Can Alzheimer Disease Be a Form of Type 3 Diabetes?

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Abstract

Alzheimer disease (AD) and metabolic syndrome are two highly prevalent pathological conditions of Western society due to incorrect diet, lifestyle, and vascular risk factors. Recent data have suggested metabolic syndrome as an independent risk factor for AD and pre-AD syndrome. Furthermore, biological plausibility for this relationship has been framed within the "metabolic cognitive syndrome" concept. Due to the increasing aging of populations, prevalence of AD in Western industrialized countries will rise in the near future. Thus, new knowledge in the area of molecular biology and epigenetics will probably help to make an early molecular diagnosis of dementia. An association between metabolic syndrome and specific single-nucleotide polymorphisms (SNPs) in the gene INPPL1, encoding for SHIP2, a SH2 domain-containing inositol 5-phosphatase involved in insulin signaling, has been described. According to recent data suggesting that Type 2 diabetes represents an independent risk factor for AD and pre-AD, preliminary results of a case–control study performed to test the putative association between three SNPs in the SHIP2 gene and AD show a trend toward association of these SNPs with AD.

Introduction

ALZHEIMER DISEASE (AD) IS THE MOST COMMON FORM of dementia, accounting for more than 50% of all cases of dementia.[1] It occurs primarily after age 65, and for this reason it is classified as an age-related disease. The exception is the familiar early-onset form (with Mendelian inheritance) that represents about 1% of all cases.[2] Its prevalence is approximately 1% between 65 and 69 years and is higher than 50% in individuals above 95 years.[3] AD is a neurodegenerative disorder with the typical features characterized by the impairment of memory, language, attention, executive functioning, apraxia, agnosia, and aphasia. Cognitive, but also behavioral, symptoms cause a reduction of functional activities compared to a previous level of functioning.[1–3]

According to the amyloid hypothesis, AD is characterized by accumulation of senile plaques constituted by deposits of the abnormal form of amyloid β (Aβ) protein (Aβ_{40-42} amino acids), present in common forms of dementia, and neurofibrillary tangles originating from hyperphosphorylation of microtubular tau protein. These structures accumulate progressively in the brain starting from the hippocampus and then spreading to the cerebral cortex, where neurons are lost, causing memory, language, and general cognitive impairment.[3]

However, today some different pathophysiological theories regarding AD exist, suggesting that the disease could be driven by inflammation, vascular changes, and metabolic disorders. These theories are not mutually exclusive, because inflammation plays a relevant role in both vascular lesions and metabolic disorders.[3–8] Indeed, several population-based studies have recently described Type 2 diabetes as a risk factor for AD. Furthermore, these data were also confirmed in the pre-AD status, the so-called mild cognitive impairment. However, data are not definitive and negative results have also been published.[9–11]

Most recently, metabolic syndrome, which represents a cluster of metabolic factors—insulin resistance, abdominal obesity, glucose intolerance, hypertension, hyperinsulinemia, and raised fasting plasma glucose—has also been described in association with an increased risk of AD.[12,13] Interestingly, strong evidence suggests that systemic inflammation and central adiposity contribute to and perpetuate metabolic syndrome.[8] All of these alterations predispose individuals to type 2 diabetes and cardiovascular disease.[8–14]

Genetic background, age, sex, diet, physical activity, and habits in general all influence the prevalence of the metabolic syndrome and its components. Twenty years ago in the Mediterranean area, it was assessed that 70% of adults have at least one of the disorders characterizing metabolic syndrome. However, in the European population, the rate

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of metabolic syndrome is 7%–30%.[15,16] Worldwide there are 1.1 billion overweight people with a body mass index (BMI) between $25 \, kg/m^2$ and $30 \, kg/m^2$ and 312 million with a BMI $> 30 \, kg/m$.[14] In the last 40 years, the rate of obesity in the United States has increased, and today 66% of adults have a BMI $> 25 \, kg/m^2$ and half of those have a BMI $> 30 \, kg/m$.[17]

