Hypothesis

Is Insulin Resistant Brain State a Central Feature of the Metabolic-Cognitive Syndrome?

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Abstract. Cumulative evidence suggests that metabolic syndrome (MetS) may be important in the development of mild cognitive impairment, vascular dementia, and Alzheimer’s disease (AD). As such, these patients might be described as having “metabolic-cognitive syndrome” – MetS plus cognitive impairment of degenerative or vascular origin. While peripheral insulin resistance appears to be of primary pathophysiological importance in MetS, the definitions of MetS and its components do not include any reference to insulin resistance or hyperinsulinemia. In the present article, we discuss the role of these factors in the development of cognitive decline and dementia, including underlying mechanisms that influence amyloid-\textbeta (A\textbeta) peptide metabolism and tau protein hyperphosphorylation, the principal neuropathological hallmarks of AD. In AD, an age-related desynchronization of biological systems results, involving stress components, cortisol and noradrenaline, reactive oxygen species, and membrane damage as major candidates that precipitates an insulin resistant brain state (IRBS) with decreased glucose/energy metabolism and the increased formation of hyperphosphorylated tau protein and A\textbeta. Unfortunately, it is very difficult to include the measurement of peripheral insulin resistance in the current MetS criteria or the identification of IRBS for the metabolic-cognitive syndrome. However, since inflammation has been suggested among the MetS components, we propose IRBS as an additional feature of the metabolic-cognitive syndrome to also identify a molecular profile in patients at high risk of developing predementia or dementia syndromes.

Keywords: Amyloid-\textbeta peptide metabolism, hyperinsulinemia, hyperphosphorylated tau protein, insulin resistance, insulin resistant brain state, metabolic syndrome, type 2 diabetes mellitus

INTRODUCTION

Metabolic syndrome (MetS) is a multifactorial disorder represented by the co-occurrence of several conditions related to central obesity that also includes impaired glucose metabolism, lower high density lipoprotein levels, elevated triglyceride levels, and high blood pressure and that depicts a risk status for both type 2 diabetes mellitus (T2DM) and coronary artery dis-
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Except for the World Health Organization criteria [2], the European Group for study of Insulin Resistance criteria [26], and the American Association of Clinical Endocrinologists criteria [27], the principal definitions of MetS do 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, even if the presence of insulin resistance cannot be taken for granted in patients with MetS. The occurrence of diabetes and dementia is very high in older patients, suggesting a possible link between the two, overall because diabetic patients have a higher chance of developing dementia [29]. T2DM has also been found consistently to be related to vascular dementia but its relation to AD is less clear, although half of the studies found an increased risk in diabetic patients [29,30]. In type 1 diabetes mellitus (T1DM), only a mild decrease of speed of information processing and psychomotor efficiency has been shown in nondemented subjects [31], while in T2DM, memory and executive functions have been found to be impaired [32]. One clue as to why T1DM and T2DM may differ in the progression of cognitive impairment is a potential interaction between diabetes and age [33]. In fact, T2DM is more prevalent with increasing age, and clinically relevant decreases in cognitive function are more likely to occur in elderly T2DM patients [34]. Another possible explanation for the differential effects on cognitive function is insulin resistance, a feature more prevalent in T2DM than in T1DM [33].

In fact, some authors hypothesized that insulin resistant brain state (IRBS) contributes to cognitive impairment and neurodegeneration. Several aspects of brain metabolism clearly responded to insulin action, and although insulin and insulin-like growth factor 1 (IGF-1) are supplied by circulation, a smaller proportion of insulin is produced in the brain itself [35]. Moreover, insulin receptors (IRs) have been found in different brain areas with variable densities, in particular, in the olfactory bulb, hypothalamus, cerebral cortex, and hippocampus [36]. Therefore, impairments of insulin and IGF-1 signaling leads to decreased energy metabolism and increased oxidative stress manifested by reduced glucose uptake and ATP production [37]. Reduced ATP adversely affects cellular homeostasis, membrane permeability, and fundamental processes required for synaptic maintenance and remodeling, which are needed for learning and establishing new memory [38]. In addition to a metabolic function, insulin and IGF-1 modulate neuronal growth, survival, differentiation, migration, gene expression, protein synthesis, cytoskeletal assembly, synapse formation, and plasticity. In addition, they regulate growth, survival, and myelin production/maintenance in oligodendrocytes [39]. On the other hand, hyperglycemia, diabetes mellitus, and insulin resistance increased the risk of developing cerebrovascular disease, micro- and macrovascular complications of varying severity [33], as well as increased carotid intima-media thickness [40–42], or greater grade of infarcted areas during a cerebrovascular event [43]. Increased concentrations of anti-fibrinolytic and other procoagulant factors have been found in diabetes mellitus as well as alterations in nitric oxide metabolism. Plasminogen activator inhibitor-1 and antithrombin III, which inhibit fibrinolysis, as well as the tissue plasminogen activator antigen, a marker of impaired fibrinolysis, were consistently found to be elevated in insulin resistance phenotypes [44,45]. Procoagulant factors, such as factor VII and VIII, and the von-Willebrand factor also rise with the degree of insulin resistance [46,47].
INSULIN RESISTANCE BRAIN STATE AND TAU PROTEIN

