The Review of DIABETIC STUDIES

REVIEW

Diabetes and Alzheimer's Disease – Is There a Connection?

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■ Abstract

It has been known for some time that diabetes may be associated with impaired cognitive function. During the last decade, epidemiological data have emerged suggesting a linkage between diabetes, particularly type 2 diabetes, and Alzheimer's disease (AD). There is evidence to suggest that impaired activities of neurotrophic factors such as insulin, IGF-1 and NGF, which occur in both diabetes and AD, may provide a mechanistic link between the two disorders. An additional probable factor that has been less evaluated to date is hypercholesterolemia, a common accompaniment to type 2 diabetes. Increased cholesterol availability is believed to play a crucial role in the abnormal metabolism of amyloid precursor protein leading to accumulation of amyloid-β. Impaired insulin signaling in particular appears to be involved in hyperphosphorylation of the tau protein, which constitutes neurofibrillary tangles in AD. The linkage between abnormal amyloid metabolism and phosphor-tau is likely to be provided by the activation of caspases both by increased amyloid-β and by impaired insulin signaling. Although the details of many of these components still await evaluation, it appears clear that commonalities exist in the underlying pathogenesis of diabetes and Alzheimer's disease. In this review we provide a brief update on linkages between these two diverse but common disorders.

Keywords: diabetes · Alzheimer's disease · insulin · hypercholesterolemia · dementia

Introduction

Cognitive impairments are more common in diabetic patients than in non-diabetic subjects [1-5], which is in part due to ischemic events resulting from cerebral micro- and/or macrovascular disease or to repeated episodes of severe hypoglycemia. These conditions have been referred to as secondary diabetic encephalopathy [6]. However, during the last decade, there is accumulating evidence suggesting that cognitive dysfunction is also caused by diabetic dysmetabolism, so-called primary diabetic encephalopathy [2, 3, 5, 6].

This appears to be true also in experimental models of diabetes. In streptozotocin-induced diabetic rats, impaired cognitive performances have been associated with impaired hippocampal plasticity, changes which are reversed by insulin treatment [7]. In type 1 diabetic BB/Wor rats, progressively impaired cognitive function is associated with suppressed insulin and insulin-like growth factor I (IGF-1) actions and neuronal apoptosis in hippocampus [8], changes which are significantly prevented by insulinomimetic C-peptide [9, 10].

The increased risk for cognitive dysfunction affects both type 1 and type 2 diabetic patients [1-5], suggesting that hyperglycemia or altered insulin signaling transduction, or both, are involved. More relevant deficits, however, occur in patients with type 2 diabetes in whom there is an increased risk for developing Alzheimer's disease (AD) [11, 12], suggesting that additional factors may be involved. In addition to hyperglycemia and impaired insulin action, type 2 diabetes is commonly associated with hypercholesterolemia, hy-

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perlipidemia and hypertension, which may provide additional risk factors. In addition, aging alone is probably a modulating factor. Experimental studies have demonstrated significantly more severe abnormalities in the expression of amyloid precursor protein (APP), β-secretase, amyloid-β (Aβ) and phosphorylated tau in the type 2 BBZDR/Wor rat model as compared to its type 1 counterpart, the BB/Wor rat [13]. The type 2 diabetic model is characterized by insulin resistant hyperglycemia, hypercholesterolemia, hyperlipidemia and hypertension, hence closely replicating the common clinical picture of type 2 human diabetes [14]. The combination of these factors comprises the "metabolic syndrome." Some of these factors have been identified as independent predictors of cerebrovascular disease, accelerated cognitive dysfunction and dementia [15, 16]. Therefore, the clustering of several potential pathogenetic factors may interact mechanistically at various levels in type 2 diabetes to produce the basis for impaired cognition and the molecular and structural substrates of Alzheimer's disease [3, 5].

Recent research has implicated hyperglycemia, insulin-resistance and impaired insulin and insulin-like growth factor-1 (IGF-1) signaling with activation of so-called stress (or tau) kinases as mechanisms in the production of phosphorylated tau, a characteristic hallmark of AD [17-19]. Less attention has been devoted to the possible role of hypercholesterolemia and its role in APP metabolism, abnormal Aβ handling and deposition, the second characteristic hallmark of AD.

