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Linking Alzheimer's Disease and Type 2 Diabetes Mellitus *via* Aberrant Insulin Signaling and Inflammation

Mohammad A. Kamal[*,1], **Shubha Priyamvada**[2], **Arivarasu N. Anbazhagan**[2], **Nasimudeen R. Jabir**[1], **Shams Tabrez**[1], and **Nigel H. Greig**[3]

[1]Metabolomics & Enzymology Unit, Fundamental and Applied Biology Group, King Fahd Medical Research Center, King Abdulaziz University, P.O. Box 80216, Jeddah 21589, Saudi Arabia

[2]Section of Digestive Diseases and Nutrition, Department of Medicine, University of Illinois, Chicago, 60612, USA

[3]Drug Design & Development Section, Translational Gerontology Branch, Intramural Research Program, National Institute on Aging, National Institutes of Health, Biomedical Research Center, 251 Bayview Boulevard, Baltimore, MD 21224, USA

Abstract

Alzheimer's disease (AD) and type 2 diabetes mellitus (T2DM) are two progressive and devastating health disorders afflicting millions of people worldwide. The probability and incidence of both have increased considerably in recent years consequent to increased longevity and population growth. Progressively more links are being continuously found between inflammation and central nervous system disorders like AD, Parkinson's disease, Huntington's disease, motor neuron disease, multiple sclerosis, stroke, traumatic brain injury and even cancers of the nervous tissue. The depth of the relationship depends on the timing and extent of anti- or pro-inflammatory gene expression. Inflammation has also been implicated in T2DM. Misfolding and fibrillization (of tissue specific and/or non-specific proteins) are features common to both AD and T2DM and are induced by as well as contribute to inflammation and stress (oxidative/glycation). This review appraises the roles of inflammation and abnormalities in the insulin signaling system as important shared features of T2DM and AD. The capacity of anti-cholinesterases in reducing the level of certain common inflammatory markers in particular if they may provide therapeutic potential to mitigate awry mechanisms leading to AD.

Keywords

Alzheimer's disease; Anti-cholinesterase; Butyrylcholinesterase; Inflammation; Type 2 diabetes mellitus

[*]Address correspondence to this author at the Metabolomics & Enzymology, Unit, Fundamental and Applied Biology Group, King Fahd Medical, Research Center, King Abdulaziz University, P.O. Box 80216, Jeddah, 21589, Saudi Arabia; Fax: + 1 (501) 636-8847; meu.fabg@hotmail.com.

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a heterogeneous, multi-factorial and polygenic disorder and one of the most common metabolic diseases. Its incidence is reaching epidemic proportions, and its prevalence increases with age [1]. Impaired insulin action and secretion in T2DM generates a general mayhem specific of this disease [2]. Evidence suggests that T2DM represents a risk factor for developing Alzheimer's disease (AD) [3]. AD, a progressive neurodegenerative disorder of hitherto unknown aetiology leads progressively to severe cognitive incapacity and ultimately to death, has been described as the pandemic of the 21st century [4]. How T2DM increases the likelihood of AD is currently an area of extensive research.

Stress (inflammatory, oxidative, nitrosative), progressive amyloidosis, atherosclerosis, obesity, metabolic syndrome are pathological mechanisms or risks related to T2DM and AD [5, 6]. In fact metabolic syndrome, T2DM and AD are considered as low-grade systemic inflammatory conditions as recent studies have demonstrated associations between elevated levels of circulating acute phase inflammatory markers, typified by C-reactive protein (CRP), and indices of insulin resistance and the development of T2DM and AD [7–9]. Moreover, elevated butyrylcholinesterase (BuChE) may represent a key trigger factor of the inflammatory processes seen in T2DM and AD consequent to down-regulation of the "cholinergic anti-inflammatory pathway" [10]. In an interesting recent review article [11], the evidence for the association of vascular risk factors such as T2DM, hypertension, obesity and dyslipidemia in relation to dementia was systematically reviewed on the basis of longitudinal population-based studies. These risk factors often occur concomitantly and, although each has been linked to an elevated risk of dementia, its ambiguous as which imposes the greatest risk and when this occurs. During midlife, the population attributable risk of dementia was greatest for hypertension, which accounted for up to 30% of cases that developed thereafter [11]. During later life diabetes emerged as conveying the highest impact on dementia [11]. Clearly, vascular risk factors have long been known to favor the development of dementia, with age and the duration of exposure as important variables. Understanding the mechanisms associated with T2DM, hypertension, obesity and dyslipidemia may aid in offsetting their adverse actions as well as developing potential treatment strategies [11].

