In recent years a rapidly increasing number of studies has focused on the relationship between dementia and metabolic disorders such as diabetes, obesity, hypertension, and dyslipidemia. Etiological heterogeneity and comorbidity pose challenges for determining relationships among metabolic disorders. The independent and interactive effects of brain vascular injury and classic pathological agents such as β-amyloid have also proved difficult to distinguish in human patients, blurring the lines between Alzheimer disease and vascular dementia. This review highlights recent work aimed at identifying convergent mechanisms such as insulin resistance that may underlie comorbid metabolic disorders and thereby increase dementia risk. Identification of such convergent factors will not only provide important insight into the causes and interdependencies of late-life dementias but will also inspire novel strategies for treating and preventing these disorders.

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This special issue highlights the relationship of disorders of metabolism to Alzheimer disease (AD) and vascular dementia (VaD). For 10 years there has been a rapidly increasing number of studies focused on the relationship between metabolic disorders such as diabetes, obesity, hypertension, and insulin resistance and dementia. Our article is not intended to be an exhaustive review of this burgeoning literature, but instead to highlight novel or integrative lines of inquiry. Substantiation of the link between metabolic disorders and dementia risk has raised new questions about the specific mechanisms underlying these associations that have critical implications for the way we define and classify dementias. The independent and interactive effects of brain vascular injury and classic AD pathological agents such as β-amyloid (Aβ) have been nicely characterized in animal and in vitro models, but have proved difficult to untangle in human patients. Similar challenges exist in determining the independent and interactive effects of metabolic disorders, which are etiologically heterogeneous, have high degrees of comorbidity, and whose expression may be distorted by treatment or time.

The lines between AD and VaD have also blurred. Vascular dementia is a heterogeneous construct with pathology that can range from multiple macroinfarcts to small vessel ischemic disease or microvascular injury. It is clear that for many patients, markers of vascular injury coexist with traditional AD hallmarks. In some cases, the AD hallmarks may conceivably be promoted by a specific form of vascular injury; for example, blood-brain barrier (BBB) dysfunction may affect Aβ transport between the brain and periphery and thereby contribute to parenchymal and neurovascular amyloid deposition. Conversely, AD pathology may cause vascular injury, as when Aβ-induced inflammation damages the endothelium. In other cases, isolated AD or vascular pathology may occur. Given such complexity, the temptation to retreat to reductionist models is understandable. Unifying themes are emerging, however, that may illuminate convergent mechanisms through which comorbid metabolic disorders promote the
development of AD and VaD. As we discuss below, one important theme is the concept that insulin resistance underlies several important metabolic disorders and their relationship to AD and VaD. Other unifying themes will undoubtedly emerge as the reader assimilates the thought-ful work presented in this issue.

CLASSIFICATION AND DIAGNOSIS OF METABOLIC DISORDERS

One source of confusion that impedes our comparison across studies concerns the terminology used to describe metabolic disorders.1 The insulin resistance syndrome occurs when tissues become unresponsive to the effects of insulin and can selectively affect insulin's actions on the muscle, liver, adipose tissue, endothelium, or brain. It is typically accompanied by compensatory hyperinsulinemia in the periphery, which has independent deleterious effects. Insulin resistance is thought to be the underlying cause of metabolic syndrome, diabetes, and vascular disorders such as hypertension and cardiovascular disease for most patients (Table). It may thus be considered a core syndrome that increases the risk of AD and VaD. Our ability to study the mechanistic relationship of insulin resistance to AD and VaD is hampered, however, by the complexity of its measurement. The hyperinsulinemic-euglycemic clamp, a method in which a standard dose of insulin is infused with dextrose, is the criterion standard, but is time and labor intensive. The integrated area under the curve for insulin during oral glucose tolerance testing has been proposed as an acceptable surrogate.2 The homeostasis model assessment for insulin resistance, which is based on fasting insulin and glucose values, correlates well with the hyperinsulinemic-euglycemic clamp,3 is relatively low in cost, and is computationally straightforward.