In this review we explore the mechanistic linkages between APP metabolism, tau abnormalities and the role of cholesterol metabolism in AD and how these abnormalities can be linked to diabetes.

Insulin effects

The emerging cognitive impairment and even the possible relationship with AD in diabetes are supported by epidemiological studies [1-4], as well as findings in animal models of diabetes [6-10,20-22]. Experimental data have demonstrated increased expression of APP, β-secretase, Aβ42 and hyperphorylated tau in hippocampi and frontal cortex of BB rats. Hence, taken together, these findings strongly suggest mechanistic and sequential links between diabetes, impaired cognitive function and molecular and structural AD-like changes.

In humans, aging alone is associated with decreased metabolic turnover, decreased glucose utilization as well as declining insulin and IGF-1 signal transduction due to receptor desensitization [23-25]. These abnormalities are magnified in Alzheimer's disease, with degradation of both the insulin and IGF-1 receptor and their consequent effects on glucose metabolism [26-28]. Other factors that contribute indirectly to impaired insulin signaling include cortisol, catecholamines and cholesterol via the caveolin signaling pathway (see below).

Furthermore, the APP derivatives Aβ40 and Aβ42 reduce the binding of insulin to its receptor, either through binding or via an ATP-mediated disruption of autophosphorylation [29, 30], hence creating a potentially self-perpetuating mechanism. Other mechanisms caused by the convergence of insulin and extracellular Aβ are the competition for insulin degrading enzyme (IDE) [31]. Due to counterregulation by GLUT transporters (GLUT1 and 3) at the blood-brain barrier [32], it appears that CNS insulin levels are increased in systematically insulinopenic situations. Hence, elevated CNS insulin levels will consume more of the already reduced levels of IDE [33], thereby intervening with the degradation of and promoting the extracellular deposition of Aβ42 [31]. Therefore, perturbations in insulin levels and its signal transduction activity will potentially provide several sites of action in promoting AD-like pathologies.

Effects of cholesterol

Epidemiological evidence exists linking elevated plasma cholesterol and lipoprotein levels with AD development [15, 16, 34]. Additionally, patients taking cholesterol-lowering drugs have been found to have a lower incidence of AD [35], although some studies have proven to be inconclusive [36]. Experimental studies examining the loading or depletion of cholesterol both *in vivo* [37-39] and in cell cultures [40] have demonstrated links between high cholesterol and increased Aβ production; however, the mechanisms underlying such linkages are poorly understood. It should be mentioned, though, that brain cholesterol is mostly independent of dietary uptake or hepatic synthesis but appears to be mainly derived from *in situ* synthesis [41] (Figure 1). There is evidence to suggest that statins, hydroxyl-3-methylglutaryl-CoA inhibitors, not only lower cholesterol levels (systemic and endogenous) but also suppress β-secretase activity in lipid rafts and increase α-secretase, thereby directly effecting APP metabolism [42].

The expression of apolipoprotein E allele 4ε (Apo4E) is a major risk factor for the development of sporadic Alzheimer's disease. It is a lipoprotein that carries and facilitates the transport and incorporation

