, and indeed diet.


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