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REVIEW

Alzheimer's disease and type 2 diabetes via chronic inflammatory mechanisms

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Abstract Recent evidence has indicated that type 2 diabetes mellitus (T2DM) increases the risk of developing Alzheimer's disease (AD). Therefore, it is crucial to investigate the potential common processes that could explain this relation between AD and T2DM. In the recent decades, an abundance of evidence has emerged demonstrating that chronic inflammatory processes may be the major factors contributing to the development and progression of T2DM and AD. In this article, we have discussed the molecular underpinnings of inflammatory process that contribute to the pathogenesis of T2DM and AD and how they are linked to these two diseases. In depth understanding of the inflammatory mechanisms through which AD and T2DM are associated to each other may help the researchers to develop novel and more effective strategies to treat together AD and T2DM. Several treatment options have been identified which spurn the inflammatory processes and discourage the production of inflammatory mediators, thereby preventing or slowing down the onset of T2DM and AD.

Contents

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1. Introduction

Alzheimer's disease (AD) is a disorder that mostly afflicts the elderly population of the world with its prevalence reaching up to 50% among 85 years and older people. Similarly, CDC has reported that at present 150 million of the world population is afflicted with type 2 diabetes mellitus (T2DM) with a predicted increase to around 215 million by the year 2010 and 300 million by the year 2025 (CDC, 2006) Several epidemiology studies, the Rotterdam study being the first one of them, have revealed that patients with T2DM are at increased risk for developing memory impairment, dementia and AD (Ott et al., 1999; Leibson et al., 1997; Qiu et al., 2005). Some studies have shown that the risk of developing AD is doubled in diabetic patients (Peila et al., 2002) while other studies reported that people with diabetes mellitus had a 65% higher risk for developing AD compared to those without diabetes (Arvanitakis et al., 2004). Likewise, a close association between AD and T2DM has been revealed in a recent community cohort study from Cache County in which AD patients were found to be more vulnerable to T2DM (Tschantz et al., 2004). Better understanding of the commonalities between T2DM and AD in their molecular mechanisms will provide us clues in the identification of novel common therapeutic targets and recently there have been some clinical trials of anti-diabetic drugs going on in AD patients (Dai and Kamal, 2014).

Preclinical studies on animal models and clinical studies provide evidence that inflammatory mechanisms which are caused directly or indirectly by AD contribute to further AD progression. Thus, neurofibrillary tangles, neuritis, damaged neurons and insoluble β-amyloid deposits in the brains of AD patients provide further stimuli for inflammatory mechanisms and these effects become cumulative over the years (Akayama et al., 2000). Inflammation refers to the localized response in any part of the body as a reaction to injury or infection (Cone, 2001). It is an essential component of tissue repair and is characterized by redness, swelling, pain and fever at the site of injury. In the past, inflammation was considered as a beneficial and necessary response to bodily injury or disease. However, with more and more experimental research, it is becoming increasingly clear that inflammation is like a double-edge sword and a mixed blessing. There are obvious benefits of short-term inflammatory processes such as tissue repair but there are certain disadvantages and harms inflicted on our bodies as a result of chronic inflammatory processes. There are several inflammatory molecules and pathways that can initiate or put a stop to inflammatory pathways. The trouble comes when those inflammatory pathways are left on, for no obvious reason (Inflammation, 2006) and this continues for a long period of time. Today, mounting evidence suggests that inflammation may be a causative factor in T2DM as well as AD as we shall discuss in this review.

2. Role of inflammation in the pathogenesis of T2DM

Low-grade inflammation plays an important role in the pathogenesis of T2DM. In fact, accumulating evidence suggests that circulating levels of inflammatory mediators are linked to insulin resistance and they are found in higher concentrations in individuals at risk of T2DM. For instance, C-reactive protein (CRP) is a type of protein found in the blood. Levels of CRP rise in the blood in response to inflammation. Thus, CRP acts as a marker for inflammation. The West of Scotland Coronary Prevention Study was conducted in order to assess the ability of CRP to accurately predict the development of T2DM among middle aged-men. This comprehensive study was performed on 5245 middle-aged men out of whom 127 were found to be going through a transition from normal glucose to overt diabetes. This study revealed that CRP predicts the development of T2DM in middle-aged men independently of other clinically employed predictors such as baseline BMI (body-mass index) and glucose concentrations (Freeman et al., 2002).

