

Does Obesity-Induced τ Phosphorylation Tip the Scale Toward Dementia?

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Obesity, a worldwide epidemic with numerous health implications, is gaining traction as a risk factor for dementia. The need for research is evident: at least 2.8 million obese or overweight adults die each year according to the World Health Organization, and more than two-thirds of American adults are overweight or obese (1). Obesity increases the risk of several health conditions, including hypertension, dyslipidemia, insulin resistance, and type 2 diabetes (2). In addition, obesity, as well as type 2 diabetes, increases the risk of cognitive dysfunction and dementia (3–5).

In this issue of *Diabetes*, Leboucher et al. (6), provide evidence that aberrant phosphorylation of the protein τ is a molecular link between obesity and impaired memory. In fact, much evidence supports the notion that τ dysfunction plays a central role in cognitive deficits. For example, intracellular neurofibrillary tangles composed of hyperphosphorylated τ are a neuropathological hallmark of Alzheimer's disease, the most common form of dementia. Moreover, the number of τ -containing neurofibrillary tangles in the neocortex of the brain in Alzheimer's disease positively correlates with severity of cognitive decline (7), and mutations in *MAPT*, the gene encoding τ , have been shown to cause frontotemporal dementia (8,9).

To gain a better understanding of the mechanisms by which obesity increases the risk of dementia, Leboucher et al. investigated the effects of diet-induced obesity in transgenic mice that develop progressive hippocampal τ pathology due to the overexpression of human τ with the G272V and P301S mutations (THY-Tau22 mice) (10). Both THY-Tau22 and wild-type mice were fed either a normal diet or one high in fat for ~5 months. This diet was initiated at 2 months of age, a time at which little if any τ pathology or memory impairments are observed in THY-Tau22 mice. By 7 months of age, wild-type and THY-Tau22 mice on the high-fat diet were similarly obese and exhibited comparable increases in circulating leptin, white adipose tissue mass, plasma triglycerides, and cholesterol concentrations. Nonetheless, only THY-Tau22 mice displayed enhanced hippocampal τ phosphorylation of Ser214, Ser404, and Ser422 residues. This heightened phosphorylation of τ was associated with activation of the τ kinases AKT and CamKII but not with an increase in total τ levels. In contrast, wild-type mice

fed a high-fat diet exhibited increased levels of total τ but no change in τ phosphorylation. Of particular interest, the high-fat diet worsened spatial learning in THY-Tau22 mice but had no effect on spatial learning of wild-type mice.

These findings suggest that obesity in mice predisposed to developing τ neuropathology and memory deficits hastens disease progression. Given the overwhelming evidence that insulin modulates cognitive processes (11), it is logical to speculate that the abnormal phosphorylation of τ and cognitive impairments in obese THY-Tau22 mice resulted from central insulin resistance that developed secondary to peripheral insulin resistance. Surprisingly, while the high-fat diet led to increased fasting glycemia and insulinemia in both wild-type and THY-Tau22 mice, plasma glucose and insulin levels were significantly lower in THY-Tau22 mice. Furthermore, glucose tolerance was similarly impaired in obese wild-type and THY-Tau22 mice, but THY-Tau22 mice did not develop peripheral insulin resistance as their wild-type counterparts did. Also of note, insulin signaling was increased in the hippocampus of THY-Tau22 mice but not wild-type mice, as evidenced by AKT activation and glycogen synthase kinase β inhibition, as well as increased expression of insulin receptor substrate-1 and a trend toward its decreased inhibition.

Overall, Leboucher et al. show that a high-fat diet enhances τ phosphorylation and learning disabilities in THY-Tau22 mice, and that this occurs independently of peripheral or central insulin resistance. Although these findings remain to be validated in other mouse models of tauopathy and in τ knockout mice, several interesting observations have emerged. One example is the unexpected observation that, in contrast to obese wild-type mice, obese THY-Tau22 mice do not develop peripheral insulin resistance. Because human τ expression is not detected in peripheral organs of THY-Tau22 mice, inhibition of peripheral insulin resistance likely involves a central τ -related mechanism. The activation of central insulin signaling, perhaps as a result of τ phosphorylation, may account for the absence of peripheral insulin resistance in obese THY-Tau22 mice given that central insulin signaling pathways regulate peripheral glucose transport and metabolism (12). Although the exact mechanisms remain to be elucidated, this study further highlights the complex interconnections among obesity, insulin resistance, τ pathology, and cognitive dysfunction.

That obesity potentiates τ pathology and learning deficits in THY-Tau22 mice in the absence of insulin resistance is congruent with the fact that obesity, without type 2 diabetes, increases the risk for developing Alzheimer's disease (13). It also raises the following question: If diet-induced obesity in THY-Tau22 mice does not result in peripheral insulin resistance, what causes the enhanced τ

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hyperphosphorylation and spatial learning deficits? Given that both obesity and type 2 diabetes increase risk of dementia (3–5), abnormalities observed in both disorders may be at play. Such abnormalities include chronic hyperglycemia, dyslipidemia, oxidative stress, accumulation of advanced glycation end products, increased production of proinflammatory cytokines, and cerebral microvascular diseases (14).