In contrast, diabetes is solely a glucocentric diagnosis that is made when fasting glucose levels exceed 126 mg/dL (to convert to millimoles per liter, multiply by 0.0555) or when random or post-glucose tolerance testing levels exceed 200 mg/dL. As such, it is a heterogeneous disorder with many potential etiologies, which complicates the determination of its relationship to late-life dementias. As noted, insulin resistance is a causal factor in most cases of adult-onset or type 2 diabetes mellitus (T2DM). Insulin resistance may be manifested only by mild glucose intolerance for many years prior to the onset of frank diabetes, as the pancreas is able to generate sufficient levels of insulin to maintain glucose levels beneath the diabetic threshold. Over time, the degree of insulin resistance increases as insulin secretion by pancreatic β cells is reduced, resulting in hyperglycemia of sufficient magnitude to warrant the diagnosis of T2DM. Of note, despite diminished insulin secretory capacity, patients with T2DM demonstrate hyperinsulinemia due to reduced insulin clearance.

The metabolic syndrome is defined by the cooccurrence of certain cardiovascular risk factors.1 The most commonly accepted definition requires 3 of the following conditions to be present: large waist circumference, hypertriglyceridemia, a low high-density lipoprotein cholesterol level, elevated blood pressure, and fasting hy-

Table. Dementia-Related Risk Factors Caused by Insulin Resistance

| Type 2 diabetes mellitus/impaired glucose tolerance |
| Obesity and/or central adiposity |
| Dyslipidemia |
| Inflammation |
| Hypertension |
| Ischemia |
| Cardiovascular disease |

perglycemia. Of note, this definition does not include any reference to insulin resistance or hyperinsulinemia despite clear evidence that these factors play a causal role in its occurrence in most patients.6

MECHANISTIC LINKS BETWEEN INSULIN RESISTANCE–ASSOCIATED CONDITIONS AND AD/VaD

In the following section, we briefly review the role of insulin in normal brain function and the potential direct effects of insulin resistance on the brain and on AD pathophysiology.

Insulin and the Brain

Recent reviews have provided comprehensive accounts of the role of insulin in normal brain function.5,6 Insulin is readily transported into the central nervous system across the BBB by a saturable receptor-mediated process. Insulin receptors, located in astrocytes and neuronal synapses, are highly concentrated in the olfactory bulb, cerebral cortex, hippocampus, hypothalamus, amygdala, and septum. Localization of insulin receptors in the hippocampus and medial temporal cortex is consistent with evidence that insulin influences memory. Likely memory-related mechanisms include modulation of synaptic structure and function, long-term potentiation, and central nervous system levels of neurotransmitters such as acetylcholine and norepinephrine that are known to influence cognitive function.6 Specific regional effects of insulin on glucose metabolism via insulin-sensitive glucose transporters 4 and 8 may also affect brain function.

Direct Effects of Insulin and Insulin Resistance on Aβ and Tau

Many of the important functions of insulin in the brain are disrupted in insulin-resistant conditions. Interestingly, prolonged peripheral hyperinsulinemia associated with insulin resistance reduces insulin transport across the BBB, subsequently lowering insulin levels and activity in the brain; this effect may be relevant to findings of reduced cerebrospinal fluid insulin and brain insulin-signaling markers in AD.6,7 Insulin resistance and hyperinsulinemia are implicated in a number of pathophysiological processes related to AD.5,6 Reduced brain insulin signaling is associated with increased tau phosphorylation and Aβ levels in a streptozotocin mouse model of diabetes.5,8 Insulin also promotes the release of
intracellular Aβ in neuronal cultures and accelerates Aβ trafficking to the plasma membrane.9 In humans, raising plasma insulin levels through intravenous infusion increased cerebrospinal fluid levels of the Aβ42 peptide; this effect was exacerbated by age.10 Intravenous insulin infusion also raised plasma Aβ42 levels in patients with AD but not in normal adults, an effect that was exaggerated in patients with AD with higher body mass indexes (calculated as weight in kilograms divided by height in meters squared).11 This finding illustrated the close relationship between insulin resistance and obesity, a relationship that may have particular implications for AD and VaD pathogenesis, as described below. Mechanisms regulating Aβ clearance (rather than production) may be of special importance in late-onset AD. Insulin may interfere with Aβ degradation via its regulation of the metalloprotease insulin-degrading enzyme.12

INSULIN RESISTANCE–RELATED METABOLIC DISORDERS AND AD/VaD

Diabetes

The relationship between diabetes and increased AD and VaD risk has recently been discussed in several excellent reviews.13,14 The weight of evidence suggests that diabetes increases the risk of both AD and VaD, and that this risk occurs regardless of the age at which diabetes occurs.15 Risk-enhancing mechanisms include the effects of insulin resistance described above, hyperglycemia-related increased advanced glycation end products, and oxidative stress, inflammation, and macrovascular and microvascular injury.

