

Plasma A β : A Possible Missing Link Between Alzheimer Disease and Diabetes

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Currently, there are more than 30 million dementia patients worldwide (1). More than half of dementia is caused by Alzheimer disease (AD), which consists of both familial and sporadic forms. Familial AD is caused by mutations in the amyloid precursor protein (APP) (2) and presenilin genes (3). Both mutations cause overproduction of amyloid- β (A β), particularly its longer form, A β 42, which is more prone to aggregate. It should be noted that familial AD accounts for a small proportion of all AD cases. On the other hand, sporadic cases comprise more than 95% of AD, and emerging evidence suggests that diabetes is a nongenetic risk factor for sporadic AD (4). While diabetes increases AD 1.5–2-fold, the mechanism whereby diabetes enhances AD risk has not been elucidated. As 285 million people battle diabetes worldwide against the backdrop of an aging society (5), understanding the relationship between AD and diabetes is of extreme importance.

Interestingly, several clinical reports have suggested that AD patients also have glucose intolerance, suggesting a bidirectional relationship between the two conditions (6,7). Supporting this idea are data from animal models such as APP + *ob/ob* mice showing that AD aggravates the diabetic phenotype (8,9). Although further evidence is still required to confirm this concept, it is intriguing to investigate the mechanisms whereby AD affects the diabetic phenotype. Several possibilities can be hypothesized. First, central control of peripheral glucose metabolism may be compromised in AD (10). Second, plasma A β may mediate peripheral insulin resistance. Third, A β accumulation occurs in the pancreas (11) and skeletal muscle (12). There are also *in vitro* data suggesting a molecular link between A β and insulin. These data indicate that insulin modulates A β level by increasing its secretion (13) or by inhibiting insulin-degrading enzyme-mediated A β degradation (14).

It has been reported that plasma A β level is increased after glucose loading in an AD model (15). In humans, although the magnitude of changes is much smaller than in AD transgenic mice, the changes in plasma A β levels after oral glucose loading are nonetheless different between AD and non-AD patients (16). It is also reported that insulin administration induces a greater increase in plasma A β

level in AD patients compared with nondemented control subjects (17). Together, this evidence suggests that one of the possible mechanisms by which AD aggravates the diabetic phenotype might be attributable to plasma A β . Zhang et al. (18) previously reported that APP/presenilin 1 (PS1) transgenic AD mice with increased plasma A β 40/42 levels have impaired glucose/insulin tolerance and hepatic insulin signaling as well as activation of the JAK2/STAT3/SOCS1 pathway. In this issue of *Diabetes*, Zhang et al. (19) extended this line of investigation by examining the role of plasma A β in insulin resistance *in vivo* (Fig. 1).

Zhang et al. (19) demonstrate that plasma A β induces hepatic insulin resistance *in vivo* via JAK2. They demonstrate that injection of A β 42 upregulated fasting blood glucose level and impaired insulin tolerance and hepatic insulin signaling in mice. Consistent with the findings from their previous work, A β 42 induced SOCS-1 upregulation and JAK2/STAT3 activation in mouse liver. In this study, Zhang et al. also tried neutralization of A β in APP/PS1 to investigate the role of plasma A β in insulin resistance. They found that neutralization of A β by anti-A β antibodies inhibited hepatic JAK2/STAT3/SOCS1 signaling in APP/PS1 mice. These findings raise the possibility that inhibition of A β signaling could be a new strategy for addressing insulin resistance and diabetes. Furthermore, the investigators showed that knockdown of hepatic JAK2 by adenovirus inhibited JAK2/STAT3/SOCS-1 signaling and improved insulin sensitivity in APP/PS1 mice. The JAK/STAT/SOCS pathway was initially identified as being downstream of inflammatory cytokines (20), by which inflammation aggravates insulin resistance in the peripheral system. Even though no receptor or mediator of A β has yet been consistently identified, the JAK/STAT/SOCS pathway is one of the candidates that A β could affect directly or indirectly. It is also noteworthy that A β causes insulin resistance in culture neurons (21) and the central nervous system (CNS) *in vivo* (8). Therefore, the detailed pathway from A β to systemic insulin resistance through JAK/STAT/SOCS might also provide insights into the role of A β in the CNS.

The most important finding of this study is that neutralization of A β downregulated fasting blood glucose level and improved insulin sensitivity in AD model mice. Whether AD aggravates diabetes in clinical settings in humans requires more intensive observational studies. It should be noted that one weakness of this study was the relatively high concentration of injected A β . When A β was injected intraperitoneally, plasma concentrations were 400 and 1,500 pg/mL, or nearly 80 and 300 pmol/L. However, plasma A β 42 level in humans is usually less than these values (22). Moreover, as intraperitoneal injection could directly affect hepatic cells in addition to the effect through vessels, a more in-depth discussion on the role of plasma A β on hepatic insulin sensitivity might be helpful. Another important question is whether plasma A β plays a role in the peripheral system such as in insulin resistance

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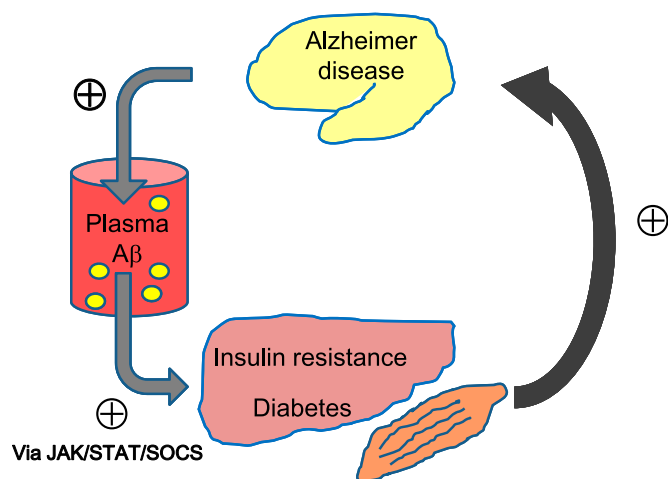


FIG. 1. Plasma A β mediates systemic insulin resistance in the interaction between Alzheimer disease and diabetes. In this issue of *Diabetes*, Zhang et al. (19) report that plasma A β causes hepatic insulin resistance via the JAK/STAT/SOCS pathway *in vivo*.

in humans, although it undoubtedly has a pathological role in the CNS. If these questions could be addressed clearly, prevention of these two devastating diseases might be strengthened by interrupting this vicious cycle.

It is still unclear whether plasma A β could be a non-invasive biomarker for AD (22). Because the measurement of plasma A β level is simple and straightforward, its clinical significance in the potential relationship between AD and diabetes warrants further investigation. Importantly, since it is known that the plasma A β level could be affected by various molecules and physiological conditions, other common diseases affecting insulin sensitivity such as hypertension, obesity, and dyslipidemia might have influence on plasma A β level and, by extension, its utility as a marker for AD. Continuing progress in pharmacotherapy to neutralize A β by vaccine or low molecular weight drugs might answer questions regarding the interaction between AD and diabetes in humans in the very near future.

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