Finally, it is noteworthy that obesity in wild-type mice increases τ levels but not τ phosphorylation and has no effect on spatial learning skills. While the relationship between diet-induced obesity and τ phosphorylation has yielded conflicting results in wild-type mice (15–17), the results of this study suggest that obesity alone may not be sufficient to cause τ pathology and cognitive deficits. Rather, obesity may be a factor that essentially tips the scale and worsens disease progression and severity, such as observed in the THY-Tau22 mice. It would thus be of great interest to conduct longitudinal studies to determine how a high-fat diet influences disease onset and rate of progression in mouse models of tauopathy and whether reverting back to a normal diet can slow disease progression well after its initiation.

Given the current obesity epidemic and the expected age-related increase in dementia incidence, gaining a better understanding of the molecular mechanisms linking obesity and dementia may lead to the development of beneficial therapeutic strategies. In the meantime, although no effective cures are yet available for Alzheimer's disease, reducing obesity is at least one attainable course of action to reduce dementia risk.

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REFERENCES

1. Flegal KM, Carroll MD, Kit BK, Ogden CL. Prevalence of obesity and trends in the distribution of body mass index among US adults, 1999–2010. *JAMA* 2012;307:491–497
2. National Institutes of Health. Clinical guidelines on the identification, evaluation, and treatment of overweight and obesity in adults: the evidence report. *Obes Res* 1998;6(Suppl. 2):51S–209S
3. Kivipelto M, Ngandu T, Fratiglioni L, et al. Obesity and vascular risk factors at midlife and the risk of dementia and Alzheimer disease. *Arch Neurol* 2005;62:1556–1560
4. Whitmer RA, Gustafson DR, Barrett-Connor E, Haan MN, Gunderson EP, Yaffe K. Central obesity and increased risk of dementia more than three decades later. *Neurology* 2008;71:1057–1064
5. Umegaki H. Neurodegeneration in diabetes mellitus. *Adv Exp Med Biol* 2012;724:258–265
6. Leboucher A, Laurent C, Fernandez-Gomez F-J, et al. Detrimental effects of diet-induced obesity on τ pathology are independent of insulin resistance in τ transgenic mice. *Diabetes* 2013;62:1681–1688
7. Arriagada PV, Growdon JH, Hedley-Whyte ET, Hyman BT. Neurofibrillary tangles but not senile plaques parallel duration and severity of Alzheimer's disease. *Neurology* 1992;42:631–639
8. Hutton M, Lendon CL, Rizzu P, et al. Association of missense and 5'-splice-site mutations in tau with the inherited dementia FTDP-17. *Nature* 1998;393:702–705
9. Spillantini MG, Murrell JR, Goedert M, Farlow MR, Klug A, Ghetti B. Mutation in the tau gene in familial multiple system tauopathy with presenile dementia. *Proc Natl Acad Sci USA* 1998;95:7737–7741
10. Schindowski K, Bretteville A, Leroy K, et al. Alzheimer's disease-like tau neuropathology leads to memory deficits and loss of functional synapses in a novel mutated tau transgenic mouse without any motor deficits. *Am J Pathol* 2006;169:599–616
11. McNay EC, Recknagel AK. Brain insulin signaling: a key component of cognitive processes and a potential basis for cognitive impairment in type 2 diabetes. *Neurobiol Learn Mem* 2011;96:432–442
12. Duarte AI, Moreira PI, Oliveira CR. Insulin in central nervous system: more than just a peripheral hormone. *J Aging Res* 2012;2012:384017
13. Whitmer RA, Gunderson EP, Quesenberry CP Jr, Zhou J, Yaffe K. Body mass index in midlife and risk of Alzheimer disease and vascular dementia. *Curr Alzheimer Res* 2007;4:103–109
14. Whitmer RA. Type 2 diabetes and risk of cognitive impairment and dementia. *Curr Neurol Neurosci Rep* 2007;7:373–380
15. Jeon BT, Jeong EA, Shin HJ, et al. Resveratrol attenuates obesity-associated peripheral and central inflammation and improves memory deficit in mice fed a high-fat diet. *Diabetes* 2012;61:1444–1454
16. Becker K, Freude S, Zemva J, Stöhr O, Krone W, Schubert M. Chronic peripheral hyperinsulinemia has no substantial influence on tau phosphorylation in vivo. *Neurosci Lett* 2012;516:306–310
17. Moroz N, Tong M, Longato L, Xu H, de la Monte SM. Limited Alzheimer-type neurodegeneration in experimental obesity and type 2 diabetes mellitus. *J Alzheimers Dis* 2008;15:29–44