Data from one randomized clinical trial have shown that increased levels of markers and mediators of inflammation such as C-reactive protein (CRP) and interleukin 6 (IL-6) are associated with future development of T2DM, suggesting the potential role of inflammatory markers in diabetogenesis (Pradhan et al., 2001). The possible connection between inflammation and T2DM is further strengthened by the finding that elevated levels of cytokines were observed in obese individuals, thereby causing hepatic insulin resistance in them. Tumor necrosis factor (TNF-α) is a cytokine which is produced by activated macrophages and it regulates the immune cells. More than a decade ago, it was discovered that TNF-α is overexpressed in the adipose tissues of obese mice, thereby establishing a clear link between obesity, T2DM and chronic inflammation (Hotamisligil et al., 1993; Diwan et al., 2012). TNF-α plays a pivotal role in systemic inflammation. In addition, TNF-α has been shown to increase the liver's production of glucose and triglycerides but, at the same time, it causes insulin resistance through its effects on metabolism. TNF-α causes a significant decrease in the peripheral uptake of glucose in response to insulin, hence, playing a role in the insulin resistance in obesity and T2DM that often accompanies obesity (Priyadarshini et al., 2012). Elevated levels of pro-inflammatory cytokines such as TNF-α are known to cause insulin resistance in T2DM. Insulin receptor substrate (IRS) proteins are among the notable intracellular substrates used by insulin receptor tyrosine kinases in the insulin signaling pathway. Cell culture studies have shown that TNF-α causes interference in insulin signaling by inhibiting insulin receptor tyrosine kinase activity and tyrosine phosphorylation of one of its substrates, IRS-1 (Peraldi and Spiegelman, 1997). Similarly, findings from *in vitro* studies indicate that TNF-α could be exerting its anti-insulin effect by disrupting the insulin-stimulated tyrosine

phosphorylation of insulin receptor and its substrates (Feinstein et al., 1993).

Oxidative stress is another underlying cause of inflammation in T2DM. Endothelial dysfunction is commonly observed in people with diabetes. This impairment in endothelium function is the common cause of diabetes-induced vascular disease. It has been hypothesized that hyperglycemia, activation of the advanced glycosylation end-product pathways and free fatty acid metabolites-induced activation of NFκB and NH2-terminal Jun kinases/stress-activated protein kinase stress pathways could be playing a central role in causing late diabetic complications such as insulin resistance and impaired insulin secretion in T2DM (Evans et al., 2002). Furthermore, oxidative stress has been shown to contribute to the fibrillization and aggregation of tissue specific as well as non-specific proteins both in T2DM and AD (Kamal et al., 2014). Hence, oxidative stress has been linked to inflammatory pathways in muscle cells and adipocytes and to impaired insulin secretion in pancreatic β-cells (Furukawa et al., 2004; Lin et al., 2005).

Another marker of inflammation is a high white blood cell (WBC) count. One study measured WBC in 352 nondiabetic Pima Indians aged 27 ± 6 years and they were followed-up for up to 5.5 years. The findings of this study revealed that a high WBC count was an independent predictor of a worsening of insulin action and the development of T2DM among Pima Indians, suggesting the role of chronic low-grade inflammation in the pathogenesis of insulin resistance and T2DM (Vozarova et al., 2002). Elevated levels of other markers of inflammation, such as orosomucoid acid and sialic acid, are also associated with later development of T2DM. In one study of 12,330 men and women, aged 45–64 years, who were followed up for a mean of 7 years, different markers of acute inflammation were analyzed. Of those individuals, 1335 had a new diagnosis of T2DM. It was found in this study that elevated levels of sialic acid and orosomucoid acid were directly related to the development of T2DM in middle-aged adults (Schmidt et al., 1999). Hence, low-grade inflammation is a pathogenic determinant of T2DM and specific inflammatory processes have been recognized to play an important role in the pathology of diabetes, especially T2DM.

