Diabetes and Alzheimer's disease: A link not as simple as it seems

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Type 2 diabetes mellitus (T2DM) is associated with an increased risk to develop Alzheimer disease (AD), however, the underlying mechanisms for this association are still unclear. In this review we will provide a critical overview of the major findings coming from clinical studies and animal models.

Introduction

The majority of Alzheimer's disease (AD) cases have a sporadic origin, although the genetic background determines strongly the risk of AD, even for sporadic cases [1]. Very little is currently known about the triggering factors of this destructive

neurodegenerative disorder [2], apart from ageing which is the most important factor for the manifestation of late-onset AD [3]. Besides ageing, metabolic disorders including type 2 diabetes *mellitus* (T2DM) has also been associated with an increased risk to develop dementia [4], however, the underlying mechanisms responsible for this association are still controversial.

Given the vast increase of incidence of AD and metabolic disorders in the aged population [2,5], a better understanding of the potential link between these two disorders is essential. In this review we will critically analyze the major findings coming from clinical and preclinical studies.

Diabetes and Alzheimer's disease: What can we learn from clinical studies?

Diabetes is a very complex metabolic disorder characterized by a rise in blood glucose levels due to an altered insulin production by pancreatic cells (Type 1) or an impaired insulin response (Type 2) [6]. The chronic hyperglycemia and insulin resistance found in diabetic patients is commonly associated with vascular complications which eventually lead to alterations in the kidney (nephropathy), retina (retinopathy) and peripheral nerves (neuropathy), among other problems [7]. Not surprisingly, besides the abnormalities in peripheral organs, diabetic patients also show structural and functional changes in the central nervous system.

In fact, several studies suggest that there is an increased risk to develop cognitive impairments in patients with diabetes [8]. Type 1 diabetic patients display defects in information processing, psychomotor efficiency, attention, and cognitive flexibility [9].

The effect of type 2 diabetes *mellitus* (T2DM) in cognition is more controversial: the Maastricht study showed that patients with T2DM performed worse in different cognitive domains including memory, processing speed and executive function, compared to individuals with normal glucose metabolism [10]. In contrast, the New

Mexico elder Health Survey could not find a significant reduction in the cognitive function in patients with T2DM compared with participants with normal glucose tolerance. [11].

Different population-based cohorts studies have also suggested an increased risk to develop dementia in T2DM patients [4]. The Rotterdam study was the pioneer report showing almost a two-fold increase risk of dementia, mainly AD and vascular dementia, in patients with T2DM [12]. Since then, many other studies worldwide have consistently shown an increased risk to develop dementia in the T2DM population [13–15]: Schnaider et al. reported that midlife diabetes is a risk factor to develop dementia three decades later in a population of Jewish male civil servants [14]. The Rochester study monitored 1,455 subjects with adult onset diabetes *mellitus* and they showed a 1.6 fold increased risk of all types of dementia [15]. The Honolulu-Asia aging study showed that diabetes increased the risk of AD 1.8 fold in a population-based cohort of more than 2500 Japanese-American men [16].

Nowadays, despite more than 2000 pubmed papers published on AD and diabetes, the underlying link between these two disorders is still unclear. The major mechanisms suggested are: hyperglycemia, vascular abnormalities, altered amyloidosis and impaired insulin signaling. However, the observations coming from clinical studies are highly controversial and have failed to elucidate clear pathways responsible for the increased risk of dementia in T2DM patients.

In this review we will make a critical analysis of the different mechanisms suggested in the literature.

a) Alterations in glucose metabolism

Diabetes is linked to peripheral hyperglycemia. However, how the rise in blood glucose affects brain function is currently unknown [17].

Yaffe et al. showed an association between glycosylated hemoglobin levels and the risk to develop AD or dementia in a group of more than 1900 postmenopausal women [18]. The Maastricht study also reported a correlation between blood glucose levels and a lower processing speed and executive function in patients using cross-sectional data from more than 2500 participants. However, the same study could not find an association between hyperglycemia and impaired memory function [10]. Scott et al. [19] and the Rotterdam study [20] also failed to demonstrate a correlation between elevated glucose levels or glucose intolerance and worse cognitive function in an older population. In line with the latter results, an intensive glycemic therapeutic strategy in patients with T2DM had no positive effects in cognitive outcomes [21].

On the other hand, T2DM patients with mild cognitive impairment (MCI) showed a general reduction in brain [^{18}F]-fluorodeoxyglucose (FDG) uptake in gray and white matter [22]. Insulin resistance has also been associated with a reduced cerebral glucose metabolic rate in frontal, temporal-parietal, and cingulate regions in patients with T2DM [23,24].