Impaired glucose tolerance is likewise associated with impaired cognition, independent of age, and there are reports of increased risk of AD with diabetes [12, 13]. Whereas the localization and pathological features of diabetes and AD differ, there are numerous commonalities. Examples amongst many are that both are chronic progressive conditions that are present before a diagnosis is made or treatment initiated. Insulin resistance (IR), impaired insulin receptor, and insulin growth factor (IGF) signaling, glucose toxicity, advanced glycation end products (AGEs) and the receptor for advanced glycation end products (RAGEs) interactions, cerebrovascular injury, vascular inflammation, are some of the mechanisms lying on the way to T2DM manifestation/complications that influence the pathogenesis of AD [14].

ABNORMAL INSULIN SIGNALING IN AD

T2DM is characterized by IR, hyperinsulinemia and glucose intolerance. The consequent hyperglycemia induces oxidative stress and non enzymatic glycation of key regulatory proteins leading to potential malfunctions in those proteins. Abnormal glucose utilization and insulin resistance or deficiency is also early events in AD pathology that can be present without any correlation to the presence of diabetes. Consequent to this, the term ‘type 3 diabetes’ has been coined by some for AD. In a similar manner, glycation induced conformational changes have been shown to initiate the fibrillization of otherwise non pathogenic proteins that leads to the hypothesis that diabetes is a conformational disease [15].

In accord with evidence suggesting that diabetics have a higher risk for cognitive dysfunction, depression and memory impairment [16], animal models of T2DM have been described to have defective transport, uptake and neuronal concentrations of insulin [17–19]. Indeed, the induction of diabetes accelerates and worsens cognitive dysfunction in transgenic AD animal models, emphasizing the role of altered insulin pathways in AD brain [20].

The brain is clearly an insulin-sensitive organ, where insulin plays a significant role in normal brain physiology [21], and disturbances in its signaling can impact synaptic plasticity as well as cell viability. Insulin receptors are localized throughout the brain, with particularly dense distributions in the hippocampus, entorhinal cortex and hypothalamus [22]. Within brain, the binding of insulin to its receptor brings about rapid autophosphorylation of the tyrosine residues in the β-subunit of the receptor and leads to activation of several second-messenger transduction pathways. One such pathway, the neural Shc/MAP (Src homology collagen mitogen-activated protein) kinase pathway induces gene expression required for neuronal cell and synapse growth, maintenance and repair processes besides modulating the hippocampal synaptic plasticity important for learning and memory [23]. In an alternate pathway, the insulin receptor substrates 1 and 2 (IRS-1 and IRS-2) bind to phosphatidylinositol 3-kinase (PI3K), which stimulates glucose transport and inhibits mitochondrial DNA damage, apoptosis induced death by mechanisms involving the activation of Akt/protein kinase B and the inhibition of glycogen synthase kinase-3β (GSK-3β) [24–26]. These processes are known to influence synaptic plasticity and memory consolidation, retrieval and extinction of contextual memory, and Aβ-induced memory loss [27–29]. This same pathway likewise induces the synthesis of nitric oxide, additionally affecting learning and memory processes [30]. Thus, any defects in insulin signaling and IR may have adverse consequences on synaptic maintenance and remodelling through direct effects on energy production and glucose uptake. Notably, AD patients have reduced insulin levels and a lowered expression of insulin receptors and IRS proteins [31]. Correction of insulin levels in AD subjects has also been correlated with improved cognition [31, 32]. Furthermore, insulin has been also described to regulate tau phosphorylation [33].