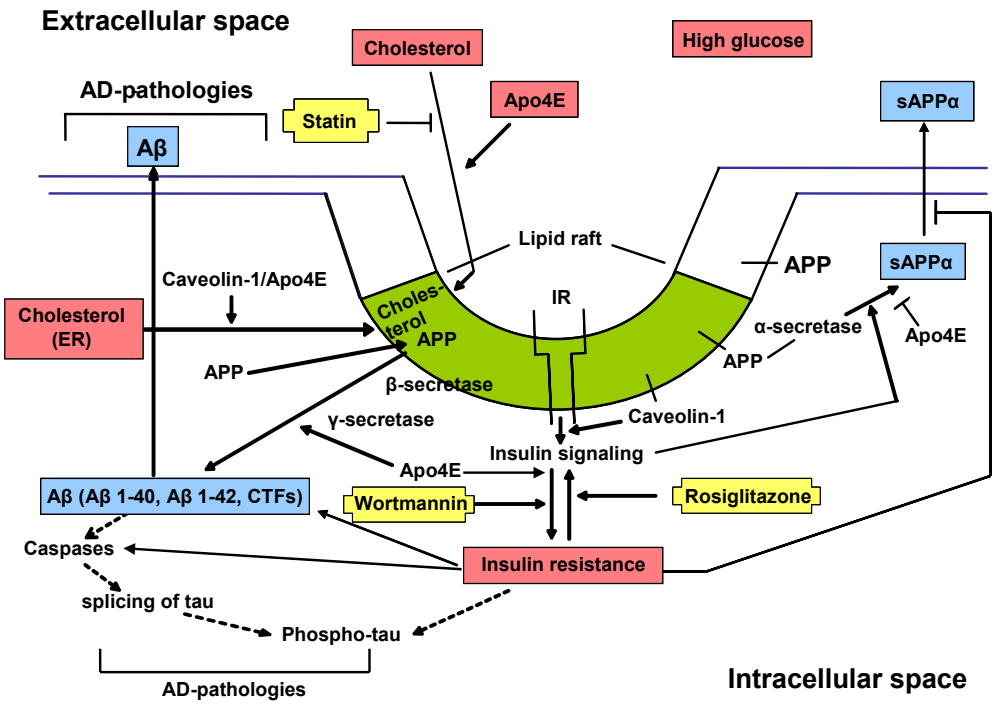

Figure 1. Simplified flow-chart of interactions between high systemic and endogenous cholesterol levels and insulin resistance in nerve cells. Shown are effects on amyloidogenic and non-amyloidogenic APP metabolism (blue) as well as intra- and extracellular accumulation of Aβ products. The insulin receptor (IR) is located within the caveolae and its signaling is promoted by caveolin-1, whereas insulin resistance (red), as existent in type 2 diabetes or modeled by Wortmannin (yellow), interferes with insulin signaling. Impaired insulin signaling inhibits the release of sAPPα from the intra- to the extracellular space (blue). It also promotes the activation of caspases and via the activation of so-called stress kinases enhances the phosphorylation of tau. Increased extra- and intracellular cholesterol becomes enriched in lipid rafts, where it is coupled with up-regulation of APP as well as α- and β-secretase resulting in increased accumulation of Aβ and CTFs (amyloidogenic pathway, blue). These amyloid peptides and fragments are released to the extracellular space or remain intracellular. Aβ products activate caspases, which in turn promote the splicing of tau and subsequent phosphorylation by stress kinases. Apo4E enhances the incorporation of cholesterol into lipid rafts, promotes formation of Aβ products, interferes with insulin signaling and inhibits non-amyloidogenic formation of sAPPα. For additional metabolic mechanisms see the text. → indicates promoting effects, ⊣ indicates inhibitory effects.

of cholesterol within lipid rafts in caveolae [43] (Figure 1). It is associated with caveolae, increasing the formation of Aβ fibrils and decreasing soluble amyloid precursor protein alpha (sAPPα), to yield a reciprocal regulation on Aβ and sAPPα [44]. Apo 4E inhibits intermediaries of signal transduction pathways that lead to phosphorylation of PI, which is impaired in AD [45] (Figure 1). This results subsequently in intracellular Ca^{++} release and perturbation of PI3 and DAG [46] leading to increased apoptotic stress. Increased cholesterol levels are associated with an increased number of caveolae, harboring lipid rafts in which cholesterol, together with sphingolipids, are enriched. Lipid rafts are thought to play a central role in membrane sorting and trafficking as well as in signal transduction, most notably of calveolin-1 and various growth factors including IGF-1 and insulin [47] (Figure 1). Growth factor receptors are concentrated to calveolae and their signaling pathways are generally suppressed, via the scaffolding domain of calveolin-1 [48], with the exception of insulin signaling, which is enhanced by calveolin-1 [29, 30, 49] (Figure 1). Cholesterol regulates calveolin-1 expression, which facilitates transport of endogenously synthesized cholesterol from the ER to lipid rafts [50] (Figure 1). Calveolin-1 localized to lipid rafts is hence believed to regulate cholesterol homeostasis.