3. Inflammation as a causative factor in the pathology of AD

Alzheimer's disease is characterized by local inflammatory response in the brain (Iadecola, 2004; Reale et al., 2013). Main stimulants of inflammation in the brains of AD sufferers consist mainly of damaged neurons and neuritis, neurofibrillary tangles and extremely insoluble Aβ peptide deposits. These stimuli exist from the onset to terminal stages of AD. Thus, neuroinflammation in AD is a major contributor to the AD pathogenesis (Griffin et al., 1998). Aβ peptide, one of the main stimulants of inflammation, is the key pathological player in AD (Reale et al., 2011). Aβ peptide is found in excess in the plaques of AD brains after postmortem analysis. Aβ peptides and insulin are substrates for the same insulin degrading enzyme (IDE), an enzyme belonging to zinc-metalloprotease class. IDE degrades insulin as well as Aβ peptide. Hyperinsulinemia results in reduced ability of IDE to degrade Aβ, which consequently results in amyloid plaque formation and deposition in the brain (Selkoe, 2001). It has been shown clinically that acute hyperinsulinemia caused by insulin infusion to human subjects resulted in increased levels of insulin as well as Aβ in the cerebrospinal fluid, especially in the older subjects. These effects were not observed in the control group which was administered saline via infusion. Additionally, it was observed that increased levels of Aβ in response to hyperinsulinemia went together with an attenuation of insulin's ability to facilitate declarative memory (Watson et al., 2003). The accumulation of Aβ peptide in the brain is linked to decline in memory functions. This is further supported by the studies conducted on Tg2576 (transgenic) mice by Kohjima et al. The Tg2576 mice are the routinely used transgenic mouse models for Alzheimer's disease. Tg2576 mice manifest increasing deterioration in their memory functions after 6 months of age, which is about the time when amyloid β-peptide (Aβ) levels begin to rise in their brains (Kohjima et al., 2010). Furthermore, recent experimental evidence suggests that Aβ causes inhibition of insulin receptor autophosphorylation via competition for insulin binding to insulin receptor and through direct binding to the insulin receptor. By interfering with insulin receptor function in the neurons, Aβ prevents the rapid activation of certain kinases which are essential for long term potentiation (Xie et al., 2002; Townsend et al., 2007). Hence, Aβ acts as a competitive inhibitor of insulin binding and action and increased levels of Aβ in AD may be linked to insulin resistance in the brain.

Microglia are the type of cells found in the brain that can be regarded as the resident macrophages of the brain. They are the first line of defense in our brain. When microglia in the brain attack and engulf foreign substances, they release cytokines, chemokines, enzymes, growth factors and reactive oxygen species similar to the ones produced by the macrophages found in the peripheral parts of the body (McGeer and McGeer, 1995). One of the inflammatory molecules generated by the microglia is TNF-α. When the sera from AD patients versus normal controls were measured by cytotoxicity bioassay and enzyme-linked immunosorbent assay, significantly raised levels of proinflammatory cytokine TNF-α were measured in the serum of AD patients as compared with controls, providing evidence for the presence of inflammatory processes in the AD brains (Fillit et al., 1991). In one cohort study of 126 Danish centenarians, high concentration of TNF-α was seen in the plasma of subjects with Alzheimer's disease. In addition, high levels of TNF-α were positively correlated with the concentrations of IL-6 and C-reactive protein in the plasma showing that inflammatory mechanisms and immune activation may play a role in age-associated pathological diseases such as dementia and AD (Bruunsgaard et al., 1999). Higher levels of TNF-α were also detected in the cerebrospinal fluid (CSF), cortex and glial cells of elderly patients suffering from AD suggesting a direct role TNF-α seems to play in the pathogenesis of T2DM and AD in the elderly (Bruunsgaard and Pedersen, 2003). In addition to microglia, the astrocytes in the brain are another category of glial cells that also produce limited pro-inflammatory products such as CRP, amyloid P and complement factors (Yasojima et al., 2000). These pro-inflammatory products are seen in increased concentrations at the sites of AD pathology in the brain.