Insulin resistance/deficiency results in an inhibition of the PI3K/Akt pathway, a rise in oxidative stress and hence hyperactivation of GSK-3β [5, 34]. This can stimulate tau protein hyperphosphorylation. In this context, it is worth noting that elevated oxidative stress is an

established feature of both T2DM and AD. Insulin may have regulatory action on both amyloid-β (Aβ) and amyloid precursor protein [35].

As IDE (insulin degrading enzyme) is known to degrade insulin along with Aβ, at high insulin concentrations that may be prevalent due to IR (e.g., hyperinsulinemia), insulin may compete with Aβ for IDE in brain, including within the hippocampus, to cause a decline in the normal clearance of Aβ, leading to Aβ brain accumulation and a higher risk of AD [36]. Insulin may also promote Aβ secretion resulting in excessive Aβ deposition in senile plaques [37]. Zhao *et al.* [38] have reported that Aβ soluble oligomers (AβOs) may initiate the loss of insulin receptors from the neuronal membranes. This may again, potentiate IR, impacting Aβ clearance and its deposition. Hence, IR and Aβ may act in cyclical manner exacerbating the process. Taken together, research suggests that insulin signaling plays a central role in learning and memory, and, in particular, in deficits when signaling is aberrant.

Bomfim *et al.* [39] experimentally demonstrated that insulin signaling is substantially disrupted in AD brain, rodents and non-human primate models of the disease. In accord with earlier reports, they proposed that in AD brain insulin signaling becomes stalled by processes leading to IR, as it does in diabetes. Amongst key mechanisms, c-Jun NH2-terminal kinase (JNK) activity is induced in conditions of chronic hyperglycaemia and IR, which ultimately leads to oxidative stress and apoptosis of pancreatic β-cells [40]. It has been suggested that AβOs activate JNK/tumor necrosis factor-α (TNF-α) pathways leading to the abnormal serine phosphorylation of IRS-1, which thereby blocks the downstream insulin signaling [41]. A high immunoreactivity for IRS-1pSer636/639 was detected in the hippocampal CA1 region in human AD brains compared to normal subjects, suggesting that serine phosphorylation of IRS-1 triggers central nervous system IR [39]. In hippocampal neuronal cell cultures AβOs induced abnormal elevations in IRS-1pSer636/639 levels and blocked IRS-1 tyrosine phosphorylation. Similar findings were additionally obtained in non-human primates. Using JNK inhibitors or transfecting the neuronal cells with GFP-fused dominant negative JNK, it was further demonstrated that JNK plays a pivotal role in mediating the neuronal IR in response to AβOs. In peripheral IR, JNK activity appears to be mediated by TNF-α. In AD also, TNF-α has been found to mediate the JNK signaling pathway [39]. Two crucial regulators of peripheral IR and stress sensitive kinases, are the double-stranded RNA dependent protein kinase and IκB kinase (IKK) that are likewise activated by AβOs. This provides additional support for a striking resemblance between inflammation-associated brain IR in AD and chronic inflammation-induced IR in peripheral tissues in T2DM (that is discussed later) [39]. Extending this work, Talbot *et al.*, [42] elegantly probed insulin and IGF-1 responsiveness in 2 brain regions - the hippocampus and cerebellar cortex that are differentially impacted by AD - retrieved from early post mortem AD cases and age-matched controls. By the use of an ex vivo stimulation protocol and near-physiological doses of insulin or IGF-1, the AD brain was determined to be insulin and IGF-1 resistant in the absence of T2DM. Two candidate biomarkers of brain insulin resistance were identified that are common to systemic IR and T2DM; specifically, elevated levels of IRS-1pS616 and IRS-1pS636/639 [42] in concordance with Bomfim *et al.* [39]. The bottom line from both studies is that insulin orchestrates numerous neuronal processes that impact synaptic plasticity, involving both the expression as well as trafficking of key receptors (e.g., N-methyl-D-aspartate, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic

acid and gamma-aminobutyric acid), the translation of critical scaffolding proteins, such as PSD-95, which are essential in regulating postsynaptic density. The development of insulin resistance at the level of the insulin receptor in AD, as a consequence of AβOs, neuroinflammation and other mechanisms, may down regulate insulin mediated signaling pathways at postsynaptic sites within the hippocampus and other key brain regions engaged in memory consolidation and retrieval.

