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http://www.jrdiabet.ro
Rom J Diabetes Nutr Metab Dis. **20**(2):177-181
doi: 10.2478/rjdnmd-2013-0022

SEARCHING THE MISSING LINK BETWEEN ALZHEIMER'S DISEASE AND DIABETES

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received: June 03, 2013 *accepted*: June 08, 2013
available online: June 30, 2013

Abstract

Recent studies strongly suggest a significant association between diabetes mellitus and Alzheimer Disease (AD) justifying the term "type 3 diabetes". Studies show that impairment of glucose metabolism occurs very early in the course of AD, leading to a broad range of consequences, among which the accumulation of amyloid beta (Aβ), which per se induces insulin resistance. Furthermore, adipocytokines, recognised markers of insulin resistance, seem to play a role in the development of AD. As for insulin resistance, when AD is considered, the most studied ones are leptin and adiponectin, but also a recently described adipokine - progranulin. It is our belief that both prospective and transversal studies on subjects with both AD and type 2 diabetes (T2D) may prove the role of adipokines not only in AD, but also in this most somber association.

key words: *insulin resistance, type 2 diabetes, Alzheimer's disease, progranulin, adiponectin, leptin*

Introduction

Recent studies strongly suggest a significant association between diabetes mellitus and Alzheimer Disease (AD), and more specifically a link between insulin, glucose and AD [1], justifying the term "type 3 diabetes". This accurately reflects the fact that AD represents a form of diabetes that selectively involves the brain and has molecular and biochemical features that overlap with both type 1 and type 2 diabetes (T2D) [2]. However, there is an ongoing debate about the association between T2D and AD, the relationship being supported by many arguments, principally by the increased risk of developing AD in individuals with T2D [2] or mid-life obesity [3].

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With more than 371 million persons affected by diabetes in 2012 [4], and an estimated 24 million people affected by dementia [2,5], there is no wonder why both pathologies represent major public health issues. The better understanding of the mechanism linking AD and T2D may lead to a wider therapeutic range, especially when referring to AD.

Insulin in the central nervous system and AD

Studies show that very early in the course of AD impairment of glucose metabolism occurs [6], leading to a broad range of consequences, among which the accumulation of amyloid beta (Aβ), a well known hallmark of AD. Furthermore, it seems that Aβ toxicity per se causes insulin resistance. Insulin stimulates Aβ extracellular secretion and also inhibits its intracellular accumulation and degradation by the insulin-degrading enzyme [6,7], which is fundamental in Aβ degradation and is competitively inhibited by insulin, resulting in a reduced Aβ clearance [7]. What is even more interestingly is that Aβ also has the ability to competitively inhibit insulin biding and to reduce insulin receptor substrates signalling in cultured cells [7].

Insulin therapy – an option in the treatment of AD?

Steps are being made in order to determine the usefulness of insulin therapy in the treatment of AD, which for the moment remains controversial. A series of studies proved that subjects with T2D and AD treated with insulin have a slower rate of cognitive decline compared to subjects treated with oral antidiabetic drugs [8]. Moreover, the administration of intravenous insulin, while maintaining euglycemia, showed important memory enhancements for patients with AD [9].

A significant improvement of the EEG parameters was noted when intravenous bolus injections and intranasal insulin were administrated [10]. The intranasal regular human insulin improved memory, cognition and daily functioning with no severe adverse effects reported [10]. The same authors showed that insulin-induced memory improvement can be further enhanced by using intranasal rapid-acting insulin analog [11]. Intranasal administration circumvents the blood-brain barrier to rapidly and directly deliver therapeutics to central nervous system, providing direct access of the hormone to the cerebrospinal fluid within 30 min without substantial uptake into the blood stream, via bulk flow transport through perineural channels. In addition to the olfactory pathway, insulin and other therapeutics have also been shown to be rapidly transported from the nasal mucosa to the brain along the trigeminal neural pathway [10,12].