Amyloid metabolism

Perturbed amyloid metabolism underlies the formation of amyloid plaques, one of the characteristic hallmarks of AD. Abnormal APP processing is believed to play a central and probably initiating role in AD and gives rise to Aβ (Figure 1). APP is a transmembranous protein, the physiological role of which remains unknown, but may be involved in neuronal regeneration. It is metabolized along two pathways; an amyloidogenic and a non-amyloidogenic pathway [42, 43]. In the latter it is cleaved by α-secretase producing sAPPα but not Aβ. In the former it is cleaved by β-secretase and βAPP is produced, which is further cleaved by γ-secretase, ultimately yielding Aβ, most

commonly as Aβ42 or Aβ40 (Figure 1). These hydrophobic peptides are the basis for amyloid plaques or amyloid angiopathy in AD [51].

There is growing evidence that amyloidogenic APP processing is facilitated in cholesterol-rich lipid rafts, whereas non-amyloidogenic APP processing by α-secretase may occur outside the rafts [37], resulting in sAPPα, which does not produce Aβ (Figure 1). The production of sAPPα is downregulated under high cholesterol conditions, whereas depletion of cellular cholesterol increases the levels of sAPPα [52]. Amyloidogenic processing of APP occurs in lipid rafts where β- and γ-secretases are found as APP, C-terminal fragments (CTFs) and Aβ itself [53, 54]. It is believed that APP is localized in two separate pools, one associated with lipid rafts and the other with non-raft domains, and would be accessible through α-, β- and γ-secretase (Figure 1). With respect to β-secretase, it appears to act at the plasma membrane level, as well as in ER and in the trans-Golgi network. The subsequent Aβ formation at the plasma membrane and CTFs are believed to be secreted, whereas those originating from the ER and trans-Golgi network probably remain intracellular [55] (Figure 1).

Further mechanisms that are likely to involve abnormal APP metabolism relate to impaired insulin signaling that has been demonstrated in the frontal cortex of the BBZDR/Wor rat [7]. Deficiencies in insulin, IGF-1 and NGF converge in their signal transduction, diminishing tyrosine-kinase signaling and impairing PI3 kinase activity, thereby activating stress kinases such as JNK and p38 which lead to activation of caspase 3. For instance, inhibition of insulin signaling by Wortmannin hampers the release of sAPPα and Aβ from the intra- to the extracellular compartment [44, 56] (Figure 1). Insulin deficiency activates FAS including NGFR-p75 with activation of caspase 8, which has been implicated in the splicing of APP into CTFs and into intracellular processing into Aβ42 [57]. Oxidative stress and mitochondrial dysfunction with activation of caspase 9 have been invoked in abnormal APP processing [46, 47]. Therefore, several apoptotic stressors are likely to contribute to abnormal intracellular processing of APP.

Apoptotic mechanisms

Insulin, C-peptide and IGF-1 all exert anti-apoptotic functions [10, 58, 59]. In diabetic neuronal tissues activation of a variety of apoptotic pathways has been identified. Deficiencies of insulin, C-peptide, IGF-1 and NGF converge in their signal transduction diminishing tyrosine-kinase signaling and impaired PI3 kinase activity, thereby activating stress kinases-like JNK and p38, particularly JNK, which lead to the activation of caspase 3 [58].

Insulin and C-peptide deficiencies activate the FAS receptor family as well as NGFR-p75, which has been implicated in apoptosis. FAS activation leads via FADD to the activation of caspase 8 or caspase-independent apoptosis [58, 59]. Caspase 8 has been implied in the C-terminal splicing of APP to CTFs and further processing of intracellular APP into soluble Aβ42 [60, 61] by increased activity of β-secretase [62]. Oxidative stress is also likely to contribute to activation of caspase 2 and 8 triggered by cytochrome C and AIF through induction of death receptors [63]. An apoptotic pathway invoked in the abnormal APP processing is caspase 9. Several stressors such as oxidative stress and mitochondrial dysfunction appear to be involved, as reflected by increased pro-apoptotic Bax, AIF and nuclear stainability for 8OHdG [22, 60, 61].