The transcription factor NFκB (nuclear factor kappa-light-chain-enhancer of activated B cells) is another protein complex besides TNF-α that is considered as a primary regulator of inflammatory process. NFκB is found in almost all cell types, including the nervous system. NFκB regulates the expression

of many genes which encode proteins that play a decisive role in the process of inflammation. Recent findings have shown the involvement of NFκB in brain processes, especially in neurodegenerative diseases such as AD (O'Neill and Kaltschmidt, 1997). For instance, Aβ peptide found in the plaques of AD patient brain sections has been shown to be a potent activator of NFκB in primary neurons and in neurons in the close proximity of early plaques from AD patients (Kaltschmidt et al., 1997). The distribution of NFκB was also explored histochemically (using polyclonal antibody against the NFκB p65 subunit) in postmortem brains of AD patients as well as healthy controls. In normal control brains, very weak staining of some neurons was noticed. However, in the AD patients' brains, strong neuronal staining for NFκB was observed in neurons, neurofibrillary tangles and dystrophic neuritis, particularly in the hippocampal formation and cerebral cortex, suggesting increased expression of NFκB in brain areas affected by AD (Terai et al., 1996). Thus, inflammation may be a causative factor in the pathogenesis of AD.

4. Inflammation as an underlying link between AD and T2DM

Since the inflammatory processes play a major role in the etiology of both AD and T2DM, studies on transgenic mouse models of AD and T2DM may shed some light on inflammation pathways as a possible mechanistic link between the two disorders. APP23 transgenic mice are a well-studied model for AD as these mice carry the gene mutation in the amyloid precursor protein (APP) derived from a large Swedish family with early-onset AD. Overexpression of human APP gene harboring the Swedish mutation in those mice results in the formation of typical β-amyloid rich plaques resembling the features of AD pathology. β-amyloid plaques appear in the neocortex and hippocampus of APP23 mice at 6 months of age and those plaques are Congo Red-positive (Sturchler-Pierrat et al., 1997). On the other hand, leptin-deficient (ob/ob) mice are a well-known model of T2DM. Leptin receptors are located on pancreatic β-cells. It has been shown that leptin exerts inhibitory effects on insulin gene expression as well as insulin secretion from pancreatic β-cells (Seufert et al., 1999). Takeda et al. crossed Alzheimer's transgenic mice (APP23) with diabetic mice (ob/ob) and looked at the metabolism and pathology of the brains in those double mutant mice (APP ± ob/ob). AD-like cognitive impairment was observed in APP ± ob/ob mice. Cerebrovascular inflammation and severe cerebral amyloid angiopathy were also noticed in APP ± ob/ob mice. More importantly, up-regulation of receptors for advanced glycation end-products and inflammatory changes in the cerebral vasculature were observed in those double mutant mice even before the appearance of cerebral amyloid angiopathy, suggesting that cerebrovascular inflammation caused by T2DM might be the basis of enhanced cognitive impairment (Takeda et al., 2010). It has been shown experimentally that the expression of receptors for advanced glycation end-products is up-regulated in neuronal cells and the cerebral vasculature in AD as well as T2DM (Deane et al., 2003; Liu et al., 2009). Furthermore, impairment of brain insulin signaling in neurons of double mutant APP ± ob/ob mice was also observed. Several clinical studies have demonstrated the pivotal role of insulin resistance and dysfunctional insulin signaling in the brain in the pathogenesis of AD (Gasparini et al., 2002; Steen et al., 2005; Ho et al., 2004; Aliev et al., 2014). Hence, findings from transgenic mouse models of AD and diabetes support the possible mutual interaction between AD and T2DM via cellular mechanisms such as neuroinflammation.