Interestingly, brain hypometabolism (observed by FDG uptake) is associated with an increased risk for AD and can be observed years before the dementia onset in the same brain regions affected in T2DM patients [25,26]. Thus, the reduced cerebral glucose metabolic rate observed in diabetic patients could be a predisposing factor for AD and MCI [22].

b) Vascular and structural brain abnormalities

T2DM is linked to alterations in cerebral microvasculature, including amyloid angiopathy [16,27]. The disorder is also associated with increased number of brain infarcts [28]. T2DM is an important risk factor for ischemic stroke [29]. Other studies have associated chronic hyperglycemia with cerebral microvascular remodeling [30].

Magnetic resonance imaging (MRI) studies revealed loss in brain volume in patients with T2DM [31]. Particularly, brain atrophy was detected in hippocampal and cortical

brain regions, which can influence the development of AD pathology [32–34]. However, the loss of brain volume does not imply neurodegeneration, and can be due to different pathological processes including loss of glial cells, axons, or white matter shrinkage [27]. In fact, diffusion tensor imaging (DTI) (a MRI technique that detects alterations in white matter tissue) has revealed white matter abnormalities in T2DM patients that correlates with cognitive dysfunction [35]. Moreover, reduced functional connectivity has also been observed in patients with T2DM [36].

c) Impaired insulin signaling in the brain

Another important mechanism suggested to link dementia and cognitive dysfunction to T2DM is insulin resistance. For years, the brain was considered an insulin-insensitive organ, as brain glucose metabolism is largely regulated in an insulin-independent manner [37]. Yet, in the last decades, strong evidences have demonstrated an important role of insulin in the central nervous system (CNS), mainly affecting feeding and cognitive behavior [38]. Mouse experiments suggest that most of the insulin present in the brain is transported from the periphery across the blood brain barrier (BBB) by a receptor-mediated process that can be saturated [39]. Wallum et al. demonstrated in the late 80' that intravenous insulin infusions increased the levels of insulin in the cerebrospinal fluid (CSF) of eight healthy men [40]. However, the effect of chronic peripheral hyperinsulinemia and insulin resistance in the brain insulin pathway is still not clear.

Liu et al. showed a significant decrease of the PI3K/AKT pathway in the autopsied frontal cortices from T2DM patients compared to heathy controls, suggesting the presence of central insulin resistance associated with diabetes [41]. On the other hand, post-mortem studies have also shown disturbances in the brain insulin signaling in AD patients. However, these findings are still controversial [42]. i.e.: some groups reported reduced mRNA levels of brain insulin, and insulin receptor (IR) in AD brains compared to controls [43], while others showed no significant differences

in IR protein levels or phosphorylation state [44]. The most convincing change in the insulin pathway observed in AD patients is a reduction of insulin receptor substrate (IRS) levels, accompanied by an increased IRS-1 serine phosphorylation (marker of insulin resistance) [45]. Nevertheless, physiological brain aging is also associated with changes in central brain insulin [46], suggesting that these insulin alterations are not a specific hallmark of neurodegenerative brains. In fact, Frolich et al. reported a reduction of brain insulin levels in AD patients that was equal to age-matched controls [47].

Considering the role of insulin in cognition, dysregulation of the brain insulin pathway could be responsible for the cognitive impairments found in AD and T2DM patients. Supporting this hypothesis, pilot clinical trials with intranasal brain insulin delivery have shown improvements in verbal memory and story recall in patients with MCI and AD [48]. Intranasal insulin delivery was used to avoid the systemic side effects of insulin and no major aversive effects were reported [49].

d) Altered amyloidosis and Tau phosphorylation

Several *in vitro* studies have proposed a link between impaired insulin signaling and the amyloid cascade, which could explain the increased risk for AD in diabetic patients. Firstly, one of the proteins potentially involved in Aß clearance and degradation is the insulin degrading enzyme (IDE), a metalloprotease that also degrades insulin [50,51]. Postmortem analysis from AD patients suggests lower levels of IDE in the brain [52]. In addition, insulin can also regulate Tau phosphorylation via de PI3K/AKT pathway. AKT activation inhibits the glycogen synthase kinase 3ß (GSK 3ß), which is the major kinase involved in Tau phosphorylation [53,54]. Diabetes and impaired glucose metabolism have also been associated with accumulation of glycated Tau or amyloid-beta. Glycation might enhance aggregation of these proteins [55]. However, the link between altered insulin signaling and amyloidosis *in vivo*, is still highly controversial. On the one hand, postmortem analysis from the Hisayama

study suggested a correlation between hyperglycemia and hyperinsulinemia with an increased amyloid load, but no link with neurofibrillary tangles [56]. On the other hand, the Baltimore longitudinal study showed no significant correlation between amyloid load (assessed *in vivo* using Pittsburgh Compound B (C-PiB) positron emission tomography (PET) studies) and either glucose intolerance or insulin resistance [57]. In addition, Roberts *et al.* also reported no differences in the C-PiB retention ratio between diabetic and non-diabetic patients [24]. Other post-mortem studies even suggest a reduced AD-type pathology in T2DM patients [58,59].