Neuropathological studies of patients with diabetes and clinically diagnosed AD and VaD have faced challenges similar to those experienced in early epidemiologic studies. Few autopsy cohorts have captured enough quality data regarding metabolic and cognitive status to allow reliable diagnosis of both diabetes and dementia subtype. Instead, studies often rely on self-reported diabetes, which underestimates prevalence by 50%, or on medical records for which completeness cannot be verified. Thus control samples may include many undiagnosed diabetic patients, obscuring differences between groups.

Historic diagnostic biases are also problematic, as patients with diabetes were often presumed to have dementia of vascular origin. Perhaps the greatest challenge has been to determine the effects of medication. Insulin and oral hypoglycemics are the most common treatments for T2DM and have been demonstrated to affect AD markers as well as vascular integrity. However, important details regarding the length and type of treatment as well as the dose are often poorly documented.

Despite these challenges, an interesting pattern has emerged in recent neuropathological studies in which patients with treated diabetes demonstrate a reduced amyloid load compared with nondiabetic patients with similar levels of dementia.16 As described in this issue, patients with treated diabetes and dementia had Aβ plaque loads similar to those without dementia and instead had increased microvascular infarcts and interleukin-6.17 In contrast, untreated diabetic patients with dementia had plaque loads that were similar to nondiabetic patients with dementia. One intriguing interpretation of these results is that diabetes treatment affected the amyloid load, but not the degree of dementia. If true, this finding would raise questions about the role of amyloid plaques in dementia symptoms. This interpretation must be considered speculative, however, given the small number of cases and the fact that treated diabetic patients typically have more severe diabetes. Similarly, the finding of increased microvascular injury in treated diabetic patients with dementia, but not in similarly affected treated diabetic patients without dementia raises the question of which diabetic factors are associated with microvascular infarcts. Clearly, all treated diabetic patients do not develop dementia, only cases with concomitant microvascular infarcts. The nature of this microvascular injury is also an important consideration. Given their small volume (Figure), it is unlikely that microvascular infarcts directly cause dementia, but rather serve as a marker for more extensive microvascular dysfunction. These findings illustrate the importance of careful assessment of treatment and metabolic status in future neuropathological studies.

Obesity

Obesity has reached epidemic proportions in many Western societies and is a primary cause of insulin resistance; 80% of obese individuals are insulin resistant.1 Evidence concerning obesity as a risk factor for AD and VaD has been mixed.13 In general, midlife obesity is consistently found to be a risk factor for later dementia, whereas more variability in risk is observed for adiposity in older age.18 Free fatty acids (FFAs) are a critical mechanistic link between obesity and insulin resistance.1 In normal metabolism, insulin inhibits adipocyte hormone-sensitive lipase activity, thereby decreasing FFA release from adipose tissue. This process is disrupted in obesity and insulin-resistant conditions, leading to persistent FFA elevation. Normalizing FFA levels results in a 50% increase in insulin sensitivity in obese adults.19 The link between FFA elevation and development of T2DM is supported by findings that normoglycemic individuals with a family history of diabetes show high fasting FFA levels20 and that elevated plasma FFAs predict progression to diabetes.24

Figure. Arteriolar microinfarct in a patient with dementia and diabetes.
Obesity-associated FFA elevation may affect AD pathogenesis. Free fatty acids inhibit insulin-degrading enzyme, the metalloprotease that plays a key role in clearance of Aβ and that is also essential for normal insulin signaling to occur. Free fatty acids stimulate the assembly of amyloid and tau filaments in vitro. They also induce inflammation, particularly through interactions with tumor necrosis factor (TNF) α. Tumor necrosis factor α is overexpressed in the adipose tissue of obese insulin-resistant rodents and humans, and neutralization of TNFα increases insulin sensitivity and decreases plasma FFA levels. Tumor necrosis factor α is a cytokine that has received increasing attention in theories of AD pathogenesis. It is elevated in the brains and cerebrospinal fluid of patients with AD and in adults with mild cognitive impairment and inhibits Aβ transport from the brain to the periphery. Thus TNFα elevations associated with obesity, insulin resistance, and hyperinsulinemia may result in increased brain accumulation of Aβ.