Extending their results, Bomfim *et al.* [39] reported that insulin and the clinically approved T2DM drug exendin-4 (Byetta/Bydurion), (a long-acting glucagon-like peptide-1 (GLP-1) agonist that stimulates the insulin signaling pathway *via* the GLP-1 receptor that is present both on pancreatic-β cells as well as on neurons within the brain [43]), prevented the AβO-dependent IRS-1pSer636/639 increase and IRS-1pTyr465 decrease. Prior studies with exendin-4 have demonstrated that it provides neurotrophic and neuroprotective actions in cellular and animal models of a host of neurological disorders, including AD, Parkinson's disease, Huntington's disease, motor neuron disease, peripheral neuropathy, stroke and traumatic brain injury [43–51]. Confirming prior studies [49–51], exendin-4 treatment in AD transgenic mice in the Bomfim *et al.*, study [39] induced a reduction in brain amyloid plaque load and improved memory and cognition [39]. These prior studies, moreover, demonstrated that the initiation of diabetes in AD transgenic mice caused an elevated induction of Aβ and tau, that was mitigated by exendin-4 [49].

In addition, it has been suggested that the JNK pathway induction, likewise, leads to phosphorylation of c-Jun and tau in brains of AD patients [52–54]. The protein JIP-1 [JNK-interacting protein 1, also known as 'islet brain 1' (IB1) protein] has been found co-localized with JNK, hyperphosphorylated tau and amyloid deposits in neurofibrillary tangles in the brain and pancreatic islets, pointing to a further potential link between AD and T2DM [55].

Obesity is a major determinant of IR and hence T2DM. Studies have associated dementia/AD with obesity [56]. However, the exact molecular mechanisms linking the two remain underinvestigated. It is suggested that disturbances in insulin cause hyperactivation of adipocyte hormone sensitive lipase, which eventually leads to high levels of free fatty acids (FFA). These FFAs are pro-inflammatory, proamyloidogenic, and reduce the Aβ clearance [as reviewed in 2]. Hence, new comprehensive research approaches towards dissecting mechanisms that underpin the coexistence of T2DM and AD may be helpful in not only understanding the pathophysiologic similarities between these two disorders but also ways to potentially offset or ameliorate these two progressive disorders.

LOW-GRADE SYSTEMIC INFLAMMATION IN AD AND T2DM

Evidence supports the concept that AD and T2DM can be considered related systemic inflammatory conditions that can potentially be mitigated, at least in part, by normalizing common pathways associated with this systemic inflammation. As an example, alterations in the levels of key inflammatory markers, such as CRP, TNF-α, interleukin-6 (IL-6) and lipid peroxides, are common to T2DM and AD.