Another link between obesity, inflammation, insulin signaling, and dementia is the amyloid precursor protein (APP),[18] a transmembrane protein from which the $A\beta_{40-42}$ fragment that forms senile plaques originates.[3] APP is considered an adipokyne, producing and processing $A\beta_{40-42}$ in adipose tissue. This fragment is expressed in fat tissues and overexpressed in abdominal adipocytes of obese patients.[18]

Recent data support an increased susceptibility for AD in patients with metabolic syndrome,[19] but from the age of 85 the association between metabolic syndrome and accelerated cognitive decline vanishes.[20] On the other hand, some American scientists hypothesize that AD is a third form of diabetes.[21] This hypothesis was formulated in 2005 when 45 AD patients were analyzed postmortem, showing lower levels of insulin in the brain. In particular, the authors analyzed the frontal cortex of AD individuals, calculating the concentration of insulin, insulin-like growth factor 1, and insulin receptor. Data showed that later stages of disease were associated with an up to 80% decrease of these parameters compared to healthy brain.[21] According to the latter association, some authors proposed the concept of "metabolic cognitive syndrome" (MCS) when describing co-occurrence of AD and metabolic syndrome. Indeed, dementia and metabolic syndrome present some overlap both in predisposition factors and in altered signaling cascade. Environmental elements like diet, lifestyle, smoking, and socioeconomic status are critical contributors in these disorders. Altered insulin signaling pathway has a key role in their pathogenesis. In particular insulin resistance might be the first step toward both disorders, constituting a bridge between AD and metabolic syndrome.[22]

Metabolic-Cognitive Syndrome: Insulin and the Central Nervous System

Insulin is known to be a peripheral regulator of nutrient storage, but it is also essential for the control of energy balance in the central nervous system (CNS). Neuronal insulin signaling pathway has an important function in mammalian fat storage and in *Caenorhabditis elegans* and *Drosophila*, the cellular signaling systems mediating these effects bear remarkable homology to those described in mammals.[23]

There is substantial evidence demonstrating insulin action in the control of neuronal function in cortical and hippocampal areas, which are involved in memory processing and cognitive functioning.[24,25] Insulin directly influences neurons by processes not linked to modulation of glucose uptake. Neurotransmitter release, neuronal outgrowth, tubulin activity, neuronal survival, and synaptic plasticity are all directly modulated by insulin.[26–29] The insulin signaling pathway modulates synaptic plasticity, promoting the recruitment of γ-aminobutyric acid (GABA) receptors on postsynaptic membranes, influencing N-methyl D-aspartate receptor (NMDA) conductance (neuronal $Ca2^+$ influx) and regulating receptor α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) cycling.[30,31]

The MCS was elaborated on 2010 by Frisardi and his colleagues. It is based on the co-existence, in patients, of metabolic syndrome and cognitive impairment of degenerative or vascular origin.[22] Insulin resistance can be manifested in peripheral tissues or directly in the brain as an insulin resistance brain state that contributes to cognitive impairment and neurodegeneration for the reason described above.[22]

Many molecules participate in the regulation of the insulin signaling pathway; therefore, an alteration in the function or expression of some of these proteins causes a reduction in glucose uptake. Consequently, glucose accumulates in the blood, determining hyperglycemia and hyperinsulinemia. Hyperglycemia induces an increase of the peripheral use of insulin, which results in a reduction of insulin disposable for the brain. Because insulin is essential for memory, learning, neuronal survivor, and longevity processes, the alteration of its concentration might cause important consequences on tau and $A\beta$ processing.[24,25] For example, an impairment of insulin signaling pathway causes a reduction of the activity of phosphatidylinositol 3-kinase (PI3K) and consequently a reduction in AKT/protein kinase B (PKB) pathway. This leads to an increase of glycogen synthase kinase 3 α/β (GSK-3 α/β) activity that phosphorylates tau protein and causes intraneuronal $A\beta$ accumulation.[21]

Moreover, glucose metabolism plays a role in the protein posttranslational modification involving the hexosamine biosynthetic pathway, which leads to the generation of O-N-acetylglycosamine (O-Glc-NAc). If insulin resistance is established, intraneuronal glucose metabolism is impaired. Consequently, the amount of O-Glc-NAcylation is reduced. This posttranslational modification competes with the phosphorylation process, thus more phosphate groups are added with an increase of the amount of phosphorylated tau protein.[32]

