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REVIEW

MODELS AND MECHANISMS FOR HIPPOCAMPAL DYSFUNCTION IN OBESITY AND DIABETES

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Abstract—Clinical studies suggest that obesity and Type 2 (insulin-resistant) diabetes impair the structural integrity of medial temporal lobe regions involved in memory and confer greater vulnerability to neurological insults. While eliminating obesity and its endocrine comorbidities would be the most straightforward way to minimize cognitive risk, structural barriers to physical activity and the widespread availability of calorically dense, highly palatable foods will likely necessitate additional strategies to maintain brain health over the lifespan. Research in rodents has identified numerous correlates of hippocampal functional impairment in obesity and diabetes, with several studies demonstrating causality in subsequent mechanistic studies. This review highlights recent work on pathways and cell–cell interactions underlying the synaptic consequences of obesity, diabetes, or in models with both pathological conditions. Although the mechanisms vary across different animal models, immune activation has emerged as a shared feature of obesity and diabetes, with synergistic exacerbation of neuroinflammation in model systems with both conditions. This review discusses these findings with reference to the benefits of incorporating existing models from the fields of obesity and metabolic disease. Many transgenic lines with basal metabolic alterations or differential susceptibility to diet-induced obesity have yet to be characterized with respect to their cognitive and synaptic phenotype. Adopting these models, and building on the extensive knowledge base used to generate them, is a promising avenue for understanding interactions between peripheral disease states and neurodegenerative disorders.

Key words: obesity, diabetes, insulin resistance, hippocampus, long-term potentiation, synapse.

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INTRODUCTION

Understanding relationships between cellular metabolism and circuit function is a central question for both basic and clinical neuroscience. Changes in energy intake and expenditure influence synaptic plasticity, and this relationship is not exclusive to brain regions classically implicated in food intake and metabolism. Decades of research in animal models have revealed correlations between metabolic efficiency at the systems level and neuroplasticity in the hippocampus and other regions involved in learning and memory (Bedford et al., 1979; Greenwood and Winocur, 1990; Dulloo and Calokatisa, 1991; Neeper et al., 1995). These relationships are

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Abbreviations: 11betaHSD1, 11beta hydroxysteroid dehydrogenase 1; AD, Alzheimer's disease; BAT, brown adipose tissue; BBB, blood–brain barrier; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; GK, Goto—Kakizaki; GR, glucocorticoid receptor; HFD, high-fat diet; HPA, hypothalamic–pituitary-adrenal axis; IBA1, ionized calcium-binding adapter protein 1; ICV, intracerebroventricular; IDE, insulin-degrading enzyme; IRAS, insulin receptor antisense; LPS, lipopolysaccharide; LPX, lipectomy; MHCII, major histocompatibility complex II; PI3K, phosphatidylinositol 3-kinase; scWAT, subcutaneous white adipose tissue; STZ, streptozocin/streptozotocin; vWAT, visceral white adipose tissue.

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considered bidirectional based on studies demonstrating enhancement of hippocampal plasticity with exercise and caloric restriction (van Praag et al., 1999; Fontán-Lozano et al., 2007), and functional impairment in obesity and diabetes (Magariños and McEwen, 2000; Molteni et al., 2002). Associations between metabolism and neuroplasticity are detectable at the systems level and the cellular level, where insulin receptor activation (Lee et al., 2011), glucose transporter expression and localization (Ferreira et al., 2011), and mitochondrial function (Cheng et al., 2012) have all been linked with synaptic mechanisms for learning and memory. Given the substantial metabolic demands required for synaptic transmission, it is perhaps unsurprising that bidirectional regulation of neuroplasticity by energetic challenges would be evident across most, if not all, brain circuits (for review, see Stranahan and Mattson, 2011). The challenge in addressing this question lies in isolating individual systems impacted by complex pathologies, such as obesity and diabetes.