Changes in human behaviour and lifestyle over the last century have resulted in burgeoning rates of obesity and metabolic syndrome, leading to a dramatically increasing prevalence of T2DM. The mechanisms that tie obesity to various metabolic abnormities in T2DM, such as insulin resistance, dyslipidemia and hyperglycemia, remain to be fully elucidated. However, research has linked obesity to the manifestations of diabetes through various fat-derived proteins, termed “adipocytokines”, including TNF-α, interleukin 1 (IL-1), IL-6, plasminogen activator inhibitor-1 (PAI-1), monocyte chemoattractant protein-1 (MCP-1) and others [8]. The deleterious effects of these include down-regulation of insulin-action at the level of target tissues (muscle, liver and adipose), acceleration of inflammatory processes as well as induction of apoptosis of pancreatic β-cells [57]. Moreover, several transcription factors and kinases, such as JNK, IKK also participate in processes [58]. Hence, these inflammatory cytokines, adipocytokines and transcription factors result in hyperglycemia, which is the biochemical hallmark of T2DM. Notably, an inflammatory response is likewise involved in atherosclerosis, which can lead to diabetic cardiovascular complications, stroke and AD [59, 60]. It has been shown that pancreatic β-cells from T2DM subjects have elevated IL-1β expression and reduced levels of the natural inhibitor of the proinflammatory effect of IL1β, the endogenous IL-1β receptor antagonist, IL-1RA [61]. Such high levels of the proinflammatory cytokine IL-1β are associated with islet cell damage, impaired insulin secretion and apoptosis [62, 63]. Conversely, IL-1RA treatment at high doses improves glucose sensitivity, insulin processing, and suppresses inflammation and infiltration of immune cells in a diabetic rat model [64]. Diabetes is associated with the production of AGE, the derivatives of lipids, proteins and nucleic acids. AGE interacts with their receptors RAGE and this interaction induces reactive oxygen species mediated inflammatory responses that are widely considered as the major culprits behind diabetic complications [65–67]. Different molecular forms of RAGE are present, which include the alternatively spliced variant, esRAGE (endogenous secretory RAGE) and the enzymatic cleavage generated sRAGE (soluble RAGE). esRAGE competes for the full length membrane bound form for AGEs and prevents the initiation of downstream inflammatory responses [68]. sRAGE has been found to be negatively correlated with the full length form in monocytes from T2DM patients, suggesting its protective role during inflammation [69, 70]. Toll like receptor (TLR) signal pathways have also been implicated in mediating inflammation associated with diabetes. Particularly notable, in this regard, are TLR2 and TLR4 whose expression increases in the presence of high glucose and FFAs [71, 72] and whose effects are mediated by NFκB activation [73]. CD36 (oxidized low-density lipoprotein receptor, oxLDL receptor), a co-receptor for TLR2 and TLR6 heterodimers in addition to TLR4 and TLR6 heterodimers [74], is likewise induced by high glucose, oxLDL, FFAs and low high density lipoprotein, cholesterol concentrations in monocytes/macrophages. This promotes vascular oxidative injury, leukocyte adhesion, and atherogenesis [75]. To the contrary, CD36 knockout transgenic mice exhibit improved insulin signaling and reduced inflammation [76, 77].

It has been widely shown that inflammatory mechanisms are classically associated with AD [78]. In support of this, elevated plasma and cerebrospinal fluid levels of inflammatory cytokines (IL-1, IL-6 as well as TNF-α) have been reported in patients with AD [79–82]. Studies have revealed that systemic administration of IL-1 lowered extracellular

acetylcholine (ACh) levels within the hippocampus and suggest that raised levels of IL-1 could be involved in AD consequent to ACh reductions [83]. In support of this, raised IL-1 levels in brain, induced by intracerebroventricular IL-1β administration, induced a significant reduction in hippocampal ACh release (that could be blocked by IL-1 RA) and this decline correlated both with memory deficits and a lowered mRNA expression of hippocampal nerve growth factor (NGF) [84].

The neurotrophin NGF is indispensable for the maintenance and differentiation of basal forebrain cholinergic neurons [85], which are one of the major neuronal populations affected that progressive degeneration in AD. It has become increasingly clear that alterations in NGF transport and signaling may play a key role both in development and progression of sporadic AD, leading to the proposition that "neurotrophic imbalance" (i.e., too little mature NGF and too much unprocessed pro-NGF, as found in AD11 mice) is an upstream driver for AD. Lowered levels of NGF as well as other neurotrophic factors can impact APP expression as well as its processing to Aβ, in addition to the induction of neuroinflammation that, in turn, impacts NGF expression and ACh release; thereby providing a self-propagating destructive cycle of events [85]. An alike NGF transport failure leading to degeneration of basal forebrain cholinergic neurons, and elevations in brain APP levels has been described in the Ts65Dn mouse model of Down’s syndrome [86].

