Commentary

John Newcomer

Department of Psychiatry, Washington University School of Medicine, St. Louis, Missouri.

Rasgon and Jarvik (1) offer a useful review of recent research spanning clinical and basic neuroscience, and an interesting synthesis of results from complex and sometimes limited or controversial areas of research. Based on their interpretation of the results of these studies, they advance the hypothesis that insulin resistance associated with affective disorders leads to hyperinsulinemia and hyperglycemia, which, in turn, promote neurodegeneration and facilitate the
onset of Alzheimer’s disease (AD). While the review highlights some very interesting areas of investigation, weaknesses in several of the building blocks of their argument compromise the strength of this hypothesis.

The historical basis for the hypothesis is the long-standing observation of an association between depression and AD. The previously reported association between insulin resistance or hyperglycemia and both depression and AD is cited by the authors, setting the stage to consider insulin resistance as a putative risk factor though which depression could lead to AD. The authors do not address a long-standing association in the literature between insulin resistance and schizophrenia, and between insulin resistance and bipolar disorder (2). This apparent lack of specificity for the relationship of insulin resistance to various major neuropsychiatric disorders offers certain challenges to the proposed hypothesis. Presumably, the authors might argue that insulin resistance is a necessary but not sufficient condition to predict the development of AD in persons with depression.

The authors suggest that complex interactions between insulin signaling and hypothalamic-pituitary-adrenal (HPA) axis function could lead to impaired glucocorticoid (GC) feedback and resultant hypercortisolemia contributing to the pattern of neuronal injury associated with AD. However, the literature describing GC effects on neuronal function and survival is complex, with limited evidence for the proposition that increased GC exposure alone can injure neurons. This literature is not critically reviewed in the authors’ article. In addition, basic neuroscience studies concerning interactions between insulin signaling and HPA axis function are quite limited in number and very difficult to interpret with respect to in vivo or clinical conditions. Further, insulin actions in the brain are only beginning to be understood, including a role for insulin in regulating glycogen storage in astrocytes (3,4), but there remains little evidence that plasma insulin plays any role in regulating brain glucose transport. This raises some challenges for hypotheses that suggest clinically significant changes in brain glucose utilization as a function of peripheral insulin resistance.

A number of interesting observations with respect to brain insulin signaling and glucose utilization are cited in the review, but many of these might be characterized as circumstantial, rather than direct, evidence for their hypothesis. The hypothesis as written takes a simple view of many of these observations and relationships, one that is sometimes not well supported by existing literature. Observations that are at odds with their hypothesis received limited coverage in the review. For example, individuals with schizophrenia and bipolar disorder, as well as those with depression, experience an increased prevalence of both insulin resistance and HPA axis dysfunction (5,6), but schizophrenia and bipolar disorder are not observed to increase risk for AD. Similarly, Cushing’s disease is also associated with hypercortisolemia and insulin resistance, but not AD.

Complicating the whole debate, the association between depression or other major neuropsychiatric conditions and insulin resistance is less than fully characterized. Most of the reported epidemiological associations have been between depression and surrogate indicators of diabetes mellitus, such as self-report or ICD [International Classification of Diseases] codes, in populations where one third to one half of cases of diabetes mellitus are undiagnosed. Few studies have utilized direct, validated measures such as fasting or postload plasma glucose that could be used to confirm diagnoses, and only rarely have studies utilized sensitive measures of insulin secretion or sensitivity. Few of the studies in this area have measured or controlled for important risk factors for diabetes or insulin resistance, such as age or adiposity.

A recent National Institute of Diabetes and Digestive and Kidney Diseases workshop on the topic of depression and diabetes mellitus underscored the need for further research in this area, rather than identifying certain conclusions from the existing literature (7). One of the better-established observations in this area is that increased adiposity, associated with the sedentary lifestyle, nutritional patterns, and medications used in individuals with depression and other neuropsychiatric diseases, can increase insulin resistance and the risk of hyperglycemia, dyslipidemia, and cardiovascular disease (e.g., cerebrovascular atherosclerosis) (8). From this perspective, abdominal and intramuscular adiposity could alternatively be hypothesized to explain more of the variance in who gets insulin resistance than does a putative central defect in insulin signaling or glucose sensing in persons with depression or AD. Whatever the implications of decreased peripheral insulin sensitivity are for brain function, reduced insulin sensitivity can contribute to the development of metabolic disturbances that increase the risk for atherosclerosis in the form of both coronary heart disease and cerebrovascular disease (9). Increased morbidity and mortality secondary to cardiovascular disease, rather AD, is the predicted outcome for depressed individuals with insulin resistance that is most clearly supported by existing research.

Address correspondence to John Newcomer, MD, Department of Psychiatry, Washington University School of Medicine, Box 8134, 660 South Euclid, St. Louis, MO 63110. E-mail: newcomer@psychiatry.wustl.edu

REFERENCES