Insulin is also involved in the APP metabolism.[33] APP competes with the insulin receptor. Thus, its inefficient degradation might play a key role in AD brain insulin resistance.[34]

SHIP2: A Modulator of the Insulin Pathway

When insulin binds to its membrane receptor, it activates a signaling cascade involving phosphoinositides and the AKT/PKB pathway.[24] To regulate cellular levels of lipid secondary messengers such as phosphatidylinositol (3,4,5)-triphosphate (PtdIns [3,4,5]P3), cells use two major classes of phosphoinositide phosphatases—the inositol polyphosphate 3-phosphatase PTEN and the SH2 domain-containing inositol 5-phosphatases 1 and 2 (SHIP1 and SHIP2).[35]

SHIP2 is a protein that catalyzes the degradation of lipid secondary messenger phosphatidylinositol 3,4,5-triphosphate (PIP3) to produce phosphatidylinositol 3,4-diphosphate (PIP2). Thus, SHIP2 is an antagonist of PI3K that takes part in insulin signaling, phosphorylating PIP2 to obtain PIP3. Because the PI3K pathway plays a key role in the biological effects of insulin, the attenuation of the PI3K-mediated insulin signaling pathway could be associated with insulin resistance in type 2 diabetes.[36]

Many studies underline the role of SHIP2 as negative regulator of insulin signaling.[35–37] Its overexpression reduces both insulin-stimulated mitogen-activated protein kinase and AKT activation, leading to downregulation of glucose uptake toward failed recruitment of GLUT4 in cell membrane and glycogen synthesis in 3T3-L1 adipocytes and L6 myotubes.[38–40] Moreover expression of SHIP2 is greatly increased in the skeletal muscle and fat tissue of diabetic mice.[41]

In addition, the SHIP2 gene (INPPL1) is localized in human chromosome 11q13–14, which is suggested to be linked to type 2 diabetes characterized by insulin resistance and hypertension.[42–44] Therefore, SHIP2 could be involved in the pathogenesis of insulin resistance of type 2 diabetes mellitus in humans and also in the metabolic syndrome, in which insulin resistance represents the first step toward.[36,41–43,45]

A study conducted by Kaisaki et al.[45] shows a significant association between single-nucleotide polymorphisms (SNPs) of INPPL1 (rs2276047, rs9886, and an insertion/deletion in intron 1) and type 2 diabetes and metabolic syndrome in European populations. This finding was partly confirmed by another study conducted by Kagawa et al. in the Japanese population.[46]

Conclusion

Metabolic syndrome and AD constitute a worldwide problem, especially for Western societies, due to co-morbidity (mainly vascular), lifestyle (*i.e.*, diet, exercise, smoking, alcohol), and increasing age. Considering the increasing data that have focused recently on the association between AD and metabolic syndrome, it could be speculated that AD could be a third form of diabetes.[21]

Metabolic syndrome is a condition that predisposes to type 2 diabetes, which is characterized by systemic inflammation, insulin resistance, obesity, high cholesterol levels, and sedentary lifestyle, all conditions related to an increased risk for AD.[47] Due to increasing age, prevalence of AD in Western industrialized populations will be higher in the future. Thus, new knowledge regarding molecular biology and epigenetics that would enable an early molecular diagnosis of dementia is welcome.[3]

Discovery of new genes and proteins involved in physiological pathways can be crucial for the identification of altered mechanisms involved in the pathophysiology of AD and consequently in signaling pathways. Such discoveries would allow finding new target proteins, developing new molecular risk profile for diagnosis and prevention, and planning early interventions.[6] In this regard, we are extending previous research on the association of INPPL1 SNPs and metabolic syndrome to AD. With this aim, we are conducting a case–control study evaluating the putative association between INPPL1 SNPs and AD. Preliminary results obtained show a trend toward association of these SNPs with AD, thus strengthening the hypothesis of a close relationship among AD, metabolic syndrome, and diabetes.

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