Neuroinflammation is considered an early event and one of the driving forces in the development of AD (Wyss-Coray, 2006). Inflammatory changes caused by the accumulation of β-amyloid deposits in the brain may contribute to neurodegeneration. To explore the underlying link between diabetes and AD, one group of researchers assessed the degree of β-amyloid metabolism, hyperphosphorylation of tau proteins (τ proteins which are abundant in the neurons of CNS), neurite degeneration and neuronal loss in two rat models with spontaneous onset of diabetes: the type 1 diabetic BB/Wor-rat and the type 2 diabetic BBZDR/Wor-rat. The frontal cortices of both groups of diabetic rats were examined 8 months at age. β-amyloid and phosphor-τ accumulation was observed in both groups of rats. However, significantly more neurite degeneration and neuronal loss were observed in type 2 diabetic BBZDR/Wor-rats compared to type 1 diabetic BB/Wor-rats. In addition, ninefold increase of dystrophic neuritis was observed in type 2 diabetic rats. This study demonstrated that experimental diabetes, especially T2DM, causes abnormalities in the brains resembling early AD, such as reduced β-amyloid clearance, hyperphosphorylation of τ protein, neuronal loss and neurite degeneration (Li et al., 2007). In the same vein, immunocytochemical evidence using protein A-gold probes has suggested that IAPP is a protein that is synthesized by pancreatic beta-cells and is stored in beta cell granules for subsequent co-secretion with insulin. Very similar to the Aβ peptide found in the brains of AD sufferers, IAPP found in the pancreatic islets of T2DM patients forms amyloid aggregates in an aqueous environment (Johnson et al., 1988; Glenner et al., 1988; Rasool et al., 2014). It has been shown clinically that disturbances of the blood–brain barrier play a role in the development of AD, especially in elderly patients (Blennow et al., 1990). This would imply that peripheral inflammation factors from T2DM could leak to the brain parenchyma and induce the activation of microglial cells to release inflammatory molecules in the brain (Breteler, 2000). Hence, peripheral inflammatory processes due to T2DM may also contribute to the pathophysiology of AD.

In transgenic mouse models of AD and diabetes, elevated levels of cytokines and tumor necrosis factor (TNF-α) were observed in the blood vessels along with increased deposits of Aβ, causing synaptic dysfunction (Takeda et al., 2011). TNF-α is a cytokine that inhibits Aβ transport from the brain to periphery. Moreover, indicators of stress have been associated with increased levels of proinflammatory cytokines such as IL-6. In turn, IL-6 has been implicated in the pathology of diabetes as well as AD progression (Kiecolt-Glaser et al., 2003). Another animal study in this regard was conducted on APP transgenic mice to examine if brain inflammation from systemic administration of lipopolysaccharides (LPS) would alter the expression of amyloid precursor protein (APP) and increase the formation and deposition of Aβ. APP transgenic mice which were treated with LPS developed three times more Aβ1–40/42 and 1.8 times more APP in their brains compared to phosphate-buffered saline (PBS) treated mice as assessed by immunoprecipitation-mass spectrometry ProteinChip analysis, ELISA and Western blotting. Increased APP expression and

enhanced accumulation of Aβ due to experimental neuroinflammation were demonstrated in this study (Sheng et al., 2003).

In recent years, increasing evidence has emerged suggesting that NFκB mediated inflammatory pathways may be serving as a link between T2DM and neurodegenerative diseases such as AD. These neuroinflammatory processes comprise of activation of microglia when they ingest β-amyloid, which in turn causes the release of pro-inflammatory cytokines such as IL-1beta, IL-6 and TNF-α. These circulating cytokines may cause neuronal death by increasing the rate of apoptosis, reducing synaptic function and inhibition of hippocampal neurogenesis (Rosenberg, 2005). Hence, T2DM may be acting as a precipitating factor in the pro-inflammatory cytokine activation in the brain resulting in neuroinflammation, an essential component of AD neurodegeneration.

It has been hypothesized that when brain glucose utilization is reduced in the early stages of AD, the glial cells detect reduced glucose availability. This results in increased ketone body production and triggering of the NFκB pathway. Due to hyperinsulinemia and central insulin deficit, hyperleptinemia contributes to the inflammatory process through the inhibition of AMP-activated protein kinase. As a result of energy deficit and inflammation, the resulting neuronal cell damage may be contributing to neurodegeneration in AD (Erol, 2008). Besides, the presence of chronic inflammation due to T2DM further affects the metabolism of insulin and Aβ. It has been observed in AD that prolonged inflammation and elevated levels of NFκB eventually result in high levels of Aβ, increased cytokine release and activation of glial cells (Granic et al., 2009). The presence of pro-inflammatory cytokines contributes to the accumulation and aggregation of Aβ in the AD brain. Experimental data on cultured human monocyte-derived macrophages suggest that pro-inflammatory cytokines reduce the expression of insulin degrading enzyme (IDE) and suppress Aβ degradation as well as its subsequent clearance in the brain (Yamamoto et al., 2008).

