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Metabolism and Memory: Obesity, Diabetes, and Dementia

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When Michelle Obama launched her Let's Move! campaign against childhood obesity in 2010, it came on the heels of data showing that 36% of U.S. adults and 17% of U.S. children and adolescents were obese (1). The associated health risks outlined by Ms. Obama's team reflected the Centers for Disease Control and Prevention's consensus, which emphasized a myriad of adverse outcomes ranging from cancer to arthritis to coronary artery disease. Among these public health messages, the neuropsychiatric consequences of obesity have narrowly focused on cerebrovascular disease, such as stroke, and the psychological consequences of stigma. However, large-scale studies showing an association between obesity, diabetes, and dementia indicate that the brain is more broadly impacted (2,3).

The dementia-obesity-diabetes connection is part of an evolving story forcing us to re-examine a long-standing conceptualization of the mind and the body as separate. When Rene Descartes famously wrote about mind–body dualism in the 17th century, he was reformulating ideas that were ancient even to him. It is now understood that cognition, affect, memory, and other mental processes are manifestations of the brain's function. Although contemporary neuroscience has largely dismantled Descartes' dichotomy, brain–body dualism continues to exist, as evidenced by virtually separate health care systems dedicated to mental and physical health.

This has important implications for the way we approach seemingly disparate, difficult-to-treat physical and mental disorders. The relationship between diabetes and dementia is the perfect example. Applying an ethos of brain–body dualism to this problem suggests that it is up to internists and endocrinologists to tackle obesity and diabetes, while psychiatrists and neurologists deal with neurocognitive disorders. However, a scientific understanding of these disorders suggests that breaking down these silos may lead to important pathologic and therapeutic discoveries.

So how does obesity or diabetes contribute to a 50% increase in the risk of dementia? What is the connection between weight, metabolism, and brain health? A key link may be the impact of inflammation and oxidative stress on the brain. Decades of study on a wide range of diseases including cancer and heart disease have demonstrated that inflammation and oxidative stress play major roles in human pathology. Many of the same processes that affect

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coronary arteries and visceral organs also impact the brain. Inflammation leads to activation of microglia and astrocytes. This causes the release of cytokines and reactive oxidants, ultimately leading to neuronal dysfunction or death. Critically, this process can unleash a vicious cycle: dying neurons can cause more inflammation, thereby creating a cascade of neurodegeneration (4).

Both diabetes and obesity increase inflammation systemically. Until recently, the blood-brain barrier (BBB) was thought to protect the brain from such systemic effects. We now know that the brain is significantly impacted by the inflammatory state of obesity/diabetes through several pathways. First, many of the systemic inflammatory mediators—cytokines, for example—actually do cross the BBB under certain conditions. Second, metabolic mediators released by adipose tissue and the pancreas—leptin, insulin, and amylin—have additional important roles in mediating central nervous system (CNS) inflammation and regulating neuronal health. Parsing some of the details of what exactly happens to the brain in diabetes and obesity (Figure 1) may provide new targets for dementia treatments.

While often thought of as inert, we now realize that fat itself may play a major role in regulating cognitive health. Adipose tissue serves a range of neuroendocrine functions. One of the most important functions is the production and release of an array of polypeptides dubbed adipokines. These have a wide range of effects, from modulating metabolism (through leptin), mediating blood clotting (via plasminogen activation inhibitors), and regulating the inflammatory pathway (including via interleukins and tumor necrosis factors) (5). In metabolically healthy people, adipokine secretion is tailored to physiologic need. However, in obesity, the adipokine environment enters a state sometimes known as adiposopathy, in which inflammatory cytokines such as interleukin-6 are secreted at higher levels and metabolic mediators like leptin cease to function properly.

Research shows that the pathologic changes of adiposopathy have major effects on the brain. Peripheral inflammation disrupts the BBB and can impede synaptic plasticity and neurogenesis in the hippocampus; cytokines such as interleukin-6 may lead to decreased hippocampal gray matter volume (5). Interestingly, the predominance of hippocampal findings early in the course of Alzheimer's disease may relate to its sensitivity to disruptions in the BBB (6). As inflammation damages structures responsible for learning, memory, and cognition, the positive neurocognitive effects of leptin are diminished.