**Dyslipidemia**

In a recent meta-analysis of 18 prospective studies examining the relationship of total cholesterol and risk for AD and VaD, midlife total cholesterol levels were consistently associated with an increased risk of AD and all dementia, whereas no increased risk was observed for late-life total cholesterol. Interestingly, no relationship between total cholesterol and VaD was observed at any age. Dyslipidemia is an important component of the insulin resistance syndrome; insulin is a primary regulator of lipid metabolism, stimulating lipogenesis and reducing lipolysis. As noted previously, in adipocytes, insulin resistance leads to accelerated lipolysis and increased FFA levels. In turn, excess FFA influx into the liver inhibits insulin suppression of hepatic very-low-density lipoprotein secretion, an essential process for preventing postprandial hyperlipidemia. Acute inhibitory effects of insulin on lipid production are essential for rapid hepatic adaptation to metabolic shifts between fasting and refeeding to maintain plasma lipids within an optimal physiologic range. Thus, insulin-resistant adults have higher and more prolonged postprandial excursions of very-low-density lipoprotein and other deleterious lipids. This tendency has important implications for AD pathophysiology. Interactions among lipids, lipoproteins, and Aβ play a critical role in Aβ production and clearance. In rodents, increased peripheral very-low-density lipoprotein secretion precedes Aβ deposition in the brain, and high fat feeding increases the brain's amyloid burden. In humans, elevated midlife cholesterol levels increase AD risk 2- to 3-fold and are associated with increased plasma Aβ40 levels. Increased postprandial chylomicron and low-density lipoprotein levels with normal fasting levels have been associated with AD. The specific mechanisms through which lipids and lipoproteins affect Aβ production and clearance are a subject of intense inquiry. β-amyloid 40, in contrast to Aβ42, is rapidly cleared across the BBB by lipoprotein receptor-related protein 2 (LRP2). Apolipoproteins (apo) E and J mediate Aβ transport between the brain and periphery. Binding of Aβ to apoE reduces efflux, whereas binding of Aβ42 to apoJ increases LRP2-mediated efflux. The lipidation status of apoE affects its interaction with Aβ. Highly lipidated apoE increases Aβ brain efflux, thereby reducing Aβ deposition, and poorly lipidated apoE increases the amyloid burden. The lipidation status of peripheral Aβ may also affect its clearance. Obstructing Aβ clearance in the peripheral “sink” may increase brain accumulation of Aβ. The specific mediators of peripheral Aβ clearance are controversial, but may include apoE and apoJ, whereas LRP1 may mediate both hepatic uptake and clearance of Aβ.

Soluble LRP (sLRP) may be a key mediator of peripheral Aβ clearance. N-terminal cleavage of LRP by β-secretase releases sLRP into the plasma, where it binds to Aβ. Peripherally administered recombinant LRP blocked Aβ transport across the BBB in mice and reduced brain Aβ40 and Aβ42 levels, brain vascular Aβ levels, and amyloid burden by 90%. Patients with AD had a 30% decrease in sLRP, a 280% increase in the proportion of oxidized sLRP (which has a lower affinity for Aβ), and large increases in the percentage of free plasma Aβ40 and Aβ42. Notably, only a small fraction of plasma Aβ was bound to apoE or apoJ, in contrast to other reports. Thus, investigations of sLRP and its modulators may provide important evidence for this promising therapeutic target. Insulin modulates LRP expression and translocation to the plasma membrane, where it may more readily encounter β-secretase and produce sLRP. In rats, insulin rapidly increased both hepatic expression of LRP1 in the plasma membrane fraction and hepatic uptake of Aβ40. Insulin resistance may interfere with this translocation, reducing levels of sLRP or increasing sLRP oxidation.

**Vascular Dysfunction and Hypertension**

Insulin resistance has many negative effects on vascular function that are directly related to impaired insulin action as well as caused by insulin resistance–induced dyslipidemia and inflammation. Insulin directly affects vasoreactivity and hemodynamic functions such as capillary recruitment, vasodilation, and regional blood flow. Hemodynamic and metabolic effects working in concert enhance energy substrate delivery. Insulin normally increases nitric oxide (NO)–mediated vasodilation and regulates vasoconstriction via endothelin-1. Conversely, insulin resistance decreases NO and increases endothelin-1 activity, favoring vasoconstriction and reducing capillary recruitment. In turn, endothelial dysfunction reduces insulin transport, ultimately reducing capillary recruitment and microvascular blood flow. This exacerbates glucose and lipid abnormalities and establishes a negative feedback loop between progressive endothelial dysfunction and increasing insulin resistance. In the brain, vasoconstriction and reduced capillary recruitment may interfere with functions of the neurovascular unit, the coordinated interaction of astrocyte, neuron, and endothelium that couples neural activity with increased blood flow.