5. Targeting inflammatory pathways to manage T2DM and AD

The inflammatory pathways play a crucial role and they may be a link in the pathogenesis of T2DM and AD. Hence, the manipulation of certain inflammatory pathways and developing enzyme inhibitors common to both AD and T2DM could be the focus in the development of new treatments for both of these diseases (Jabir et al., 2014; Kamal et al., 2011). Certain drugs with anti-inflammatory action which are effective in the treatment of T2DM have also shown promise to delay the onset of AD. For instance, the use of GLP-1 analogs offers a possibility in the realm of treatment options to halt or delay the early onset of AD. Glucagon-like peptide-1 (GLP-1) is an endogenous incretin hormone that is 30 amino acids long. GLP-1 is a potent antihyperglycemic hormone that facilitates insulin signaling by stimulating insulin release while it also inhibits glucagon secretion. Currently, GLP-1 receptor agonists such as exendin-4 and liraglutide are approved as therapeutics for T2DM (Lovshin and Drucker, 2009). These novel long-lasting analogs of the GLP-1 incretin hormone have also been shown clinically to have anti-inflammatory effects.

When the effects of the GLP-1 analog exendin-4 were studied on human peripheral lymphocytes in T2DM patients, it was observed that exendin-4 down regulated pro-inflammatory responses by suppressing mitogen activated protein kinase signaling pathways in CD4+ T helper lymphocytes and monocytes. Exendin-4 treatment of T2DM patients resulted in reduction of inflammation response. Likewise, exendin-4 treatment has also been shown in T2DM patients to reduce serum inflammatory markers such as high-sensitivity-CRP and cytokines such as monocyte chemoattractant protein-1 when compared to the control group (Wu et al., 2011). In the same vein, it was demonstrated in another study conducted on systemic LPS inflammation model in mice that two day-intraperitoneal injection of liraglutide resulted in noticeable reduction of pro-inflammatory cytokines and enhanced anti-inflammatory cytokines in the blood, spleen and brains of those mice (Hunter and Holscher, 2012).

In addition to GLP-1's anti-inflammatory role in the treatment of T2DM, *in vitro* studies have provided evidence that GLP-1 may be a modulator of inflammation in the central nervous system due to its direct role in reducing cytokine release (Iwai et al., 2006). This is further supported by the findings that GLP-1 induces neurite growth in the brain and protects against oxidative injury in cultured neuronal cells (Perry et al., 2007). Furthermore, it has been shown that GLP-1 reduces the endogenous levels of Aβ in the brain *in vivo* and reduces the levels of amyloid precursor protein in cultured neuronal cells. The same study also demonstrated that GLP-1 protects cultured hippocampal neurons against death induced by Aβ and iron, a type of oxidative insult (Perry et al., 2003). This is not surprising because studies on the permeability across the blood–brain barrier (BBB) have demonstrated that the GLP-1 and GLP-1 analogs like Val(8)GLP-1 can cross the BBB, facilitating their effects on the brain cells (Kastin et al., 2002; Gengler et al., 2012). McClean et al. tested the effects of peripherally injected GLP-1 analog, liraglutide, in an Alzheimer's mouse model, APPswe/PS1ΔE9 (APPSP1). In APP/PS1 mice dosed with liraglutide for 8 weeks, memory impairment was prevented in addition to prevention of deterioration of synaptic plasticity in the hippocampus. The amount of overall β-amyloid plaque in the cortex of mice was reduced to one-half and the number of dense-core Congo red-positive plaques was reduced even more. Most importantly, the degree of inflammation response as measured by activated microglia numbers was reduced to one half in liraglutide-treated APP/PS1 mice (McClean et al., 2011). The reduction of the inflammation response in the brains of AD-mouse model with a GLP-1 analog, which is commonly used to treat T2DM, provides an important link between the two diseases, especially when it has already been established that GLP-1 analogs also reduce inflammatory response in the serum of T2DM patients.