Altogether, most of the current evidence suggest that T2DM does not accelerate the development of the core neuropathological features of AD: amyloid plaques and neurofibrillary tangles [60].

What can we learn from animal models?

During the last decades, many groups have tried to investigate the mechanisms underlying the link between diabetes and dementia, using animal models. As T2DM is usually associated with obesity and other comorbidities, the most widely used models for T2DM are obese animals. Obesity and T2DM can be triggered by either genetic manipulations such as disruptions in leptin (ob/ob mice) or leptin receptor (db/db mice or Zucker rats) [61], or by special diet treatments. Another commonly used method for the induction of diabetes is the streptozotozin (STZ) injection, which kills the pancreatic ß-cells triggering defects in insulin production and glucose metabolism similar to the ones observed in diabetic patients [62]

These diet-induced models, proposed as obesity induced by environmental factors, are considered more accurate models mimicking the T2DM human condition [63]. These models usually display hyperglycemia, glucose intolerance and insulin resistance [64].Most of the diets used for these studies are based on higher intake of fat, glucose, cholesterol or different combinations of the three [65]. However, the composition and duration of the diet exposure differ from one study to another, making it difficult to

achieve general conclusions. In addition, metabolic responses to high fat diet feeding can be very heterogeneous even within the same mouse strain [66].

Given the number of the different models used, the outcomes from these studies are highly variable. Hence, similarly to the situation in humans, the effect of T2DM-like alterations on brain function remains unclear and controversial. Several potential underlying factors have been discussed in the literature. Here, we will summarize what we consider the most important ones.

a) Hyperglycemia

Chronic hyperglycemia is associated with increased levels of reactive oxygen species (ROS), which is not only responsible for the ß-cells deterioration and development of insulin resistance, but also affects brain functions [67]. The brain is particularly vulnerable to oxidative damage due to its high oxygen consumption [68]. Different studies in rodents have shown that high fat diet treatment increased oxidative stress in the brain [69–71]. Another group also demonstrated a deleterious effect of acute hyperglycemia (induced by a single STZ injection) in a rat model of lacunar stroke [72].

However, hyperglycemia is usually accompanied by other comorbidies including insulin resistance, obesity, systemic inflammation, etc. Therefore, it is very difficult to dissect out the specific effect of hyperglycemia itself on brain function. To circumvent this problem, the group from Prof. Holtzman used glycemic clamps in a transgenic mouse model for AD, and measured changes of brain metabolites using *in vivo* microdialysis [73]. This study elegantly showed that acute peripheral hyperglycemia raises hippocampal interstitial fluid (ISF) glucose and amyloid beta levels. Authors claimed that the increase in Aß presumably happened as a consequence of a glucose-induced increased in neuronal activity.

b) Central insulin resistance in T2DM and AD animal models

In the last decades, several groups have tried to elucidate whether the peripheral insulin resistance found in diabetic patients, also affects the central insulin pathway using animal models. Yet, the outcomes from these studies is still under discussion.

Some groups claimed a clear link between peripheral and central insulin resistance. Ho et al. for instance revealed alterations in the brain insulin pathway upon diet-induced hyperinsulinemia, including reduced insulin receptor phosphorylation and activation of the downstream pathway and decreased IDE levels [74]. Arnold et al. also reported insulin insensitivity in the frontal cortex from C57BL/6J young mice after 17 days of diet treatment [75]. Another study even suggested that a single intraperitoneal insulin injection is able to rescue amyloidosis and cognitive impairments induced by the high fat diet treatment in 3xTg-AD mice [76].

In contrast, our group has shown that 10 months of high fat diet treatment did not affect hippocampal insulin sensitivity or the downstream insulin pathway [77]. Supporting our observations, the group from Prof. Holtzman also reported no changes in brain ISF or CFS insulin levels in response to peripheral hyperinsulinemia induced with hyperinsulinemic-euglycemic clamps [42].

