Adipose-derived amyloid protein exerts cardiometabolic effect

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An epidemiological link between type 2 diabetes and Alzheimer's disease has been observed (Ott *et al.*, 1999), yet the molecular mechanisms responsible are unknown. Both diseases are characterized by increased circulating amyloid beta 42 (Aβ42) levels (Vignini *et al.*, 2013), and there is a correlation between circulating Aβ42 and fat mass (Balakrishnan *et al.*, 2005). However the role of Aβ42 in metabolic disorders such as type 2 diabetes remain unresolved. We hypothesized that Aβ42 is released from fat and that systemic Aβ42 contributes to alterations in glucose metabolism.

Ex vivo Aβ42 release from adipose tissue of diabetic db/db mice was greater than from control mice, but was not different when normalized for adipose tissue mass. To determine the metabolic consequences of elevated circulating Aβ42, male C57BL6 mice were administered Aβ42 (1μg/day) or a scrambled Aβ42 peptide (control) for a period of 5 weeks. Aβ42 administration increased circulating Aβ42, but had no effect on glucose or insulin tolerance. However, glucose uptake into the heart during the glucose tolerance test (GTT) was reduced in Aβ42 administered mice. No changes in cardiac insulin signalling were observed, but markers of an oxidative stress and inflammatory responses were elevated. In primary cardiomyocytes, Aβ42 exposure reduced both glycolytic flux and glucose oxidation, and increased reactive oxygen species production, which were restored to control levels by co-treatment with the glutathione precursor and anti-oxidant, N-acetylcysteine. To assess the functional impact of elevated circulating Aβ42 on the heart, an additional cohort of mice was administered Aβ42 or a scrambled Aβ42 for assessment of cardiac morphology and function by echocardiography. Aβ42 administration did not alter cardiac morphology, but reduced the ejection fraction and fractional shortening, key indices of systolic function.

These data suggest that systemic Aβ42 is a link between obesity, impaired cardiac glucose metabolism and cardiac dysfunction.

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