The usefulness of intranasal insulin in the therapy of AD shall be verified in a large multisite trial that has begun in April 2013 and will last for 5 years, being part of the National Alzheimer Project Act signed by President Barack Obama; the study will recruit 240 volunteers for a year-long treatment trial at many sites across the United States [12].

Adipocytokines – the missing link between AD and diabetes?

As previously discussed, the main systemic link between AD and diabetes is dysregulated insulin signalling which leads to neurodegeneration and cognitive impairment [7]. Moreover, even from an anatomo-

pathological point of view there are similarities between these two disorders, both having a degenerative basis and involving beta-cell destruction, respectively neuronal loss [7].

Many epidemiological studies proved the bidirectional relationship between AD and T2D. The association was observed for the first time in 1999 [13] and since then many studies have come to confirm that subjects with T2D have a 2-fold higher risk of developing AD. The risk ratio is the same regardless of ApoE ε4 allele [7], the only well confirmed genetic risk factor for sporadic AD [14], capable to modulate the effect of other putative risk factors such as T2D and hyperinsulinemia [15]. However, although still controversial, there are studies that support the idea that the relationship is bidirectional and subjects with AD are more vulnerable to T2D [16].

But, if T2D has well established diagnosis criteria, if at the present date we have many biological biomarkers related to insulin resistance, when talking about AD the situation is far from similar. Although a set of international diagnosis criteria is available, the confirmation of the diagnosis can be made only post-mortem. Furthermore, even if a wide range of biological biomarkers have been proposed, none has confirmed the expectations of both clinicians and scientists. Among these we can count Aβ, a candidate biomarker when measured in cerebrospinal fluid (CSF), but which decreases with disease progression [1]. Taking into account the complex relationship between AD and glucose metabolism, a recent study [1] suggested the usefulness of dosing the plasma Aβ (Aβ40 and Aβ42) at baseline, 15 and 30 minutes after performing a 75 g glucose loading test, which led to an elevation of this biomarker only in subjects with AD dementia.

Taking into consideration the aspects previously presented, a question comes to mind: "*What about adipocytokines?*", recognized biomarkers of insulin resistance. As for insulin resistance, the most studied ones are leptin and adiponectin, but also a recently described adipokine - progranulin.

Leptin is involved in learning and memory [17,18]. Furthermore, in the prospective Framingham study [18] it was demonstrated that higher leptin levels at baseline were prospectively associated with a lower incidence of AD and dementia. The authors consider their findings intriguing, given the hypothesis that one reason for the observed association between mid-life central obesity and the risk of AD might be an acquired resistance to leptin's effects, including its neuroprotective ones [19].

Adiponectin also seems to play a role in the development of all-cause dementia and particularly AD. A recent study [20] proved that increased plasma adiponectin levels are an independent risk factor for the development of AD in women. Furthermore, another study [21] found higher adiponectin levels both in plasma and CSF in subjects with AD, suggesting a critical role of this molecule in the onset of AD.

Progranulin (PGRN) is a multifunctional protein, which has been implicated in cell growth, wound repair, tumorigenesis, inflammation, neurodevelopment, neurodegeneration and, as shown recently, in insulin resistance [22-27]. Some granulin peptides increase the expression of pro-inflammatory cytokines interleukin-1β, interleukin -8 and

TNF-α, whereas PGRN is a potent inhibitor of TNF-α; a tight control of the conversion of full-length PGRN into granulin peptides appears to be pivotal [22]. Recent studies showed that elevated PGRN serum concentrations are associated with visceral obesity, elevated plasma glucose, T2D and dyslipidemia [23-27]. PGRN was also proposed as a biomarker for AD, but its role is still unclear and controversial [28-30].

Future perspectives

Although the association AD – T2D is well proved based on many scientific and epidemiological evidences, the linking mechanisms between these two disorders remain to be discovered. It is our belief that both prospective and transversal studies on subjects with both AD and T2D may prove the role of adipokines not only in AD, but also in this most somber association.

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