Leptin is best known for regulating satiety and energy intake. However, it also promotes axonal growth and enhances long-term potentiation through modulation of *N*-methyl-D-aspartate function. These characteristics suggest its importance in memory and learning. Obesity states are associated with leptin resistance. Resistance to the effects of leptin is not limited to its ability to regulate eating—it may also dull leptin's role in cognitive enhancement (7).

As with adipose tissue, pancreatic peptides also have important roles in the brain. While insulin is best known for its role in cellular glucose intake, research into its role in cognition is gaining momentum. Insulin receptors are involved in learning and memory, with high

concentrations of receptors in the cortex and the hippocampus. In addition, insulin (and insulin-like growth factor 1) act as neurotrophic factors that promote synaptic plasticity (4).

In type 2 diabetes, the body becomes resistant to insulin, forcing the pancreas to produce increasingly large quantities of insulin to promote glucose uptake by cells. As is the case with leptin, systemic insulin resistance blunts the procognitive effects of insulin in the brain: insulin resistance is associated with decreased verbal fluency, low gray matter volume in the temporal lobes, and declarative memory impairments (4). What's more, insulin transport into the brain may be downregulated by peripheral insulin resistance, and this can affect glucose metabolism in the CNS, contribute to oxidative stress, and inhibit insulin's neurotrophic effects. At the same time, because the absolute quantities of insulin are increasingly elevated (although the effect is lessened), hyperinsulinemia leads to the formation of peripheral and central amyloid- β plaques similar to those seen in the neuropathology of Alzheimer's disease and other neurodegenerative disorders. These plaques may activate inflammation in the CNS, leading to further neuronal death and plaque formation (4).

Yet another piece of the story may come from amylin, a hormone produced primarily by the pancreas. Like leptin, amylin functions to regulate energy metabolism by decreasing energy intake/increasing satiety. In this issue of *Biological Psychiatry*, Reiner *et al.* (8) explore how this effect is mediated. A separate study from 2014 showed that among elderly people, plasma amylin positively correlated with cognitive health, even after controlling for other metabolic risk factors such as diabetes and hyperlipidemia (9). In addition, preliminary findings suggest that amylin might compete with pathologic amyloid- β proteins for receptor binding sites and even help clear CNS amyloid (10). These data suggest that dysregulation of amylin, as seen in obesity and diabetes, could contribute to the accumulation of amyloid- β plaques (and subsequent inflammation and neuronal death) seen in Alzheimer's disease.

Thinking across the brain-body divide is not easy. As clinicians and scientists, we are trained to look for the one pathway: the elegant, simple explanation. But explanations for mental or physical disease that consider individual organs, such as the brain, apart from the broader context of the body are outdated. Pathogenic factors linking psychiatric and physical illness may run as deep as shared genetic predisposition. Even within the relatively isolated problem of the obesity-diabetes-dementia connection, there are a dizzying number of interrelated but distinct pathways knotted together. However, within that knot lies potential solutions to health problems that have a massive human cost. Imagine if we could prevent Alzheimer's disease with weight and metabolic management? Or if obesity and diabetes treatments could help protect the brains of people with early cognitive disorders? These ideas may not be so far-fetched. Although still in the first stages of study, intranasal insulin has shown promise in promoting cognitive health. In a small, double-blinded, randomized, placebo-controlled trial, 4 months of intranasal insulin improved memory, cognition, and function (4). Larger and more robust trials are underway to determine whether treating dementia with intranasal insulin may be a viable therapeutic strategy. And so many other health problems may lend themselves to rethinking along similar lines: the link between depression and inflammation and the role of the gut microbiome in psychiatry are two examples. These problems are remarkably complex; effectively addressing them will require

integrated approaches to research and clinical care. Such approaches hold the potential to revolutionize the tools we can offer our patients to improve their health—body and brain alike.

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Figure 1.

Metabolic and inflammatory mediators released by adipose tissue and the pancreas impact the brain in both health and disease. Diabetes and obesity may contribute to dementia via these mediators. CNS, central nervous system.