Insulin and IGF-1 after binding to IRs mediate signal transduction by activation of phosphatidylinositol-3 kinase (PI3-K) that stimulates glucose transport and inhibits apoptosis by activating protein kinase B (Akt/PKB) [38]. Insulin resistance signaling impairment induces PI3-K dysfunction leading to reduced Akt/PKB activity, decreased glucose/energy metabolism, and ATP production, compromising all ATP-dependent processes, which may include also insulin degrading enzyme (IDE) activity regulation [48]. Additionally, PI3-K dysfunction leads to reduced glycogen synthase kinase 3 α/β (GSK-3α/β) phosphorylation, and by GSK-3α/β activation, to phosphorylation of tau protein and intraneuronal amyloid-β (Aβ) accumulation (Fig. 1). The understanding of this mechanism allowed new perspectives into research of disease-modifying drugs, such as GSK3 inhibitors [49]. Glucose metabolism also participates in posttranslational protein modification involving the hexosamine biosynthetic pathway, which leads to the generation of O-N-acetylglucosamine (O-GlcNAc). O-GlcNAcylation of proteins is proposed to compete with protein phosphorylation, and if intraneuronal glucose metabolism decreases because of insulin resistance, O-GlcNAcylation is decreased and consequently increased protein phosphorylation, including tau protein [50].

There is now solid evidence that insulin and IGF-1 signaling cascades are involved in expression and phosphorylation regulation of tau protein and also in cytoskeletal functions via phosphorylation [51]. Recently, in a mice experimental model, two distinct mechanisms were hypothesized to explain the role of impaired insulin signaling in tau hyperphosphorylation [52]. One, inherent to insulin depletion, probably causes inhibition of the PI3K/Akt pathway, in particular by inhibition of protein phosphatase 2 (PP2A) activity and increasing activation of GSK-3β [53]. In addition, inhibition of insulin/IGF-1 signaling blocks the Wnt pathway [54], which negatively regulates GSK-3/β via a PI3K/Akt-independent mechanism. In AD, both PI3K/Akt and Wnt signaling have been linked to key molecular abnormalities [55]. The other mechanism was consequent to hypothermia. In fact, deficits in peripheral glucose/energy metabolism lead to relative hypothermia, with direct inhibition of PP2A activity, finally resulting in hyperphosphorylation of tau [52], which cannot be transported into axons, and that then accumulates and aggregates in neuronal perikarya [56]. This contributes to neurodegeneration by enhancing oxidative stress and triggering pathophysiological cascades...
that lead to increased apoptosis destabilizing the microtubule network and other cellular functions [57].