The involvement of a heightened neuroinflammatory process in AD is further supported by the observation that inhibiting or neutralizing the actions of TNF-α and other inflammatory cytokines has been beneficial to AD patients [87, 88]. In this regard, studies in subjects with mild cognitive impairment (MCI) that progress to develop AD suggest that raised CSF TNF-α levels represent an early event, and their increase correlates with disease progression [89]. In accord with this, Janelsins and colleagues [90] noted an increased expression of TNF-α transcripts within the entorhinal cortex of transgenic AD mice at 2 months, occurring before the appearance of classical amyloid and tau pathology, and this increase correlated with the onset of cognitive deficits in these mice [91]. These studies, together with others reporting that (i) TNF-α polymorphisms that increase TNF-α production may elevate AD risk, particularly in patients carrying one or more apolipoprotein E ε4 alleles [92–94] and that (ii) genetic ablation of TNF-α receptor 1 (TNFR1) in APP23 AD mice [95] or a selective lowering of secreted TNF-α brain levels in AD transgenic mice [96–98] reduces AD progression, reinforce the view that TNF-α inhibition/reduction may be beneficial treatment strategy for AD [99,100]. From a mechanistic perspective, a pre-pathological upregulation of TNF-α and associated enhancement of activated microglia have been consistently described in AD transgenic mouse models [90, 99, 100], and it has been proposed that such activated immune cells are essential in the clearance of extracellular Aβ. A likely result of increased Aβ exposure, however, is microglia TLR4 stimulation and a resulting elevated cytokine production and release [101]. TNF-α as well as IL-1β can correspondingly elevate Aβ generation by stimulating γ-secretase activity [102], thereby initiating a self-propagating positive feedback loop of Aβ induction of inflammation and TNF-α signaling that, in turn, may provoke further Aβ generation.

The formation and accumulation of AGEs has also been identified immunohistochemically within senile plaques and neurofibrillary tangles, the pathological hallmarks of AD [103].

Elevated AGE levels in AD brain upregulate CD36, augmenting proinflammatory responses, oxidative stress, and altering the microglial uptake of Aβ [104]. RAGE is also expressed in neurons, microglia and astrocytes [105–107].

An increased expression of RAGE has been observed in AD pathology afflicted regions of brain, including the hippocampus [108]. Notably, Aβ has been reported to be a specific RAGE ligand, interacting with its N-terminal domain and inducing an oxidative stress mediated activation of NF-κB, expression of inflammatory genes and proteins [105]. RAGE mediated microglia activation and neuro-inflammation has been experimentally demonstrated using double transgenic mice that over-express both the human RAGE gene and human amyloid precursor protein [109]. Such mice exhibited elevated levels of IL-1β and TNF-α, increased amyloid plaque infiltration by microglia and astrocytes, increased levels of Aβ40 and Aβ42, reduced AChE activity, and a rapid loss of memory. These effects were mitigated by blocking the RAGE mediated signal transduction. In addition to this, the level of sRAGE and hence its anti-inflammatory effects are reported reduced in AD, a scenario quite similar to T2DM [110]. Brought together, these findings support the concept that inflammation is an underlying thread in the coexistence of T2DM and AD.

COMMON THERAPEUTIC TARGETS OF AD AND T2DM

In general, drug developments, particularly for neurological disorders, are a field of high risk and attrition, but also of huge gain - if successful [111–113]. As alterations in the levels of key inflammatory markers (CRP, TNF-α, IL-6) and lipid peroxides are common to T2DM and AD and a close association exists between these two frequent progressive disorders, selectively blocking inflammatory signal cascades and restoring appropriate insulin signaling appears to be a justifiable approach towards treatment of both these disorders. For example, the inhibition of BuChE and TNF-α by selective and well-tolerated inhibitors may have potential for the treatment of both. In addition to the examples provided, BuChE and TNF-α, there are likely further endogenous proteins that are gatekeepers of awry biological cascades that impact the pancreas and brain that may warrant investigation and thereby provide additional apparent links between T2DM and AD, as new avenues for potential treatment [114]. BuChE, in addition to its role in co-regulating ACh levels and cholinergic neurotransmission, has non-cholinergic functions related to differentiation, proliferation and apoptosis [115]. Likewise, ACh modulates interactions between the nervous system and the immune system. Indeed, the ACh mediated cholinergic anti-inflammatory pathway acts by inhibiting the production of TNF-α, IL-1, macrophage migration inhibitory factor (MIF), and high-mobility group B1 protein (HMGB1) and suppresses the activation of NF-κB expression [116]. Progress in the characterization of both disease mechanisms and drug targets has provided the insight that a number of common players are involved across a broad variety of biological cascades, and thus relatively focused approaches such as (i) restoring ACh levels by selectively inhibiting the catalytic activity of BuChE, and (ii) selectively inhibiting pro-inflammatory cytokines (e.g., TNF-α) can potentially inhibit a number of destructive cycles of events. ACh, to extend this example, has a regulatory role on dopamine, serotonin as well as several neuropeptides, providing a close interaction between immune responses and neurotransmission [117]. Elevated levels of BuChE, are reported in diabetes and AD and have been hypothesized to result in a low-grade systemic inflammation