Another promising candidate which may be targeting inflammatory pathways to manage T2DM and AD simultaneously is the Chinese herbal extract "SK0506". In one study reported by Kamal et al., when rats were fed with high fat diet (HFD), elevated levels of serum and hepatic triglycerides, TNF-α, IL-6, liver ALT and AST enzymes and butyrylcholinesterase (BuCHE) in various rat tissues were observed in addition to weight gain. However, SK0506 treatment not only significantly prevented weight gain induced by HFD feeding but also lowered the levels of serum and hepatic triglycerides as well as liver ALT and AST enzymes. More importantly, SK0506 treatment improved the abnormally elevated levels of both inflammatory markers (TNF-α and IL-6) in HFD

fed rats. In addition, treatment with SK0506 resulted in reduced BuCHE activity in skeletal muscle and adipose tissues of rats (Kamal et al., 2009).

In a recent double-masked, placebo controlled trial, the efficacy of an NSAID salsalate (a nonacetylated salicylate) was assessed in obese adults at risk for the development of T2DM. It was found that salsalate improved glycemia and reduced the levels of circulating inflammatory markers. Compared with placebo, salsalate administered group had their levels of CRP decreased by an average of 34% and their glycated albumin by 17% (Fleischman et al., 2008). This study supports the contention that subacute-chronic inflammation contributes to the onset of T2DM. Likewise, epidemiologic studies have reported that long-term use of oral non-steroidal anti-inflammatory drugs (NSAIDs) may protect against the development of AD through their anti-inflammatory properties and delay the onset of the disease provided that such use would occur well before the onset of dementia. More importantly, the benefits were observed among long-term users of NSAIDs who showed substantially lower incidence. The greatest risk reduction to develop AD was seen among those with extended exposure to NSAIDs (In't Veld et al., 2001; Zandi et al., 2002; Aisen et al., 2002). However, orally administered NSAIDs may work as a preventative measure against AD but they are not a treatment for AD because the dose of NSAID that reaches the brain is only 1% to 2% of the total plasma concentration. Therefore, recently intranasal delivery of NSAID flurbiprofen has been suggested which is many times more potent than the oral NSAID ibuprofen. Alzheimer's disease begins in the entorhinal cortex region of the brain which is located close to the olfactory nerves and a nasal NSAID would be much more effective because it can quickly reach that region of the brain (Lehrer, 2014).

A meta-analysis has concluded that angiotensin converting enzyme (ACE) inhibitors reduce the incidence and/or delay the onset of T2DM and studies have also found that ACE inhibitors reduce some markers of inflammation (Al-Mallah et al., 2010; Di Napoli and Papa, 2003). In the same vein, ACE inhibitors have shown promising results to delay AD progression perhaps due to their ability to reduce inflammation and to penetrate the brain (de Oliveira et al., 2014). In one four-year cohort study conducted on AD patients from memory clinics at 16 different university hospitals in France, it was found that the use of ACE inhibitors in older adults with AD was associated with slower cognitive decline in older adults with AD (Soto et al., 2013). Similarly, ACE inhibitors' use was reported to reduce the risk of AD dementia in participants with normal cognition in the Ginkgo Evaluation of Memory Study (Yasar et al., 2013).