Nearly 15 years since the first report of increases in dementia risk among diabetics in the Rotterdam study (Ott et al., 1996), obesity and diabetes have yet to be clinically implemented as risk factors for cognitive impairment and dementia. Consequentially, there have been no efforts to develop therapeutics to reduce dementia risk in individuals with diabetes and obesity, and the promise of greater efficacy based on treatments tailored to individual risk factors has yet to be realized. Some of the impediments to translation are likely attributable to variability in the degree to which different animal models of diabetes and obesity mimic features of these conditions in human populations. Type 1 (insulin-deficient) diabetes is typically diagnosed early in life and the most frequent cause is autoimmune destruction of the insulin-producing pancreatic beta cells (Hamman et al., 2014). Type 1 diabetics are not typically overweight or obese, and with adherence to an insulin administration regimen, there is little to no cognitive risk in later life (Lobnig et al., 2006). Type 2 (insulin-resistant) diabetes is a progressive disease, with the earliest stages characterized by elevated fasting glucose levels and compensatory increases in insulin production (American Diabetes Association, 2014). Over time, the pancreatic beta cells become exhausted and the patient converts from insulin-resistant to insulin-deficient diabetes (American Diabetes Association, 2014). Individuals with Type 2 diabetes are frequently, but not always, overweight or obese (Sullivan et al., 2005), and dementia risk is elevated in Type 2 diabetes independent of body mass index (BMI; Xu et al., 2009).

Obesity is a complex disorder that occurs as a consequence of genetic and lifestyle factors (Ogden et al., 2014). While some obese individuals do not develop insulin-resistant diabetes, data from twin studies and longitudinal studies indicate that, even in the absence of metabolic and cardiovascular comorbidities, obesity increases risk for multiple forms of dementia, including vascular dementia and Alzheimer's disease (AD) (Whitmer et al., 2007; Xu et al., 2011). These reports are consistent with other studies that came to similar conclusions using statistical methods to separate the effects of obesity from those of diabetes (Profenno et al., 2010).

The goal of identifying cellular and systems-level mechanisms for changes in synaptic plasticity and cognition in obesity and diabetes would be significantly advanced by incorporating sophisticated model systems developed in the field of obesity and metabolism. These models include transgenic mice with vulnerability or resistance to the metabolic effects of diet-induced obesity and surgical approaches for manipulating the amount and distribution of adipose tissue. Comparing learning and plasticity measures across model systems with selective deficits in glycemic control or body weight homeostasis could distinguish the effects of diabetes from those of obesity. This approach would enable subsequent studies of synergy between the two conditions and may also assist in refinement of risk criteria in clinical populations. This review highlights recent developments in the literature on mechanisms for impaired hippocampal neuroplasticity in obesity and diabetes, with reference to the importance of addressing related questions in future studies using metabolic models that have yet to be characterized with respect to their cognitive and synaptic phenotype.

PHARMACOLOGICAL MODELS USED TO STUDY HIPPOCAMPAL PLASTICITY IN OBESITY AND DIABETES

Streptozotocin (STZ) is a pancreatic beta-cell toxin injected intravenously or intraperitoneally to create a model of insulin-deficient diabetes (Lenzen, 2008). Either STZ or alloxan, a related nitrosylurea compound, causes rapid-onset insulin-deficient diabetes that is accompanied by reductions in body weight in some, but not all studies (Biessels et al., 1998; Magariños and McEwen, 2000; Stranahan et al., 2008a). Studies of hippocampal plasticity in diabetes make frequent use of STZ as a rapidly inducible model with robust deficits in neurogenesis (Zhang et al., 2008; Ho et al., 2015), synaptic plasticity (Biessels et al., 1998; Stranahan et al., 2008a), and cognition (Kamal et al., 2000; Stranahan et al., 2008b). Although some mechanisms identified in the insulin-deficient STZ model have also been demonstrated in insulin-resistant rodents (Clodfelder-Miller et al., 2005; Stranahan et al., 2008a; Kim et al., 2009), many studies using STZ assert that the observed changes in hippocampal function are relevant to both insulin-deficient and insulin-resistant diabetes without demonstrating that this is the case (Diegues et al., 2014). This element of interpretation is flawed, as insulin resistance develops over years and typically is detected in middle-aged human populations, but insulin deficiency is generally identified in pediatric populations (Hamman et al., 2014). Even when scaled down to the shorter lifespan in rodents, the development of insulin deficiency and hyperglycemia following one to three days of STZ treatment in no way resembles the gradual time course for development of insulin resistance in humans (American Diabetes Association, 2014). The use of STZ as a