(often seem in the elderly, and associated with geriatric depression [118] as well as sarcopenia [119, 120] and other disorders [121]), consequent to dysregulation of the described pathway (Fig. 1). Elevated systemic BuChE activity is a marker of low-grade inflammation, is found in Alzheimer brain, and may have a role in the altered lipoprotein metabolism in hyper triglyceridemia associated with insulin insensitivity or insulin deficiency in T2DM, and thus may be a target worth pursuing [122, 123]. Interestingly, the BuChE K variant allele is more common among subjects with T2DM versus non-diabetics, suggesting a close association of the BuChE gene (3q26) with T2DM that could be related to an identified susceptibility locus on chromosome 3q27, but independent of islet function [123, 124]. The normalization of elevated BuChE activity found in AD [125–127] may hence be of value for T2DM, which, as indicated, is associated with incidence of AD and drives its progression. The design and development of cymserine analogues for brain BuChE inhibition [128–131], and application of innovative and quantitative enzyme kinetic analyses [132–135] provides an immediately clinically translatable approach [136]. Such studies aid in moving agents from the laboratory to clinical assessment to both test new hypotheses and define the role of key proteins in health, aging and disease, and the compound bisnorcymserine has just entered the clinic [http://clinicaltrials.gov/ct2/show/NCT01747213?term=bisnorcymserine&rank=1]. Other approaches too have moved forward, as exemplified by Nizri *et al.* [137] investigating both the use of bi-functional compounds designed for multiple targeting and enhanced CNS permeability, and of recombinant alpha-fetoprotein (AFP), for the treatment of CNS inflammation. Their bi-functional compounds showed a novel pharmacokinetic profile providing an alternative potential strategy for future drug modalities.

CONCLUSIONS

A growing body of research continues to associate AD to T2DM, as well as with obesity and cardiovascular disease. Certainly, people with T2DM have an increased incidence of sporadic AD. Neuropathological studies suggest that vascular disease, in particular, is the key pathology that drives the elevated risk of dementia in T2DM. Other features underpinning how diabetes potentially exacerbates AD pathology include the common denominators - amyloidogenesis, impaired brain insulin signaling, abnormal brain glucose metabolism, mitochondrial dysfunction, inflammation and oxidative stress. These factors also underlie brain dysfunction and/or cognitive decline in a number of neurological disorders [138–140]. The interrelations between these factors are multiple, complex and require extensive research to pinpoint intersecting points of regulation amenable to pharmacological manipulation. A better understanding of risk factors across a lifetime is additionally needed for AD, and other neurological disorders ans T2DM, to identify potentially modifiable ones to support promising lifestyle changes for those most vulnerable and to define the optimal window(s) of opportunity to initiate remedy.

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LIST OF ABBREVIATIONS

ACh	Acetylcholine
AChE	Acetylcholinesterase
AD	Alzheimer's disease
AGEs	Advanced glycation endproducts
Aβ	Amyloid-β peptide
AβOs	Amyloid-β oligomers
BuChE	Butyrylcholinesterase
BuChE-Is	Butyrylcholinesterase inhibitors
CNS	Central nervous system
IL-6	Interleukin 6
IRS	Insulin receptor substrate
JNK	c-Jun N-terminal kinase
RAGE	Receptor for advanced glycation endproducts
T2DM	Type 2 diabetes mellitus
TNF-α	Tumor necrosis factor α