Drugs belonging to the PPARs (peroxisome proliferator-activated receptors), especially the PPAR-γ (PPAR < gamma >) class, have been approved by the Food and Drug Administration (FDA) as treatment for T2DM for more than a decade. In addition to its presence in pancreatic beta cells, PPAR-γ is expressed in adipocytes where it regulates adipogenesis and enhances the uptake of fatty acids into adipocytes (Ferre, 2004; Gurnell, 2003). In the brain, PPAR-γ is localized to neurons and astrocytes, where it is involved in the regulation of cell survival and inflammatory responses (Moreno et al., 2004). Studies have shown that PPAR-γ is linked to reduced levels of inducible nitric oxide synthase expression and microglial activation in the brain (Heneka et al., 2000; Kitamura et al., 1999). Thiazolidinediones (TZDs) are a class of drugs that work by activating PPARs (peroxisome proliferator-activated receptors), with greatest specificity for PPAR-γ. TZD drugs lower the risk of developing T2DM. In addition, TZDs lower the circulating levels of inflammatory markers and this effect is independent of adiposity of patients (Di Gregorio et al., 2005). For instance, troglitazone is one of the derivatives of TZDs and it is a PPAR-γ agonist for treatment of T2DM. It has been shown clinically that troglitazone treatment of T2DM patients not only decreased their fasting plasma glucose and HbA1c levels but also resulted in 60% reduction in their circulating CRP levels (Chu et al., 2002). In another double-blind study, troglitazone has been shown clinically to delay or prevent the onset of T2DM in high-risk subjects (Buchanan et al., 2002). Rosiglitazone, a member of TZD class, is another PPAR-γ agonist approved by FDA for the treatment of T2DM. It lowers glucose and lipid levels in T2DM patients (Willson et al., 2001). In fact, both pioglitazone and rosiglitazone have been shown to increase peripheral insulin sensitivity and lower concentrations of insulin (Landreth et al., 2008). In addition to its effects on insulin resistance, rosiglitazone has anti-inflammatory effects (Mohanty et al., 2004).

In addition to their therapeutic role in the treatment of T2DM, PPAR-γ agonists are potential drugs for the treatment of AD. PPAR-γ agonists have been shown *in vivo* to inhibit β-amyloid-stimulated expression of IL-6 and TNFα (Combs et al., 2000). Glimepiride is a TZD-derivative and an oral anti-diabetic drug with PPAR-γ-stimulating activity. Glimepiride has been shown to attenuate Aβ production in primary cortical neurons by suppression of BACE1 activity which makes it a promising drug for the treatment of AD associated with T2DM (Liu et al., 2013). Likewise, a small clinical study of 30 patients with mild AD or mild cognitive impairment found that patients treated with rosiglitazone for 6 months demonstrated memory enhancement and enhanced attention (Watson et al., 2005). In a larger study of more than 500 patients with mild to moderate AD, 6 months of treatment with rosiglitazone resulted in a statistically significant cognitive improvement in patients that did not possess an Apo-epsilon-4 allele (Risner et al., 2006). In an animal study, it has been shown that 9–14% of rosiglitazone crosses the blood–brain barrier after oral treatment (Strum et al., 2007). Pioglitazone is another TZD-derivative with PPARγ-receptor agonist properties that holds promise as a therapeutic candidate for AD. Chronic use of pioglitazone has been shown to improve long term and visuo-spatial memory in mouse model of AD (Gupta and Gupta, 2012). More importantly, in a recently reported 6-month, randomized, open-controlled trial of patients with mild AD accompanied with T2DM, it was shown that patients in the pioglitazone treated group not only showed a decrease in fasting plasma insulin levels but also improved cognition and regional cerebral blood flow in the parietal lobe. Thus, pioglitazone-dosed T2DM patients exhibited cognitive and functional improvements (Sato et al., 2009). Since both T2DM and AD are disorders possessing an inflammatory component, PPAR-γ-receptor agonists such as TZD-derivatives may prove beneficial for the treatment of T2DM as well as AD (Heneka et al., 2011).

Hence, various anti-inflammatory agents have been clinically shown to prevent or delay the onset of T2DM and AD and this clinical evidence in itself confirms the pathogenic role

of inflammation in the onset or progression of T2DM and AD. The well-studied AD-diabetic transgenic mouse models may provide further insights into developing novel therapeutic solutions for the prevention or treatment of AD. However, there is still a need for more specific inhibitors targeting the inflammatory pathways in order to gain maximum benefit in the prevention or treatment of T2DM and AD at the same time. Such drugs will provide us with new opportunities for using anti-inflammatory strategies to correct the root cause underlying the pathology of T2DM and AD.

Conflict of interest

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

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