It therefore appears that several apoptotic stressors identified in diabetic brain [9, 10] may be involved in abnormal intracellular processing of APP forming both C-terminal fragments, as well as intracellular cleavage to Aβ40 and Aβ42 (Figure 1). The apoptotic stressors exert these functions before the cell undergoes apoptotic cell death, a phenomenon that appears to be regulated by upregulation of contraregulatory proteins, among others heat shock proteins 27 and 70, which have recently been demonstrated in diabetes [64, 65].

Decreased PI3-K activity and associated activation of stress-kinases such as JNK and p38 promote the abnormal processing of APP [66]. Phosphorylated p38 MAPK has been demonstrated in early Braak stages of AD. Indirect evidence for a mechanism for JNK and p38 kinases is provided by inhibition of insulin signaling by Wortmannin, which alters the metabolism of APP [67] and hampers the release of sAPPα and Aβ from the intracellular to the extracellular compartment [68]. Under normal conditions, PKC and PKA promote utilization of non-amyloidogenic processing of APP by redistributing it to compartments of α-secretase activity with increase in sAPPα levels and decreased release of Aβ, the so-called reciprocal relationship between these APP products [69].

Furthermore, JNK and p38 activations are involved in the hyperphosphorylation of tau, via Aβ-induced oxidative stress and apoptosis. Puig *et al.* reported increased expression of JNK and p38 in brain homogenates and their immunocytochemical association with hyperphosphorylated tau in neurites surrounding amyloid plaques [70].

Tau pathology

One of the most important pathobiological events in AD is the formation of hyperphosphorated tau, which leads to a toxic insult to terminal neurites and progressive retrograde neurite degeneration [71-73]. This is not specific for AD, but occurs in a variety of neurodegenerative conditions, the so-called tauopathies [74]. However, in these conditions, the tau pathology is not associated with amyloid pathology, suggesting that several mechanisms result in hyperphosphorylation of abnormal tau. The hyperphosphorylation of tau results in loss of its function in promoting the assembly and stabilization of microtubules. It also sequesters normal tau [75].

In AD, Aβ42 induces several apoptotic pathways [76-78]. Caspase activation is present in AD brains and active caspase is found within tangle-bearing neurons [79, 80]. Tau is initially cleaved by proteolytic caspases and undergoes subsequent hyperphosphorylation (Figure 1). The latter seems to be mainly mediated by increased GSK3β activity, although decreased phosphatase activity of PP2B [81] and abnormal activity of the p25-Cdk5 complex [82] have been invoked. As referred to earlier, the insulin and related neurotrophic factor signal transduction activities are compromised in both AD and diabetes [6, 10, 28, 67], leading to inhibition of glucose metabolism, ATP formation and impaired PI3-kinase signaling. As a consequence, downstream PKB becomes downregulated, with disinhibition of GSK-3β and excessive phosphorylation of truncated tau [83-85] (Figure 1). Simultaneous disinhibition of GSK-3α may promote storage and misfolding of APP metabolites with secondary reduction of extracellular Aβ42 [86]. The subsequent accumulation of both Aβ42 and hyperphosphorylated tau leads to neurite and neuronal degeneration [71, 86, 87]. It is, therefore, unlikely that the commonalities between the sequence of molecular events leading to AD and the abnormalities of diabetic dysmetabolism are coincidental. Instead, evidence to date suggests causal relationships between these common disorders.

Conclusions

There is no doubt that mechanistic linkages exist between diabetes and Alzheimer's disease. Although these are not completely defined, they provide today a very active area of investigative research. The major abnormalities that appear to present commonalities between the two entities are impaired neurotrophic actions, particularly by insulin, but probably also by IGF-1 and NGF. They result in increased apoptotic activities with abnormalities in the tau protein rendering it more susceptible to hyperphosphorylation. The abnormalities in insulin signaling provide several stress kinases, which facilitate excessive phosphorylation of tau. Increased exposure to cholesterol promotes abnormal APP metabolism with extra- and intracellular accumulation of toxic amyloid-β products, which in turn activate several caspases promoting abnormal tau products. In these interactions hyperglycemia per se probably plays a lesser role. Both the accumulation of amyloid-β products and hyperphosphorylated tau exert toxic effects on neuronal neurites with their subsequent degeneration and eventual neuronal death.

The further examination of the intricate and complex interplay between the pathogenetic events of these two disorders is likely to provide biologically meaningful targets for future therapy.

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