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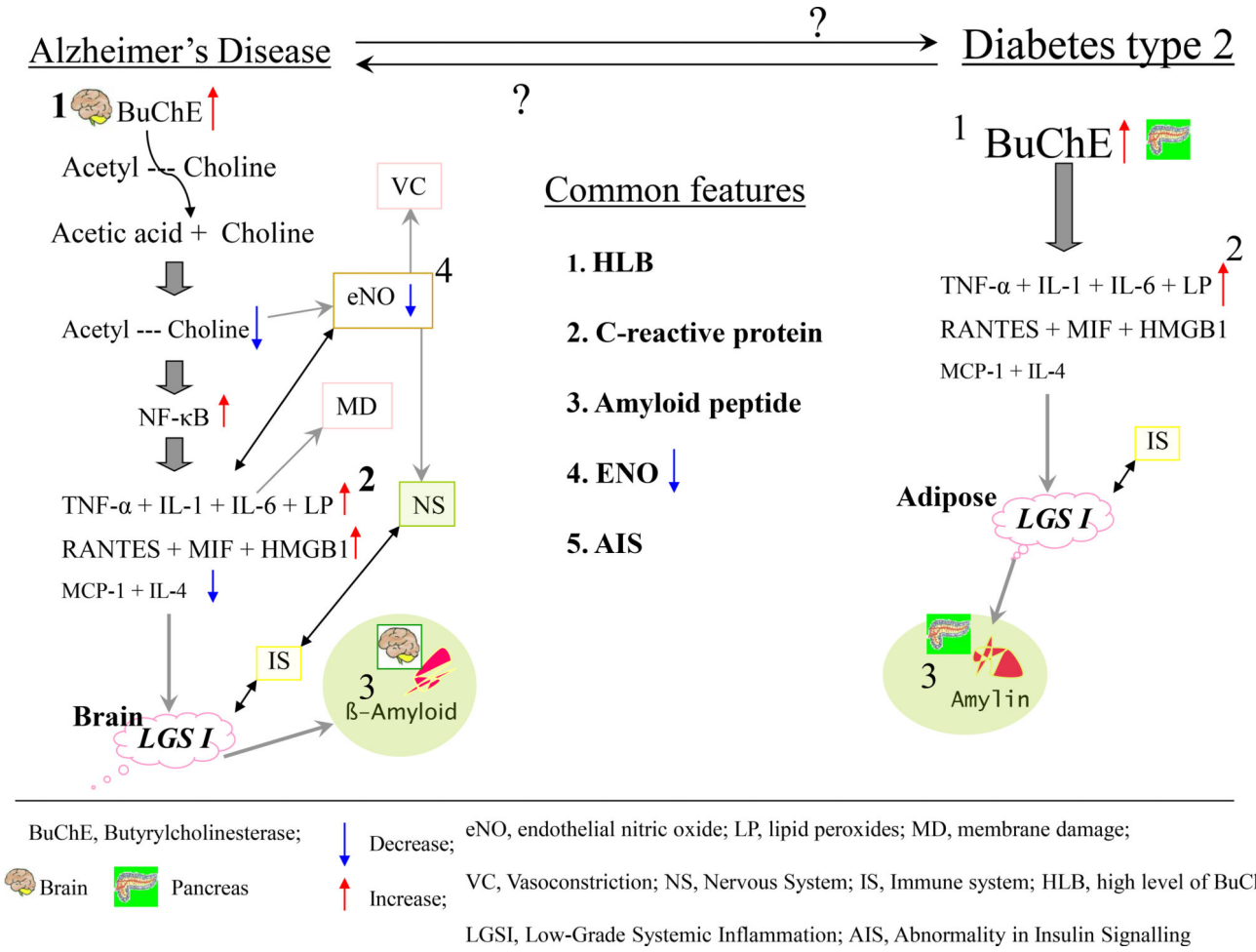

Fig. (1).

Similarities between Alzheimer's disease and type 2 diabetes mellitus reflecting the key role of BuChE in regulating acetylcholine (the critical neurotransmitter linking the nervous and immune systems).