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Insulin also influences Aβ peptide metabolism by accelerating its trafficking to the plasma membrane from the trans-Golgi network, where it is generated. Insulin also increases extracellular levels of amyloid-β protein precursor (AβPP) by promoting its secretion and inhibiting its degradation by IDE and, finally, disrupting physiological processing of AβPP [38] (Fig. 1). Conversely, alterations in insulin signaling may be secondary and not primary factors in relation to AD. In particular, extracellular soluble oligomers of Aβ peptides [also termed Aβ-derived diffusible ligands (ADDLs)] [58] can bind to synapses and decrease membrane IRs through an insulin signaling-dependent mechanism [59,60]. Intracellular Aβ inhibits insulin signaling in neurons by interfering with the association between phosphoinositide-dependent kinase 1 and Akt1 and precluding Akt1 activation [59,60]. Therefore, since AβPP competes with insulin for receptor binding, inefficient degradation of soluble AβPP could represent an important mediator of brain insulin resistance in AD through a competitive mechanism with IDE [61,62]. If AβPP interferes with IDE function, the outcome should be to increase rather than decrease insulin levels and their actions in the central nervous system (CNS). Nonetheless, in AD, the opposite is true, i.e., increased levels of AβPP are associated with reduced levels of CNS insulin and IGF-1 [63]. This suggests that a dual mechanism of cognitive impairment and neurodegeneration mediated by insulin resistance is possible and that it may be distinguished the brain insulin deficiency action from peripheral insulin resistance. In the absence of peripheral insulin resistance, AD most likely represents a brain-specific form of diabetes mellitus, i.e., type 3 diabetes mellitus (T3DM) due to the combined effects of brain insulin deficiency and insulin resistance. Because etiological factors responsible for T3DM have not been clearly proven in the case of sporadic AD [64], some authors proposed the term IRBS instead of “T2DM confined to the brain” or T3DM to avoid misunderstandings. With aging, desynchronization of biological processes, together with the activity of susceptibility genes (e.g., apolipoprotein E), hypothalamic-pituitary-adrenal (HPA) axis impairment (i.e., cortisol and noradrenaline) and oxidative injury may induce an IRBS [48]. From a diagnostic point of view, after a 1-minute cold pressure test, both cortisol and noradrenaline increased in sporadic AD patients, indicating HPA-axis hyperactivity and an increased sympathetic tone significantly higher than in age-matched controls [65]. The induction of an IRBS may be of predominating significance for the generation of sporadic AD in absence of MetS. On the contrary, besides the mechanism speculated above, among individuals with peripheral insulin resistance, there is another pathological process relative to excess generation of cytotoxic lipids, including ceramides, that cross the blood-brain barrier and cause IRBS, neuro-inflammation, oxidative stress, DNA damage, and lipid peroxidation [38]. Ceramides are lipid signaling molecules with wide-ranging modulatory effects, including cell proliferation, motility, plasticity, inflammation, apoptosis, and insulin resistance [66]. In particular, ceramides cause insulin resistance by activating pro-inflammatory cytokines and also inhibiting insulin-stimulated signaling through PI3-K/Akt in the brain [38]. Finally, impaired insulin signaling increases oxidative stress by expression of pro-oxidant genes belonging to nitrous oxide systems, incorporation of 8-hydroxy-2'-deoxyguanosine, which destabilizes DNA, lipid peroxidation with 4-hydroxynonenal accumulation, and activation of pro-apoptosis genes. In fact, the progressive worsening of insulin/IGF resistance with regard to stage of AD is correlated with all these cellular alterations but in a different manner according to whether the insulin resistance disease is in or outside the CNS.

CONCLUSIONS

A growing body of evidence from epidemiological and basic research has proposed a model of cognitive impairment of vascular or degenerative origin linked to MetS and metabolic disorders. This MCS may have as central feature, the IRBS, notwithstanding the absence in current operational clinical criteria for MetS of insulin resistance or hyperinsulinemia. However, although the hypothesis that the IRBS and MetS may be important for AD pathogenesis, they are distinct entities and may not be related to each other. Elucidation of the interactions among various metabolic disorders and identification of convergent pathophysiology underlying comorbidities will likely provide important clues to dementia-related mechanisms. In fact, there is very strong evidence that obesity, hyperinsulinemia,
and T2DM are related to dementia and AD. The potential mechanisms linking the continuum of obesity, hyperinsulinemia, and T2DM are multiple, overlapping, and highly correlated. Conversely, obesity is also strongly associated with hypertension via sympatho- 
avic activation of the sympathetic nervous system by leptin [67]. Clearly, it is very difficult to include the measurement of peripheral insulin resistance in the current research-applied MetS criteria or the identification of IRBS for the MCS. However, as inflammation has been suggested for inclusion among the MetS components in the few last years [68], we proposed the IRBS as an additional feature of the MCS to identify in these patients a molecular profile of higher risk to develop predementia or dementia syndromes.

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