AD itself has been suggested a risk factor for diabetes and metabolic alterations as well [78]. This is mainly based on work in mouse models for AD. Different groups have reported peripheral insulin resistance and signs of T2DM including obesity, hyperglycemia and hyperinsulinemia in such aged models [79,80]. However, it is not clear whether these mice develop central insulin resistance (i.e. whether their brains becomes insensitive to insulin). On the one hand, Ho et al. proposed that Tg2576 and 3xTg-AD models develop central insulin signaling dysregulation prior to peripheral insulin resistance [81]. In contrast, Stanley et al. showed by direct central insulin delivery, that the brain from old APP/PS1 mice is still responsive to insulin even in the presence of aberrant amyloidosis [42].

c) Diabetes mellitus and amyloidosis

To study the potential link between T2DM and amyloidosis *in vivo*, most of the groups used transgenic AD models that already show amyloid plaques aggregation and analyzed whether a high fat diet treatment altered the levels of amyloid in the brain. The conclusions from these studies are highly variable depending on the animal model used or the type of diet treatment [71,82,83]. However, even when using the same mouse model (3xTg-AD) and the same diet composition (60% Kcal from fat), one group reported an increase of amyloid beta levels [76], while the other did not [84].

Some studies also showed different outcomes depending on the duration of the diet. i.e.: Vandal et al. reported increased levels of soluble Aß40 and Aß42 in the cerebral cortex after 9 but not 4 months of diet treatment [76]. Busquets et al. even suggested *de novo* plaques aggregation in a C57BL/6J wild type background [85]. In contrast, in our group we used an APP knock-in model which does not develop amyloid plaques, but contained the Swedish mutation that cause AD in humans. In this model, we could not trigger amyloid alterations even after 16 months of high fat diet treatment [77].

In summary, in the last years it has been commonly accepted that metabolic disorders such as obesity and insulin resistance have a detrimental effect on brain amyloidosis. However, the *in vivo* data in human and mice do not support consistently this hypothesis [71,77,84]. In addition, as discussed above, clinical studies also support a lack of correlation between metabolic disturbances and an increased amyloid load [24,57].

d) Others

Besides the mechanisms mentioned here, there are several other alterations occurring in both, T2DM and AD, that may also be important to link the two disorders. For example, mitochondrial dysfunction as a consequence of increased oxidative stress has been suggested to be a key contributing factor to diabetes and AD pathology [86].

Moreria et al. showed brain mitochondrial dysfunction in old diabetic rats [87]. However, another group reported no defects in brain mitochondria after 1 year of high fat diet treatment in Wister rats [88]. Interestingly, Carvalho et al. found similar mitochondrial alterations in the brain from WT mice fed with high sucrose water, and 3xTg-AD mice [89]. In addition, a mitochondria-targeted antioxidant drug (mitoQ) prevents loss of spatial memory in 3xTg-AD mice [90].

Neuroinflammation also plays an essential role in the pathogenesis of AD and might also be affected in T2DM. Obesity, an important risk factor for T2DM and AD [91,92], is associated with a chronic systemic inflammation characterized by the release of pro-inflammatory cytokines [93] and might be associated with inflammation in the brain [94]. In fact, Buckman et al. showed that high fat diet treatment induced recruitment of peripheral immune cells into the CNS [95]. Other studies have also reported an increased gliosis and increased levels of pro-inflammatory cytokines upon high fat diet treatment in rodent models [84,96]. However, our group could not detect changes in pro-inflammatory cytokines or gliosis after 18 months of high fat diet treatment in an APP knock-in model [77].

Finally, misfolded amyloid aggregation is another common pathology in diabetes and AD: amyloid-beta aggregates in the brain from AD patients, while islet amyloid polypeptide (IAPP) accumulates in pancreatic cells from T2DM patients. Moreno-Gonzalez et al. proposed that IAPP present in diabetic patients may act as a seed promoting the misfolding and aggregation of the amyloid-beta peptides [97]. In fact, it has been shown that both aggregates colocalized in brain parenchyma deposits [97,98].

Conclusions and future directions

Epidemiological studies have provided evidence for a link between diabetes and an increased risk to develop dementia. However, in spite of several proposed mechanisms for this association, we are not able to make final conclusions with regard to what

specific metabolic alterations could be responsible for this increased predisposition to dementia.

The high heterogeneity between the different cases of AD and T2DM, and the effects of aging on the CNS and peripheral organs, make it very complicated to dissect the specific mechanisms responsible for a general association observed in population-based cohort studies. Given the fact that both disorders are highly heterogeneous, it is likely that the link between the two is a consequence of a combination of different molecular, cellular and systemic factors which are difficult to unravel. Caution when proposing specific mechanisms or treatments seems indicated.

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