Hypertension affects 25% of the adult population and is diagnosed when systolic blood pressure exceeds 140 mm Hg or diastolic pressure exceeds 90 mm Hg. Although heterogeneous in etiology, 50% of hypertensive
patients are insulin resistant and manifest insulin resistance–induced endothelial dysfunction due to previously described direct effects on vasoreactivity and microvascular blood flow as well as indirect effects of related dyslipidemia and inflammation. Hypertension impairs functional hyperemia, the process by which brain activity and blood flow are coordinated. This impairment is induced by dysregulation of vasoactive mediators such as NO and endothelin-1, by oxidative stress, by structural alteration of the blood vessels, and by inadequate cerebral autoregulation. All of these processes have been linked to insulin resistance. As with obesity, midlife hypertension is a risk factor for AD and VaD in epidemiologic studies, whereas patients with AD appear to show reduced blood pressure at disease onset. Recent reviews have summarized evidence from animal models in which deposition of Aβ is increased with hypertension and, in turn, induces vascular dysfunction that impairs functional hyperemia.

Comorbidity of Metabolic Disorders

We have noted the challenges of determining the independent and interactive roles of metabolic disorders. Kloppenborg et al reviewed epidemiologic results from studies of T2DM, hypertension, and dyslipidemia and noted the paucity of work that adequately examines interactive effects. They also note the potential value of a heuristic approach focusing on the underlying construct of insulin resistance rather than individual metabolic conditions. Unfortunately, few studies have directly characterized insulin resistance and instead have focused on related conditions such as obesity and T2DM. Support for the additive effects of metabolic conditions has been observed in studies documenting that midlife obesity, hypercholesterolemia, and high systolic blood pressure increase dementia risk additively.

CHALLENGES FOR FUTURE RESEARCH

As this review indicates, considerable progress has been made in establishing relationships among metabolic disorders and late-life dementing illnesses. A number of challenges must be addressed as we move forward to determine the key mechanisms underlying these associations. A consistent nosology of brain vascular injury and delineation of the interactions between subtypes of vascular injury and AD pathology will be critical in defining the interface between AD and VaD. Similarly, elucidation of the interactions among various metabolic disorders and identification of convergent pathophysiology underlying comorbidities will likely provide important clues to dementia-related mechanisms. Careful attention to the measurement and characterization of insulin resistance syndrome may further this effort.

An additional question with important implications concerning the timing of risk is why the associations between many metabolic disorders and dementia are strongest at midlife. A commonly cited reason is that dementia onset may be associated with counter-regulatory factors that alter the presentation of the risk-initiating metabolic condition. This phenomenon is likely contributory, but raises the question of what pathogenetic mechanisms are induced by these disorders at midlife. Identification of a clear risk profile or risk-related pattern of biomarkers in midlife may guide strategies for early diagnosis and prevention. It is also possible that long-term treatments for these disorders obscure or change the nature of their association at the time of dementia onset. Ascertaining the effects of treatment on dementia-related pathology is a daunting but necessary task complicated by the fact that the treatments for one class of disorders affect the expression of other disorders; for example, some antihypertensives reduce the risk of diabetes and some antidiabetic agents improve blood pressure. These interactive effects may provide clues to shared etiologies among metabolic disorders. Notably, the same interrelatedness that has complicated efforts to derive simple linear models of association may benefit therapeutic efforts, as targeting one metabolic disorder may improve related conditions. Candidate therapies currently under study include statins, antihypertensive therapies, and insulin-sensitizing drugs. Considerable interest has also arisen regarding the effects of lifestyle interventions such as exercise and dietary/nutriceutical manipulations. Future research aimed at identifying mechanisms that underlie comorbid associations will not only provide important insights into the causes and interdependencies of late-life dementias, but will also inspire novel strategies for treating and preventing these disorders.

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